Use of Pharmacogenomics (PGx) as a Medication Optimization Strategy

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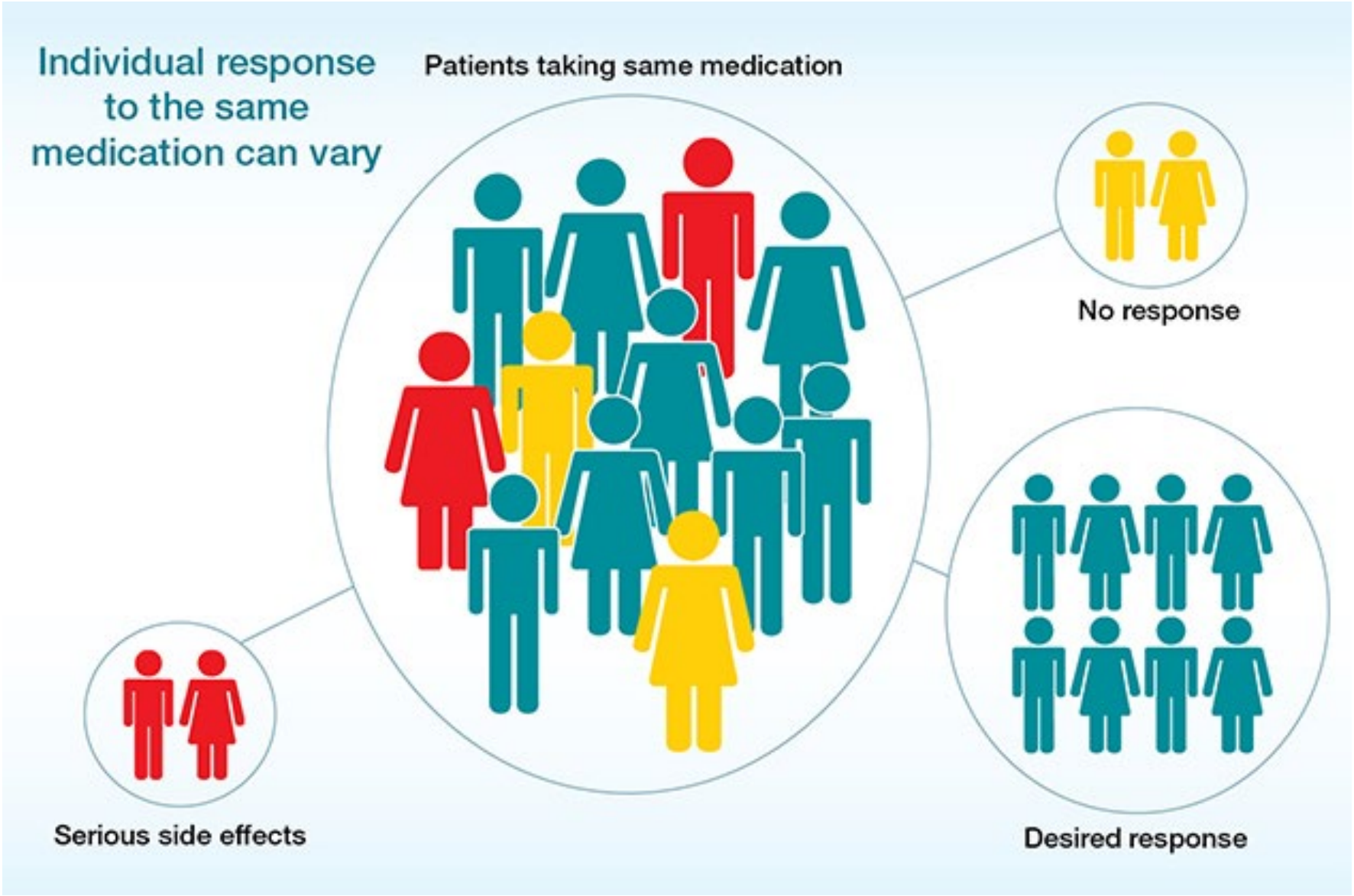
Pharmacogenomics (PGx)

How your genetics affects your response to medications



https://www.mayo.edu/research/centers-programs/center-individualized-medicine/patient-care/pharmacogenomics

CYP2D6 Extensive Metabolizer (normal rate of metabolism)

- The CYP2D6 enzyme catalyzes the demethylation reaction of the prodrug codeine to its active metabolite morphine.
- CYP2D6 enzyme activity determines the codeine/morphine ratio and the strength of opiate effect.
- This is a simplified pathway. The actual pathway can be found at: https://www.pharmgkb.org/pathway/PA146123006.

- CYP2D6 Poor Metabolizers are unable to convert codeine to morphine efficiently and may not experience pain relief.
- Did CYP2D6 poor metabolism contribute to the death of Elvis Presley? The full story can be found at: https://www.thecarlatreport.com/blogs/2-the-carlat-psychiatry-podcast/post/4319-elvis-presley-and-pharmacokinetics-part-2

- CYP2D6 Ultra-rapid Metabolizers convert codeine to morphine more rapidly and completely with a consequence of higher than expected morphine levels. This can result in respiratory depression and signs of an overdose, even at therapeutic doses.
- Prevalence: 1-10% for European and North Americans, 3-4% for African Americans, 1-2% for East Asians, and greater than 10% in certain racial/ethic groups.

Pain

Drug Class	Standard Precautions	Use With Caution	Consider Alternatives
Fibromyalgia Agents	Milnacipran (Savella®)		
Muscle Relaxants	Cyclobenzaprine (Flexeril®, Amrix®) Metaxalone (Skelaxin®) Methocarbamol (Robaxin®)	Carisoprodol (Soma®) Tizanidine (Zanaflex®)	
NSAIDs	Celecoxib (Celebrex®) Diclofenac (Voltaren®) Flurbiprofen (Ansaid®) Ibuprofen (Advil®, Motrin®) Indomethacin (Indocin®) Ketoprofen (Orudis®) Ketorolac (Toradol®) Meloxicam (Mobic®) Nabumetone (Relafen®) Naproxen (Aleve®) Piroxicam (Feldene®) Sulindac (Clinoril®)		
Opioids	Alfentanil (Alfenta®) Buprenorphine (Butrans®, Buprenex®) Dihydrocodeine (Synalgos-DC®)	Benzhydrocodone (Apadaz®) Hydrocodone (Vicodin®) Methadone (Dolophine®) Oliceridine (Olinvyk)	Codeine (Codeine; Fioricet® with Codeine) Tramadol (Ultram®)

Personalized Medication Insights

Codeine

Codeine; Fioricet® with Codeine

CYP2D6 Poor Metabolizer

Greatly Decreased Exposure to Codeine Active Metabolite

Actionable

The patient genotype is associated with greatly decreased conversion of codeine to its active metabolite (morphine), which may result in decreased effectiveness.

Consider avoiding prescribing codeine and instead use alternative opioids other than tramadol, or a non-opioid analgesic such as an NSAID or a COX-2 inhibitor. Alternative opioids may include: fentanyl, morphine, hydromorphone, oxymorphone, and tapentadol.

- Crews KR, Monte AA, Huddart R, Caudle KE, Kharasch ED, Gaedigk A, Dunnenberger HM, Leeder JS, Callaghan JT, Samer CF, Klein TE, Haidar CE, Van Driest SL, Ruano G, Sangkuhl K, Cavallari LH, Müller DJ, Prows CA, Nagy M, Somogyi AA, Skaar TC. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. Clin Pharmacol Ther 2021 10;110(4):888-896.

Laboratory Results

Results Summary

Gene	Genotype	Phenotype	Clinical Implications
CYP2D6	*4/*4	Poor Metabolizer	Consistent with a significant deficiency in CYP2D6 enzyme activity. Exercise caution if CYP2D6 drug substrates are prescribed.

CYP2D6

- One of the key pharmacogenes involved in the implementation of pharmacogenomics
- Highly polymorphic
- Involved in the metabolism of up to 25% of drugs
- Involved in guidelines for:
  - Pain medications including codeine, tramadol
  - Antidepressants including TCA, paroxetine, fluvoxamine, venlafaxine
  - Tamoxifen
- List of all guidelines with CYP2D6: https://www.pharmgkb.org/gene/PA128/prescribingInfo#guideline-annotations

CYP2D6 & Tramadol

FDA Table of Pharmacogenetic Associations

Ultra-rapid metabolizers – Results in higher systemic and breast milk active metabolite concentrations, which may result in respiratory depression and death. Contraindicated in children under 12 and in adolescents following tonsillectomy/adenoidectomy. Breastfeeding is not recommended during treatment.

Poor metabolizers - Results in lower systemic active metabolite concentrations and may result in reduced efficacy.

Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy

Table 3 Tramadol therapy recommendations based on CYP2D6 phenotype

Phenotype	Activity score	Implications	Recommendations	Classification of recommendation[a]
CYP2D6 ultrarapid metabolizer	> 2.25	Increased formation of O-desmethyltramadol (active metabolite) leading to higher risk of toxicity	Avoid tramadol use because of potential for toxicity. If opioid use is warranted, consider a non-codeine opioid.	Strong
CYP2D6 normal metabolizer	$1.25 \leq x \leq 2.25$	Expected O-desmethyltramadol (active metabolite) formation	Use tramadol label recommended age-specific or weight-specific dosing.	Strong
CYP2D6 intermediate metabolizer	$0 < x < 1.25$	Reduced O-desmethyltramadol (active metabolite) formation	Use tramadol label recommended age-specific or weight-specific dosing. If no response and opioid use is warranted, consider non-codeine opioid.	Optional
CYP2D6 poor metabolizer	0	Greatly reduced O-desmethyltramadol (active metabolite) formation leading to diminished analgesia.	Avoid tramadol use because of possibility of diminished analgesia. If opioid use is warranted, consider a non-codeine opioid.	Strong
CYP2D6 indeterminate	n/a	n/a	No recommendation	No recommendation

n/a, not applicable.
[a]Rating scheme described in the **Supplementary Material**.

https://files.cpicpgx.org/data/guideline/publication/opioids/2020/33387367.pdf

Case Study

- John is an 76 year old patient who was prescribed Tramadol 50mg BID for chronic knee pain. He continued to complain about pain so his provider increased his dose to 50mg QID. After several weeks of being on Tramadol 50mg QID his pain scores continue to be a 6-8/10. What should his provider do?
- A – Assume he is a drug seeker and no longer prescribe opioids
- B – Increase his dose to 100mg QID
- C – Consider pharmacogenomic testing
- D – Switch him to Codeine
- E – Switch him to Hydrocodone/APAP

Clinical Pharmacogenetics implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy

Table 4 Hydrocodone therapy recommendations based on CYP2D6 phenotype

Phenotype	Activity score	Implications	Recommendations	Classification of recommendation[a]
CYP2D6 ultrarapid metabolizer	> 2.25	Minimal evidence for pharmacokinetic or clinical effect.	No recommendation for hydrocodone therapy because of minimal evidence regarding adverse events or analgesia.	No recommendation
CYP2D6 normal metabolizer	$1.25 \leq x \leq 2.25$	Normal hydromorphone formation	Use hydrocodone label recommended age-specific or weight-specific dosing.	Strong
CYP2D6 intermediate metabolizer	$0 < x < 1.25$	Minimal evidence for pharmacokinetic or clinical effect.	Use hydrocodone label recommended age-specific or weight-specific dosing. If no response and opioid use is warranted, consider non-codeine or non-tramadol opioid.	Optional
CYP2D6 poor metabolizer	0	Decreased metabolism of hydrocodone to active metabolite, hydromorphone, but there is insufficient evidence to determine if these effects on pharmacokinetics translate into decreased analgesia or side effects.	Use hydrocodone label recommended age-specific or weight-specific dosing. If no response and opioid use is warranted, consider non-codeine and non-tramadol opioid.	Optional
CYP2D6 indeterminate	n/a	n/a	No recommendation	No recommendation

https://files.cpicpgx.org/data/guideline/publication/opioids/2020/33387367.pdf

Cytochrome P450 (CYP) family

- Six CYP P450 enzymes are responsible for the metabolism of almost 90% drugs: CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.
- Phenotype (enzyme activity) has been simplified into four categories:
  - Poor metabolizer: no to little activity
  - Intermediate metabolizer: reduced activity
  - Extensive metabolizer: normal activity
  - Ultrarapid metabolizer: increased activity
- For an active drug – loss of function alleles may reduce its clearance and increase the parent drug concentration (drug toxicity risk)
- For a prodrug – loss of function alleles reduce the conversion to the active metabolite (lack of efficacy risk)

Clopidogrel

- Antiplatelet drug (P2Y12 purine receptor blocker) that inhibits ADP-mediated platelet activation and aggregation.
- Most widely prescribed P2Y12 inhibitor worldwide for the prevention of thrombotic events.
- Prodrug that requires a functional CYP2C19 to become an active antiplatelet drug.
- 5-30% of the global population carries a CYP2C19 loss of function allele associated with an increased risk of major adverse cardiovascular events.

Clopidogrel Boxed Warning

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

- **Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)**
- **Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)**
- **Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)**
- **Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)**

CPIC Guidelines for CYP2C19 Genotype and Clopidogrel Therapy: 2013 Update

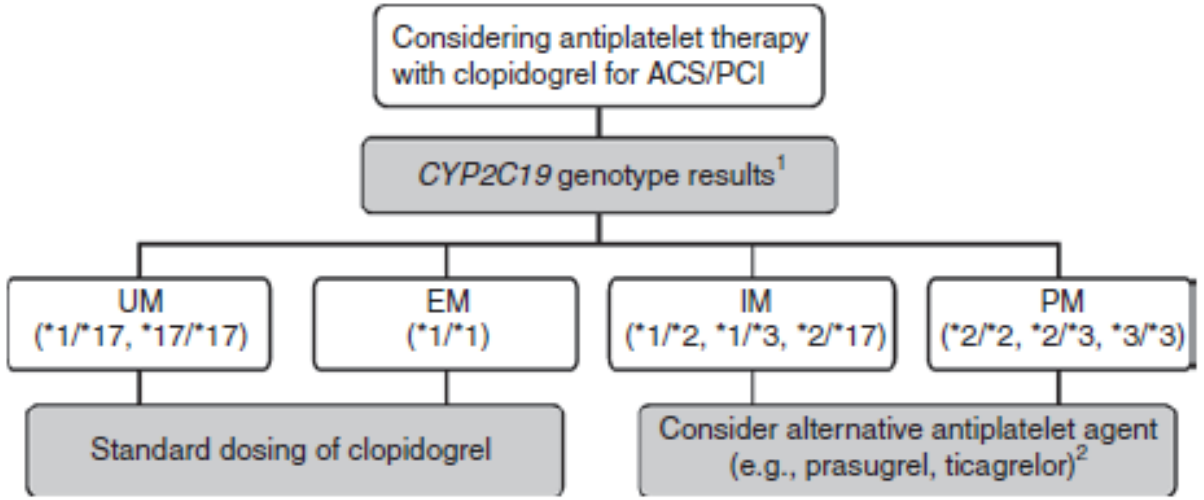


Figure 1 Algorithm for suggested clinical actions based on *CYP2C19* genotype when considering treatment with clopidogrel for ACS patients undergoing PCI (ACS/PCI). [1]Other rare *CYP2C19* genotypes exist beyond those illustrated (see **Supplementary Materials and Methods** online for other genotypes and frequencies). [2]Note that prasugrel and ticagrelor are recommended only when not contraindicated clinically. ACS, acute coronary syndrome; EM, extensive metabolizer; IM, intermediate metabolizer; PCI, percutaneous coronary intervention; PM, poor metabolizer; UM, ultrarapid metabolizer.

Clopidogrel
Plavix®
CYP2C19 Poor Metabolizer

Significantly Reduced Exposure to Clopidogrel Active Metabolite

Actionable

The patient's genotype is associated with possible decreased clopidogrel exposure. Patients may be at an increased risk for adverse cardiac and cerebrovascular events.

Cardiovascular and Neurovascular Indications:
Consider an alternative such as prasugrel (contraindicated in TIA/stroke) or ticagrelor.

- Plavix [package insert]. Bridgewater, NJ: Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership; 2021.
- Lee CR, Luzum JA, Sangkuhl K, Gammal RS, Sabatine MS, Stein CM, Kisor DF, Limdi NA, Lee YM, Scott SA, Hulot JS, Roden DM, Gaedigk A, Caudle KE, Klein TE, Johnson JA, Shuldiner AR. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C19 Genotype and Clopidogrel Therapy: 2022 Update. Clin Pharmacol Ther 2022 Jan;():.

Cardiovascular

Drug Class	Standard Precautions	Use With Caution	Consider Alternatives
Angiotensin II Receptor Antagonists	Azilsartan (Edarbi®, Edarbyclor®) Candesartan (Atacand®) Eprosartan (Teveten®) Irbesartan (Avapro®) Losartan (Cozaar®, Hyzaar®) Olmesartan (Benicar®) Telmisartan (Micardis®) Valsartan (Diovan®, Entresto®)		
Antianginal Agents	Ranolazine (Ranexa®)		
Antiarrhythmics	Amiodarone (Nexterone®, Pacerone®) Disopyramide (Norpace®) Flecainide (Tambocor®) Mexiletine (Mexitil®) Propafenone (Rythmol®) Quinidine (Quinidine®) Sotalol (Betapace®, Sorine®, Sotylize®)		
Anticoagulants	Apixaban (Eliquis®) Betrixaban (Bevyxxa®) Dabigatran Etexilate (Pradaxa®) Edoxaban (Savaysa®) Fondaparinux (Arixtra®) Rivaroxaban (Xarelto®)	Warfarin (Coumadin®)	
Antiplatelets	Aspirin (Ecotrin®) Prasugrel (Effient®) Ticagrelor (Brilinta®)		Clopidogrel (Plavix®)

CYP2D6 & Beta blockers

- Carvedilol, metoprolol, nebivolol, propranolol – PGx biomarkers in the FDA's Table of Pharmacogenetic Associations – metabolized by CYP2D6 (PM = higher systemic concentrations)
- DPWG Guideline for Metoprolol & CYP2D6
  - For CYP2D6 poor and intermediate metabolizer patients, if a GRADUAL REDUCTION in HEART RATE is desired, or in the event of SYMPTOMATIC BRADYCARDIA, use smaller steps in dose titration and/or prescribe no more than 25% or 50% of the standard dose, respectively.
  - For CYP2D6 ultra metabolizers, use the maximum dose for the relevant indication as a target dose, and if the effectiveness is still insufficient: increase the dose based on effectiveness and side effects to 2.5 times the standard dose or select an alternative drug.
- Poor metabolizers will have increased (several-fold) metoprolol blood levels
  - Decreases metoprolol's cardioselectivity

Statins

- Statins are one of the most widely prescribed medications worldwide.
- SLC01B1 is a gene that encodes for organic anion transporting peptide 1B1, involved in the transport of statins into hepatic cells.
- Reduced function of the transporter leads to reduced statin transport into the liver. This can lead to higher plasma concentrations and an increased risk of side effects such as myopathy.
- SLC01B1 mediates transport of all statins but to varying degrees
  - Simvastatin – most impacted
  - Atorvastatin, Lovastatin, Pitavastatin
  - Pravastatin, Rosuvastatin – least impacted
- 2022 CPIC guidelines recommend poor and decreased function SLC01B1 phenotypes initiate with low dose regardless of the drug.
- ABCG2 – decreased function increases Rosuvastatin concentration (dose 20mg or less)
- CYP2C9 – use lower doses of Fluvastatin for IMs and PMs

What can we do with PGx?

ADJUST THE DOSE

EXTRA MONITORING

AVOID THE MEDICATION

Benefits

- An individualized approach to assist in finding the most effective medications for a patient
- Prevention of side effects
- Evidence-based
- You can use it the rest of your life

Limitations

- Not all medications have PGx drug labeling, prescribing information, or genotype-based clinical guidelines
- The swab will not predict everything
- Cost
- Provider buy-in
- Implementation

PGx Resources

- CPIC – Clinical Pharmacogenetics Implementation Consortium
  - Cpicpgx.org
  - Posts freely available, peer-reviewed, evidence-based, updatable, and detailed gene/drug clinical practice guidelines
- PharmGKB
  - Pharmgkb.org
  - Pharmacogenomics knowledge resource center
- FDA Table of Pharmacogenomic Biomarkers in Drug Labeling
  - https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling
  - Table that lists products from Drugs@FDA with pharmacogenomic information found in the drug labeling

- Pain
- Cardiovascular
- Oncology
- Gastrointestinal
- Psychiatry
- Rheumatology
- Neurology
- Hematology
- Urology
- more

Who would benefit from PGx testing?

- Patients experiencing side effects.
- Patients who cannot find the right medication.
- Patients taking multiple medications
- Patients who want to be proactive.
- Vulnerable populations

- 1076 patients with schizophrenia, major depressive disorder and bipolar disorder
- Patients with an actionable phenotype in the PGx-guided arm had:
  - 48.5% reduction of treatment costs
  - 34.1% less adverse drug reactions
  - 41.2% less hospitalizations
  - 40.5% less re-admissions
  - Less duration of initial hospitalizations and less duration of readmission hospitalizations
  - Lower doses on average and less polypharmacy
  - Less deaths (9 to 1)

OHSU to pay $1 million, promises change to settle lawsuit from widow of cancer patient

ADVOCATES FOR UNIVERSAL DPD/DPYD TESTING

Nursing Home Study

- 85 patients tested
  - 16 severe gene-drug interactions
  - 149 moderate gene-drug interactions
  - CYP2C19 (Clopidogrel)
    - 1 – PM
    - 20 – IM
  - CYP2D6
    - 8 – PM
    - 40 – IM
    - 35 – Normal
    - 2 – UR
  - SLC01B1
    - 67 – Normal
    - 15 – Decreased
    - 3 - Poor
  - Coupled with a deprescribing initiative
    - Average # of medications/patient 16.8 → 14.46 (5,967 less doses/30 days if each med was only given once daily)
    - PHQ scores remained about the same
    - Pain scores 4.8 → 3.4

The Deprescribing Clinic

- Amlodipine 2.5mg QPM
- Analgesic Balm PRN
- Bacitracin PRN
- Carvedilol 12.5mg AM + 6.25mg PM
- Escitalopram 20mg daily
- Fentanyl 50mcg/hr Q72 hours
- Flonase 1 spray EN BID
- Gabapentin 100mg TID
- Methenamine 1gram BID
- Hydro/APAP 5/325mg BID + Q6 hours PRN
- Loperamide PRN
- Isosorbide Mononitrate 30mg BID
- Furosemide 20mg Q Mon and Thursday
- Leflunomide 20mg QD
- Levothyroxine 137mcg daily
- Lorazepam 0.5mg TID + Q6 hours PRN
- Magnesium oxide QD
- Miralax QD
- Myrbetriq 50mg QD
- Nitrostat PRN
- Pantoprazole 40mg QD
- Potassium 10mEQ QD
- Ropinirole 0.25mg QD
- Systane Balance 1 drop OU Q6 hours PRN
- Trazodone 25mg QHS
- Acetaminophen 650mg Q6 hours PRN
- Vitamin D 1000 IU daily
- Ondansetron 4mg PRN

Carvedilol 12.5mg BID
Duloxetine (tapering up)
Fentanyl 50mcg/hr Q72 hours
Methenamine 1gram BID
Levothyroxine 137mcg daily
Lorazepam 0.5mg TID + Q6 hours PRN
Miralax daily
Myrbetriq 50mg QD
Nitrostat PRN
Methylfolate
Magnesium glycinate

Case Study

- Nellie is an 82 year old female at your long term care facility. Nursing ask you for a medication review due to dizziness and hallucinations.
- She had a PGx test done previously which showed Nellie is a CYP2D6 poor metabolizer and CYP2C19 ultra-rapid metabolizer.
- Her current medication list includes:
  - Omeprazole 20mg daily
  - Metoprolol ER 100mg daily
  - Lisinopril 5mg daily
  - Clopidogrel 75mg daily
  - Acetaminophen 650mg TID
  - Albuterol 2 puffs Q4 hours PRN

What do you recommend?

A – Decrease the dose of metoprolol to help with the dizziness.

B – Tell the nurse to get a psych consult and start Quetiapine 25mg daily.

C – Recommend switching from Metoprolol to Atenolol.

D – Recommend switching from Metoprolol to Propranolol.

E – Recommend switching from Clopidogrel to Prasugrel.

References

1. Mayo Clinic Center for Individualized Medicine. Pharmacogenomics in Patient Care. Accessed June 2024. https://www.mayo.edu/research/centers-programs/center-individualized-medicine/patient-care/pharmacogenomics
2. Codeine and Morphine Pathway, Pharmacokinetics, accessed 6/17/24, https://www.pharmgkb.org/pathway/PA146123006.
3. CYP2D6, Accessed 6/17/24, https://www.pharmgkb.org/gene/PA128.
4. Clinical Pharmacogenomics Implementation Consortium. Clinical Pharmacogenomics Implementationj Consorium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. Accessed 6/17/24. Available at: https://files.cpicpgx.org/data/guideline/publication/opioids/2020/33387367.pdf.
5. Clinical Pharmacogenetics Implementation Consortium. CPIC Guideline for Clopidogrel and CYP2C19. Accessed 6/17/24. Available at: https://cpicpgx.org/guidelines/guideline-for-clopidogrel-and-cyp2c19/.
6. T P A, M SS, Jose A, Chandran L, Zachariah SM. Pharmacogenomics: the right drug to the right person. J Clin Med Res. 2009 Oct;1(4):191-4. doi: 10.4021/jocmr2009.08.1255. Epub 2009 Oct 16. PMID: 22461867; PMCID: PMC3299179.
7. Clopidogrel (Package Insert). Bridgewater, NJ. Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership. August 2010.
8. Clinical Pharmaogenomics Implementation Consortium. (2013). Clinical Pharmacogenetics Implemenatation Consortium Guidelines for CYP2C19 Genotype and Clopidogrel Therapy: 2013 Update. Available at: https://cpicpgx.org/guidelines/guideline-for-clopidogrel-and-cyp2c19/.
9. Skokou, M., Karamperis, K., Koufaki, MI., Tsermpini, EE., Pandi, MT., Siamoglou, S., et al. (2024). Clinical implementation of preemptive pharmacogenomics in psychiatry. The Lancet. https://doi.org/10.1016/j.ebiom.2024.105009.
10. PharmGKB. Available at www.pharmgkb.org. Accessed 6/13/24.
11. United States Food and Drug Administration. Table of Pharmacogenomic Biomarkers in Drug Labeling. Available at www.fda.gov. Accessed 6/13/24.