Pharmacogenomics: personalizing medications for our patients

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CPFI 2025 Annual Conference & National Student Retreat

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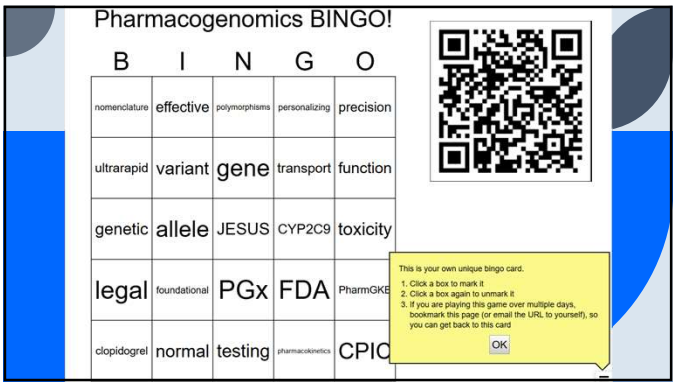

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Learning Objectives

1. Explain the terms precision medicine and precision pharmacotherapy
2. Discuss ways that pharmacogenomics affects pharmacodynamics (PD) and pharmacokinetics (PK) and how it can be used to improve prescribing and outcomes
3. Categorize the Core Pharmacists Competencies in Genomics into Foundational Genetic Concepts and Clinical Pharmacogenomics Concepts
4. Given a clinical scenario, formulate an appropriate medication regimen using pharmacogenomics resources

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Precision medicine and precision pharmacotherapy

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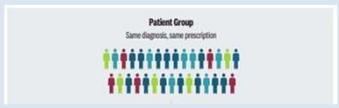
One drug does not fit all



Harvard Business Review Analytic Services. White Paper 2020. Genetic Testing Brings Big Changes to the Health Care System. https://hbr.org/sponsored/2020/03/genetic-testing-brings-big-changes-to-the-health-care-system Accessed 8.5.2024

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Precision medicine and pharmacotherapy

Precision Medicine

- An approach to disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person

Precision Pharmacotherapy

- Customize medications to subgroups of patients, categorized by shared molecular and cellular biomarkers, to improve treatment outcomes

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Medication classes impacted by pharmacogenomics

Cardiology	Psychiatry	Neurology	Oncology
Pain management	Infectious disease	Rheumatology	Solid organ transplant
	Respiratory	Immunology	

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Pharmacogenomics, Pharmacokinetics and Pharmacodynamics

PGx, PK, PD

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What is pharmacogenomics (PGx)?

- Combines pharmacology and genomics to determine an individual's response to medications
- Can help healthcare providers better predict if a medication will be effective but not toxic for their patient
- PGx testing can reduce the risk of adverse effects by up to 30%

Pharmacogenomics Fact Sheet. Genome.gov. Published 2023. https://www.genome.gov/about-genomics/educational-resources/fact-sheets/pharmacogenomics
Apted T, Huff A. Pharmacogenomics for improved outcomes and decreased costs in health care. AJMC. Published December 15, 2023. https://www.ajmc.com/view/pharmacogenomics-for-improved-outcomes-and-decreased-costs-in-health-care

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PGx, Pharmacokinetics (PK), and Pharmacodynamics (PD)

Pharmacodynamics
- Gene variants
- Adverse effects
- Receptor functions

Pharmacokinetics
- Absorption
  - Acid suppression
- Distribution
  - Bioavailability at target sites
- Metabolism
  - Metabolic rate
  - Hepatic function
  - Drug interactions
- Excretion
  - Renal function

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Pharmacokinetics

Types of metabolizer	Description	Example
Ultrarapid metabolizer (UM)	Increased enzyme activity compared to rapid metabolizers	*CYP2C19 *17/*17*
Rapid metabolizer (RM)	Increased enzyme activity compared to normal metabolizers but less than ultra-rapid metabolizers	*CYP2C19 *1/*17*
Normal metabolizer (NM)	Fully functional enzyme activity	*CYP2C19 *1/*1*
Intermediate metabolizer (IM)	Decreased enzyme activity (activity between normal and poor metabolizer)	*CYP2C19 *1/*2*
Poor metabolizer (PM)	Little to no enzyme activity	*CYP2C19 *2/*2*

CPIC SOP for Assigning Allele Function – CPIC. Cpicpgx.org. Published 2025. https://cpicpgx.org/resources/cpic-draft-allele-function-sop/. Accessed April 15, 2025.

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Pharmacodynamics

Transporter function	Description	Example
Increased function	Increased transport function compared to normal function	*SLCO1B1 *1/*14*
Normal function	Fully functional transporter function	*SLCO1B1 *1/*1*
Decreased function	Decreased transporter function (between normal and poor function)	*SLCO1B1 *1/*5*
Poor function	Little to no transporter function	*SLCO1B1 *5/*5*

CPIC SOP for Assigning Allele Function – CPIC. Cpicpgx.org. Published 2025. https://cpicpgx.org/resources/cpic-draft-allele-function-sop/. Accessed April 15, 2025.

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Role of the Pharmacist in Pharmacogenomics

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Role of the Pharmacist in PGx

- Foundational Genetic Concepts: 6
- Clinical Pharmacogenomics: 24
- Last updated 2021

Pharmacists Leading the Way to Precision Medicine: Updates to the Core Pharmacist Competencies in Genomics | American Journal of Pharmaceutical Education (ajpe.org) Accessed April 9, 2025.

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Foundational Genetic Concepts

1. Explain basic genetics concepts using appropriate nomenclature
2. Recognize the 4 factors in the manifestation of disease and drug response
3. Differentiate between the clinical diagnosis of disease informed by genetics and the identification of genetic predisposition of disease
4. Assess differences in genetic testing technologies
5. Recognize the legal protections against discrimination based on genetic test results

Pharmacists Leading the Way to Precision Medicine: Updates to the Core Pharmacist Competencies in Genomics | American Journal of Pharmaceutical Education (ajpe.org) Accessed April 9, 2025.

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Clinical Pharmacogenomics Concepts

1. Identify PGx test results that are relevant to a patient's care
2. Interpret PGx test results
3. Determine the impact of genetic variation on pharmacokinetics and/or pharmacodynamics
4. Understand the influence of ethnicity in genetic polymorphisms and associations of polymorphisms with drug response

Pharmacists Leading the Way to Precision Medicine: Updates to the Core Pharmacist Competencies in Genomics | American Journal of Pharmaceutical Education (ajpe.org) Accessed April 9, 2025.

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Beware that…

- Phenotype can change if a new medication is added = PHENOCONVERSION

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PGx Resources

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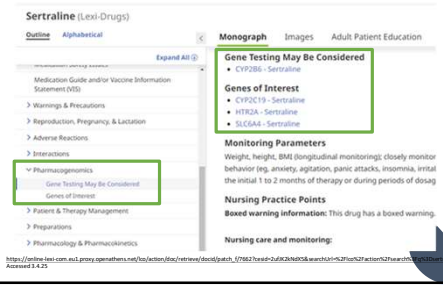
Lexicomp: Pharmacogenomics section



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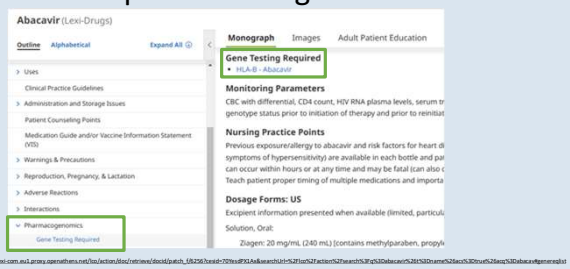
Lexicomp: Pharmacogenomics section



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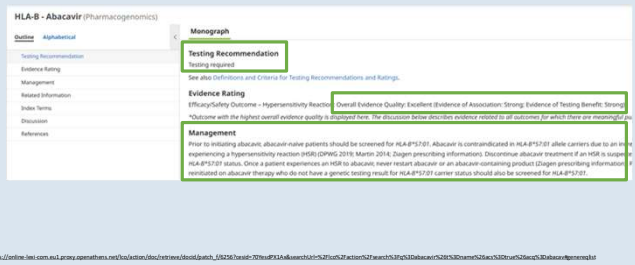
Lexicomp: Pharmacogenomics section



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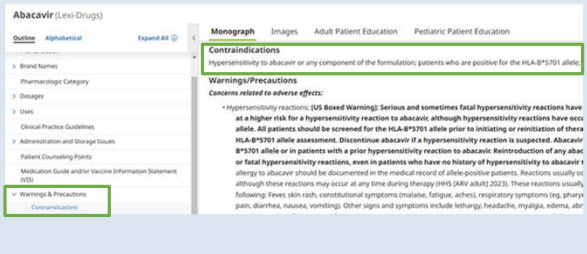
Lexicomp: Pharmacogenomics section



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Pharmacogenomics databases

PharmGKB
- Pharmacogenomics knowledge base
- https://www.pharmgkb.org/

Clinical Pharmacogenetics Implementation Consortium Guidelines (CPIC)
- Guidelines – typically summarized in "Table 2"
- https://cpicpgx.org/

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PharmGKB

Search for medications, genes, or specific genetic variants

- FDA Drug label annotations
- Drug label annotations
- Curated pathways
- Clinical guideline annotations

'Comprehensive resource that curates knowledge about the impact of genetic variation on drug response for clinicians and researchers.'

https://www.pharmgkb.org/ Accessed 3.4.25

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CPIC

CPIC creates and posts peer-reviewed, evidence-based, updatable, and detailed gene/drug clinical practice guidelines

'CPIC is an international consortium of individual volunteers and a small dedicated staff who are interested in facilitating use of pharmacogenetic tests for patient care.'

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Active Learning

Case #1

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Active Learning - Case #1

LP is a 59-year-old woman with ST segment elevation myocardial infarction (STEMI) who is undergoing percutaneous coronary intervention (PCI). Pharmacogenetic testing reveals that her genotype is *CYP2C19 *17/*17*. Using the information in the next 2 slides, which of the following is the MOST appropriate recommendation regarding clopidogrel use in this patient (assuming no contraindications)?

a. do not administer clopidogrel
b. administer clopidogrel at standard doses
c. increase the clopidogrel dose by 50%
d. decrease the clopidogrel dose by 50%

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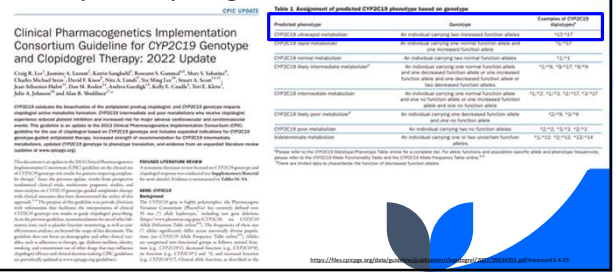
Active Learning - Case #1

CPIC – Guidelines

Example: clopidogrel and *CYP2C19*



Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2C19* Genotype and Clopidogrel Therapy: 2022 Update

CPIC UPDATE

Table 1. Assignment of predicted CYP2C19 phenotype based on genotype

Predicted phenotype	Genotype	Examples of CYP2C19 diplotypes[a]
CYP2C19 ultrarapid metabolizer	An individual carrying two increased function alleles	*17/*17
CYP2C19 rapid metabolizer	An individual carrying one normal function allele and one increased function allele	*1/*17
CYP2C19 normal metabolizer	An individual carrying two normal function alleles	*1/*1
CYP2C19 likely intermediate metabolizer[b]	An individual carrying one normal function allele and one decreased function allele or one increased function allele and one decreased function allele or two decreased function alleles	*1/*9, *9/*17, *9/*9
CYP2C19 intermediate metabolizer	An individual carrying one normal function allele and one no function allele or one increased function allele and one no function allele	*1/*2, *1/*3, *2/*17, *3/*17
CYP2C19 likely poor metabolizer[b]	An individual carrying one decreased function allele and one no function allele	*2/*9, *3/*9
CYP2C19 poor metabolizer	An individual carrying two no function alleles	*2/*2, *3/*3, *2/*3
Indeterminate metabolizer	An individual carrying one or two uncertain function alleles	*1/*22, *2/*22, *22/*34

[a]Please refer to the CYP2C19 Diplotype-Phenotype Table online for a complete list. For allele functions and population-specific allele and phenotype frequencies, please refer to the CYP2C19 Allele Functionality Table and the CYP2C19 Allele Frequency Table online.[b,c]
[b]There are limited data to characterize the function of decreased function alleles.

https://files.cpicpgx.org/data/guideline/publication/clopidogrel/2022/35034351.pdf Accessed 3.4.25

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Active Learning – Case #1

CPIC – Guidelines

Example: clopidogrel and *CYP2C19*

Table 2 Antiplatelet therapy recommendations based on CYP2C19 phenotype when considering clopidogrel for cardiovascular indications

CYP2C19 phenotype[a]	Implications for phenotypic measures	Therapeutic recommendation	Classification of recommendation[b] - ACS and/or PCI[c]	Classification of recommendation[b] - Non-ACS, non-PCI cardiovascular indications[d]
CYP2C19 ultrarapid metabolizer	Increased clopidogrel active metabolite formation; lower on-treatment platelet reactivity; no association with higher bleeding risk	If considering clopidogrel, use at standard dose (75 mg/day)	Strong	No recommendation
CYP2C19 rapid metabolizer	Normal or increased clopidogrel active metabolite formation; normal or lower on-treatment platelet reactivity; no association with higher bleeding risk	If considering clopidogrel, use at standard dose (75 mg/day)	Strong	No recommendation
CYP2C19 normal metabolizer	Normal clopidogrel active metabolite formation; normal on-treatment platelet reactivity	If considering clopidogrel, use at standard dose (75 mg/day)	Strong	Strong
CYP2C19 likely intermediate metabolizer	Reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events	Avoid standard dose clopidogrel (75 mg) if possible. Use prasugrel or ticagrelor at standard dose if no contraindication	Strong[e]	No recommendation[e]
CYP2C19 intermediate metabolizer	Reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events	Avoid standard dose (75 mg) clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication	Strong	No recommendation
CYP2C19 likely poor metabolizer	Significantly reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events	Avoid clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication	Strong[e]	Moderate[e]
CYP2C19 poor metabolizer	Significantly reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events	Avoid clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication	Strong	Moderate

ACS, acute coronary syndrome; PCI, percutaneous coronary intervention.
[a]The online CYP2C19 Allele Frequency Table provides phenotype frequencies for major race/ethnic groups, and the online CYP2C19 Diplotype-Phenotype Table provides a complete list of possible diplotypes and phenotype assignments.[b,c]
[b]Rating scheme described in the **Supplementary Material** online.
[c]ACS and/or PCI includes patients undergoing PCI for an ACS or non-ACS (elective) indication.
[d]Non-ACS, non-PCI cardiovascular indications include peripheral arterial disease and stable coronary artery disease following a recent myocardial infarction outside the setting of PCI.
[e]The strength of recommendation for "likely" phenotypes are the same as their respective confirmed phenotypes. "Likely" indicates the uncertainty in the phenotype assignment, but it is reasonable to apply the recommendation for the confirmed phenotype to the corresponding "likely" phenotype.

https://files.cpicpgx.org/data/guideline/publication/clopidogrel/2022/35034351.pdf Accessed 3.4.25

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Active Learning - Case #1 - ANSWER

LP is a 59-year-old woman with ST segment elevation myocardial infarction (STEMI) who is undergoing percutaneous coronary intervention (PCI). Pharmacogenetic testing reveals that her genotype is *CYP2C19 *17/*17*. Which of the following is the MOST appropriate recommendation regarding clopidogrel use in this patient (assuming no contraindications)?

a. do not administer clopidogrel
✓ b. administer clopidogrel at standard doses
c. increase the clopidogrel dose by 50%
d. decrease the clopidogrel dose by 50%

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Active Learning

Case #2

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Active Learning - Case #2

LC is a 34-year-old African American female who was recently diagnosed with major depressive disorder. She had PGx testing done and the providers asks if paroxetine is still an appropriate option. Her genotype is *CYP2D6 *1/*1x3*. Using the information in the next 2 slides, which of the following is the MOST appropriate recommendation regarding escitalopram use in this patient (assuming no contraindications)?

a. Do not administer paroxetine; select an alternative
b. Administer paroxetine at standard doses
c. Consider a lower starting dose and slower titration
d. Consider a 50% reduction in recommended starting dose, slower titration schedule, and a 50% lower maintenance dose

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Active Learning - Case #2

Table 1 Assignment of predicted phenotypes based on diplotypes

Phenotype	Activity score range	Activity score/diplotypes	Examples of *CYP2D6* diplotypes[a]
Assignment of predicted CYP2D6 phenotypes based on diplotypes			
CYP2D6 ultrarapid metabolizer	>2.25	>2.25	**1/*1xN, *1/*2xN, *2/*2xN*
CYP2D6 normal metabolizer	1.25≤*x*≤2.25	1.25 1.5 1.75 2.0 2.25	**1/*10, *1/*9, *1/*41* **1/*17, *1/*29* **1/*10x3* **1/*1, *1/*2* **2x2/*10*
CYP2D6 intermediate metabolizer	0<*x*<1.25	0.25 0.5 0.75 1	**4/*10, *4/*41* **10/*10, *10/*41* **10/*29, *9/*14, *17/*41* **1/*5, *1/*4, *1/*5*
CYP2D6 poor metabolizer	0	0	**3/*4, *4/*4, *5/*5, *5/*6*

https://files.cpicpgx.org/data/guideline/publication/serotonin_reuptake_inhibitor_antidepressants/2023/37032427.pdf. Accessed April 10, 2025.

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Active Learning - Case #2

Table 2 Dosing recommendations antidepressants based on CYP2D6 phenotype

Phenotype	Implication	Therapeutic recommendation	Classification of recommendation[a]	Considerations
Dosing recommendations for paroxetine based on CYP2D6 phenotype				
CYP2D6 ultrarapid metabolizer	Increased metabolism of paroxetine to less active compounds when compared with CYP2D6 normal metabolizers. Lower plasma concentrations decrease the probability of clinical benefit. The extent to which ultrarapid metabolizers phenoconvert to normal, intermediate, or poor metabolizers due to paroxetine autoinhibition of CYP2D6 is unclear	Select alternative drug not predominantly metabolized by CYP2D6	Moderate	Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when selecting an alternative therapy
CYP2D6 normal metabolizer	Normal metabolism of paroxetine to less active compounds. Paroxetine-associated phenoconversion of normal metabolizers to intermediate or poor metabolizers due to CYP2D6 autoinhibition may occur and is dose-dependent and greater at steady state concentrations	Initiate therapy with recommended starting dose	Strong	
CYP2D6 intermediate metabolizer	Reduced metabolism of paroxetine to less active compounds when compared with CYP2D6 normal metabolizers when starting treatment or at lower doses. Higher plasma concentrations may increase the probability of side effects. Paroxetine-associated phenoconversion of intermediate metabolizers to poor metabolizers due to CYP2D6 autoinhibition may occur and is dose-dependent and greater at steady-state concentrations	Consider a lower starting dose and slower titration schedule as compared with normal metabolizers	Optional	Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose or selecting an alternative therapy
CYP2D6 poor metabolizer	Greatly reduced metabolism when compared with CYP2D6 normal metabolizers. Higher plasma concentrations may increase the probability of side effects. The impact of paroxetine-associated autoinhibition of CYP2D6 is minimal in poor metabolizers	Consider a 50% reduction in recommended starting dose, slower titration schedule, and a 50% lower maintenance dose as compared with normal metabolizers	Moderate	Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose or selecting an alternative therapy

https://files.cpicpgx.org/data/guideline/publication/serotonin_reuptake_inhibitor_antidepressants/2023/37032427.pdf. Accessed April 10, 2025.

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Active Learning - Case #2 - ANSWER

LC is a 34-year-old African American female who was recently diagnosed with major depressive disorder. She had PGx testing done and the providers asks if paroxetine is still an appropriate option. Her result for *CYP2D6 *1/*1x3*. Which of the following is the MOST appropriate recommendation regarding escitalopram use in this patient (assuming no contraindications)?

✓ a. Do not administer paroxetine; select an alternative
b. Administer paroxetine at standard doses
c. Consider a lower starting dose and slower titration
d. Consider a 50% reduction in recommended starting dose, slower titration schedule, and a 50% lower maintenance dose

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Education for pharmacists

- Continuing Education (CE) impact – 1 hour CE, 8-hour certification course
- RxGenomix Clinical Pearls videos
- Books on Amazon
- Join CPIC (free) – monthly meeting on the first Thursday of every month at 11:00 am EST
  - Update on new guidelines or guidelines in progress
  - Presentation – someone who is implementing PGx in clinical practice/ambulatory care/hospital and the results

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Summary

- Utilize PGx data to avoid the "trial and error" approach to pharmacotherapy management.
- Include PGx along with PK and PD considerations in your patient monitoring practices
- Recall Core Pharmacists competencies as foundational genetic concepts and clinical pharmacogenomics concepts
- Refer to PGx-specific resources to assist in formulating an appropriate medication regimen

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Thank you

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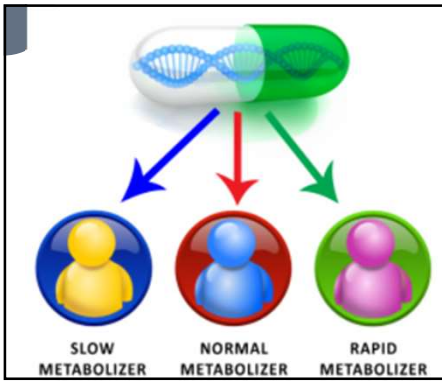

Questions?

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References

- Bousman CA, Stevenson JM, Ramsey LB, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC)) Guideline for CYP2D6, CYP2C19, CYP2B6, SLC6A4, and HTR2A Genotypes and Serotonin Reuptake Inhibitor Antidepressants. *Clin Pharmacol Ther* 2023;114(1):51-68. DOI: https://doi.org/10.1002/cpt.2903
- Clinical Pharmacogenetics Implementation Consortium. CPIC. Accessed April 25, 2025. https://cpicpgx.org/
- CPIC SOP for Assigning Allele Function. CPIC. Published 2024. Accessed April 15, 2025 https://cpicpgx.org/resources/cpic-draft-allele-function-sop/
- Lee CR, Luzum JA, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2C19* genotype and clopidogrel therapy: 2022 update. *Clin Pharmacol Ther* 2022;112(5):959-967. DOI: https://doi.org/10.1002/cpt.2526
- Pharmacists Leading the Way to Precision Medicine: Updates to the Core Pharmacist Competencies in Genomics. Am J Pharm Educ. Accessed April 9, 2025. https://www.ajpe.org/
- Pharmacogenomics fact sheet. National Human Genome Research Institute. Updated August 10, 2023. Genome.gov. Published 2023. https://www.genome.gov/about-genomics/educational-resources/fact-sheets/pharmacogenomics. Accessed April 25, 2025
- Pharmacogenomics for improved outcomes and decreased costs in health care. Published December 15, 2023,. Accessed April 25, 2025. https://www.ajmc.com/view/pharmacogenomics-for-improved-outcomes-and-decreased-costs-in-health-care
- Pharmacogenomics Knowledgebase. PharmGKB. Accessed April 25, 2025. https://www.pharmgkb.org/

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Company	Testing Options & Costs	Genes Tested	Purchase Method
ClarityX https://clarityxdna.com/products	**Mindwell ($299.25)**: Evaluates response to depression medications, analyzing 135+ medications **MaxRX ($374.25)**: Assesses response to 275+ medications across 21 therapeutic areas	Mainly *CYP2D6, CYP2C19,* and *MTHFR* for the therapeutic tests Other genes available: *ABCB1, GLP1R, CYP1A2, CYP3A5, CYP3A4, ANKK1, OPRM1, DRD2, COMT, VKORC1, APOE,* etc.	Patients can purchase directly from their website. Providers can order test kits to be sent to their office to test patients
OneOme https://oneome.com/rightmed-test/	**RightMed® Test**: Analyzes a patient's DNA to provide insights on over 100 medications. Self-pay cost is $349, with financial assistance reducing the cost to $199 for eligible patients.	100 alleles that covers 27 genes (*CYP1A2, CYP2B6, CYP2C cluster, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, CYP4F2, COMT, DPYD, DRD2, F2, F5, GRIK4, HLA-A, HLA-B, HTR2A, HTR2C, IL28B, MTHFR, NUDT15, OPRM1, SLC6A4, SLCO1B1, TPMT, UGT1A1, VKROC1*)	Ordered through healthcare providers and pharmacists. Patients can also request the test directly from OneOme.
23andMe https://shorturl.at/5xYFg	**Health + Ancestry Service ($199)**: Includes ancestry and trait reports, health predisposition reports and wellness reports	Tests some alleles through saliva for *CYP2C19, SLCO1B1,* and *DPYD* *Health predisposition reports include those approved and not approved by the FDA *Testing on the pharmacogenetics report should be confirmed by an independent test prescribed by a healthcare provider	Direct-to-consumer; kits can be purchased online
GENETWORx https://genetworx.com/services/effectivrx-comprehensive-tests/	**Comprehensive Panel**: includes all genes listed **Neuro Panel** also available for patients only looking to test genes for mental health medications Medicaid & Medicare Part B- should be $0. Contact for estimated cost for uninsured or commercial insurance	*MTHFR, CYP2C9, CYP2C19, CYP3A4/5, VKORC1, ADRA2A, ANKK1, COMT, CYP1A2, CYP2B6, CYP2D6, OPRM1, SLC6A4, HTR2C/2A, GRIK4, APOE, F2/5, DPYD, IFNL3, ITGB3, OPRK1, UGT1A1, UGT2B15*	Ordered through provider for patient
GeneSight https://shorturl.at/su4hm	**Psychotropic Test** for patients only looking to test genes for mental health medications **MTHFR Test**- only tests for *MTHFR* gene Cost estimated $330 or less. Medicaid and Medicare Part B $0	*MTHFR, CYP2D6, CYP2C19, CYP3A4, CYP2B6, CES1A1, CYP1A2, UGT1A4, UGT2B15, CYP2C9, SLC6A4, HLA-A, HLA-B, ADRA2A, HTR2A, COMT*	Ordered by healthcare providers. Test can be sent to the patient's home or to the healthcare provider's office

Please note that all pricing, available tests, genes, alleles, and ordering options are subject to change. We strive to provide the most accurate and up-to-date information, but changes may occur based on laboratory updates or provider availability. Final details should be confirmed prior to ordering.

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QR Code to access testing options

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