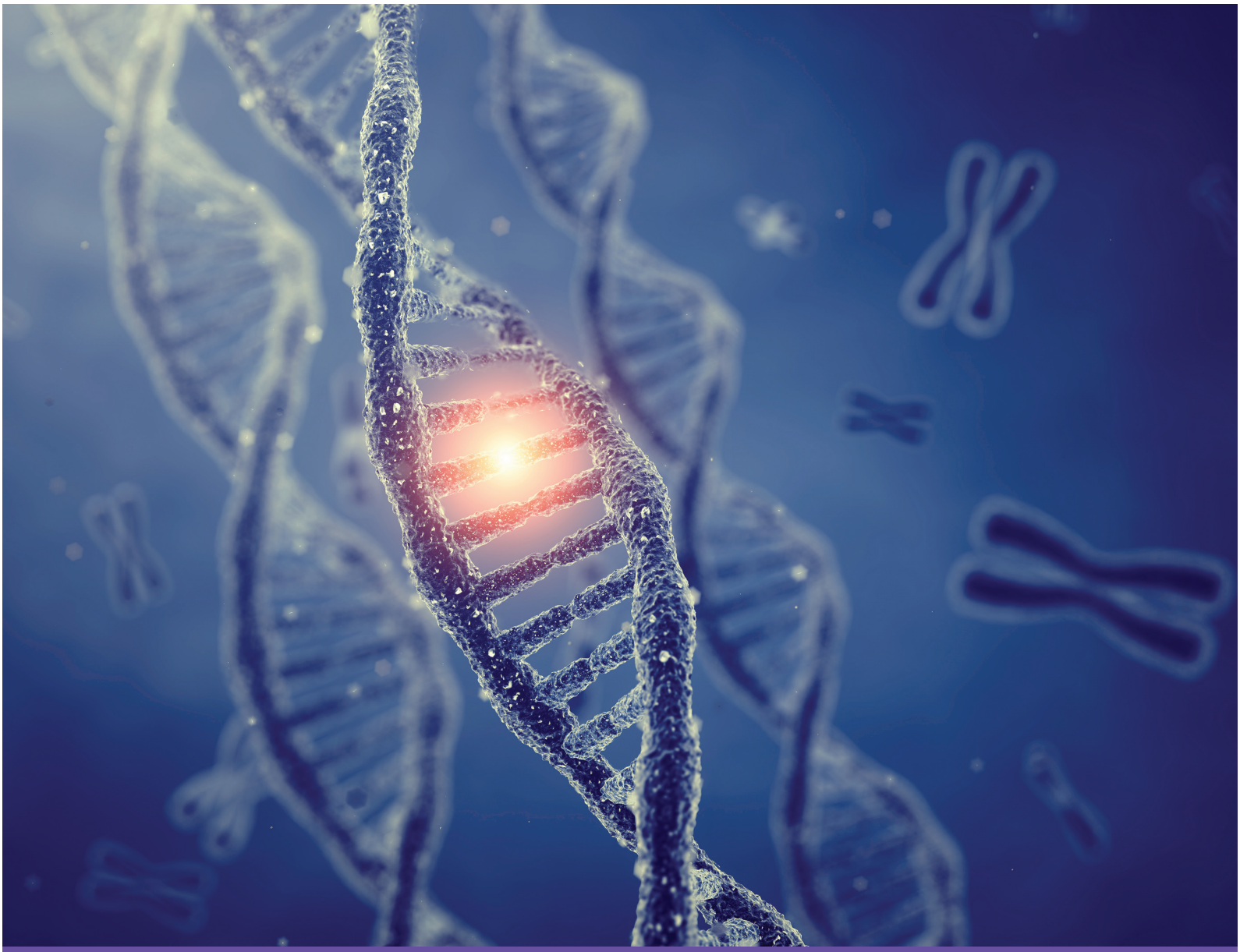

An Introduction to Pharmacogenomics

A VA Clinician's Summary (2025)

VA

U.S. Department of Veterans Affairs

Veterans Health Administration

PBM Academic Detailing Services

Contents

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These materials were developed by:

VA PBM Academic Detailing Services

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VA PBM Academic Detailing Services Email Group:

PharmacyAcademicDetailingProgram@va.gov

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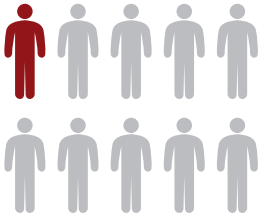
Overview of pharmacogenomics (PGx)

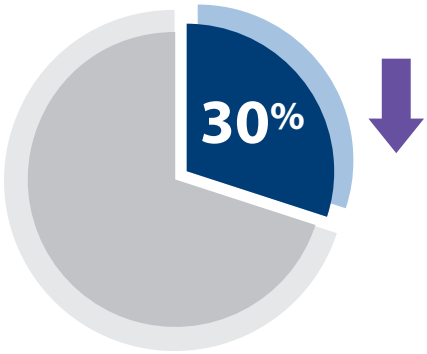
PGx testing is a proactive medication safety and optimization strategy. It uses a Veteran's genomic profile to tailor the selection and dose of medications prescribed.[1,2]

Most Veterans carry at least one pharmacogenetic variant that may influence pharmacotherapy decisions.[1,3-5]

Many commonly prescribed medications including antidepressants, statins, NSAIDs, and PPIs have pharmacogenomic information on the label.



1 in 10 Veterans are prescribed a medication that is impacted by PGx test results.

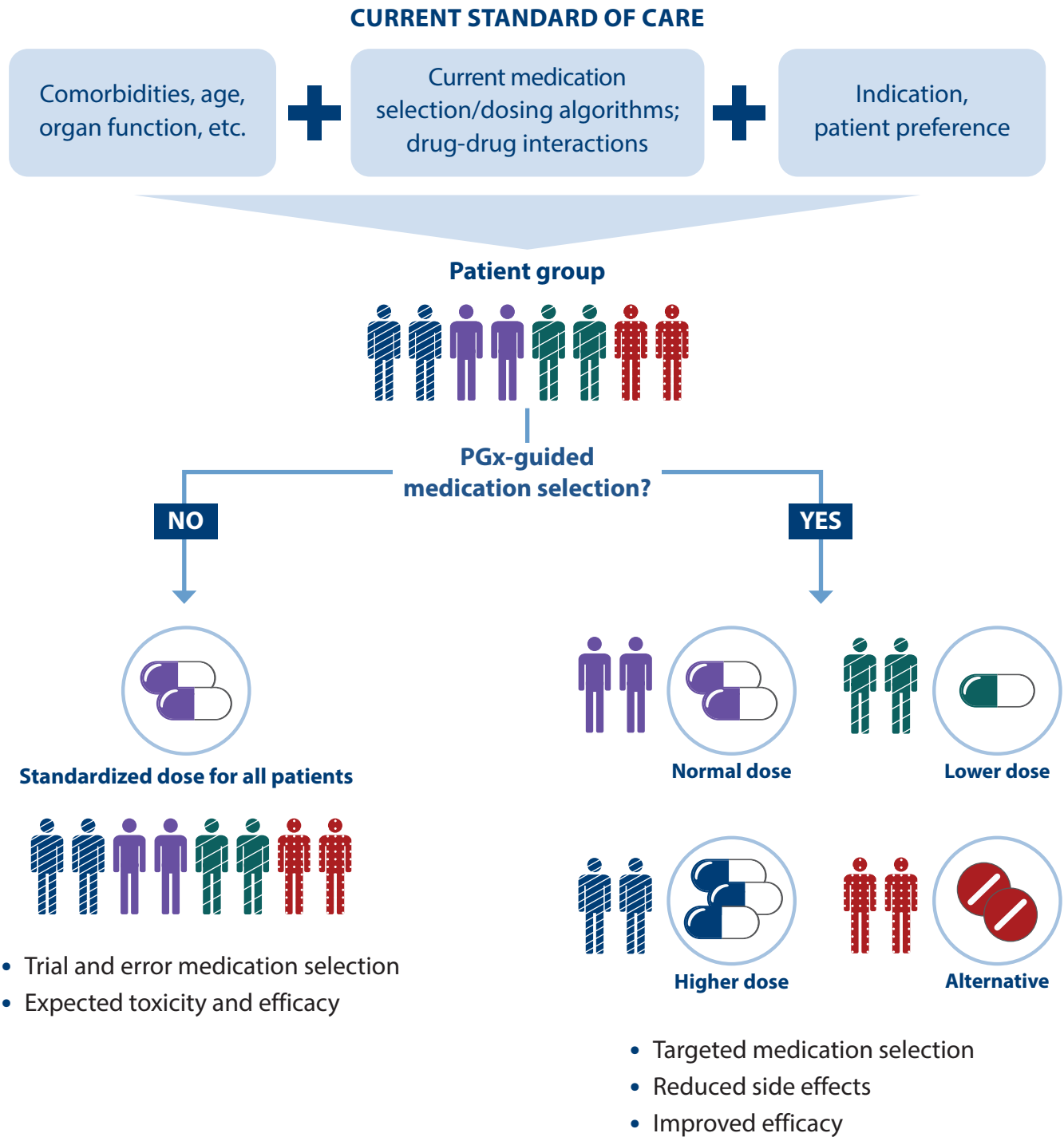


Genotype-guided treatment can decrease the risk of **adverse drug reactions** by 30%.

The PREPARE study was an open-label, multicenter, controlled, cluster-randomized, crossover implementation study evaluating genotype-guided treatment using a 12-gene pharmacogenomic panel.[6]

PGx testing: a tool for more precise prescribing

Figure 1. PGx testing helps identify when medication selection or dosing may need to be modified to reduce toxicity and improve efficacy.



Many factors contribute to how individuals metabolize medications differently. Utilizing PGx testing allows for more targeted medication selection based on patient specific factors. Using PGx test results to select medications may reduce side effects in some cases, while in others it may allow drug selection that improves efficacy. In the absence of PGx test information, often a standard dose is selected for all patients which can result in using trial and error to select medications.

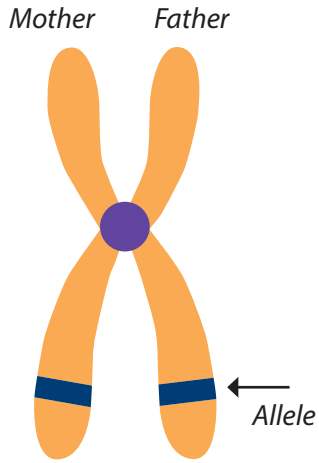
Pharmacogenomics basics

A primary focus of PGx testing is to identify genetic variation that leads to changes in proteins involved in absorption, transportation, and metabolism.

Much of the current pharmacogenomic literature focuses on gene-drug interactions that involve the **cytochrome (CYP) P450 enzyme system**.[7] This system accounts for the metabolism of 70-80% of medications.[8] Genetic variations of this system can produce CYP450 enzymes that vary in their ability to metabolize medications.[7] This can increase the risk of adverse effects or therapy failure.

To assist in the interpretation of PGx testing results, it is important to know some basic nomenclature.

Pair of Chromosomes



*Genotype/diplotype: *2/*2*

Normal metabolizer
*Phenotype for CYP2D6*2/*2*

Terminology:[3]

Allele is one version of a DNA sequence at a given chromosome location. When there is variation in a DNA sequence, or allele, it is referred to as a **polymorphism**. Polymorphisms can influence medication sensitivity, toxicity, and dosing.

Genotype/diplotype is a pair of two alleles inherited by an individual for a particular gene. An individual inherits two alleles, one from each parent. If the two alleles are the same, the individual is homozygous for that allele. They are often represented by star nomenclature. For example, *2/*2 could represent **homozygous** variants of the *CYP2D6*. If the alleles are different, the individual is **heterozygous**.

Phenotype is the manifestation of the genotype/diplotype on its encoded protein. For example, the predicted function of an enzyme that metabolizes a medication could be normal, intermediate, poor, rapid, or ultrarapid. Genetic makeup (genotype) determines phenotypes, but phenotypes can also be influenced by patient-specific pharmacokinetics and pharmacodynamics.

PGx testing can optimize medication safety and efficacy

1 Safety

One example of the safety implications of PGx testing includes polymorphisms in the genes encoding for the **human leukocyte antigen (HLA)** system. These can influence the risk of life-threatening immune-mediated drug reactions like Stevens-Johnson Syndrome. This has led to FDA recommendations for testing **prior to initiation** of medications (e.g., carbamazepine) for patients in genetically at-risk populations.[9,10]

Figure 2. HLA-B variants responsible for life-threatening hypersensitivity reactions[9,10]

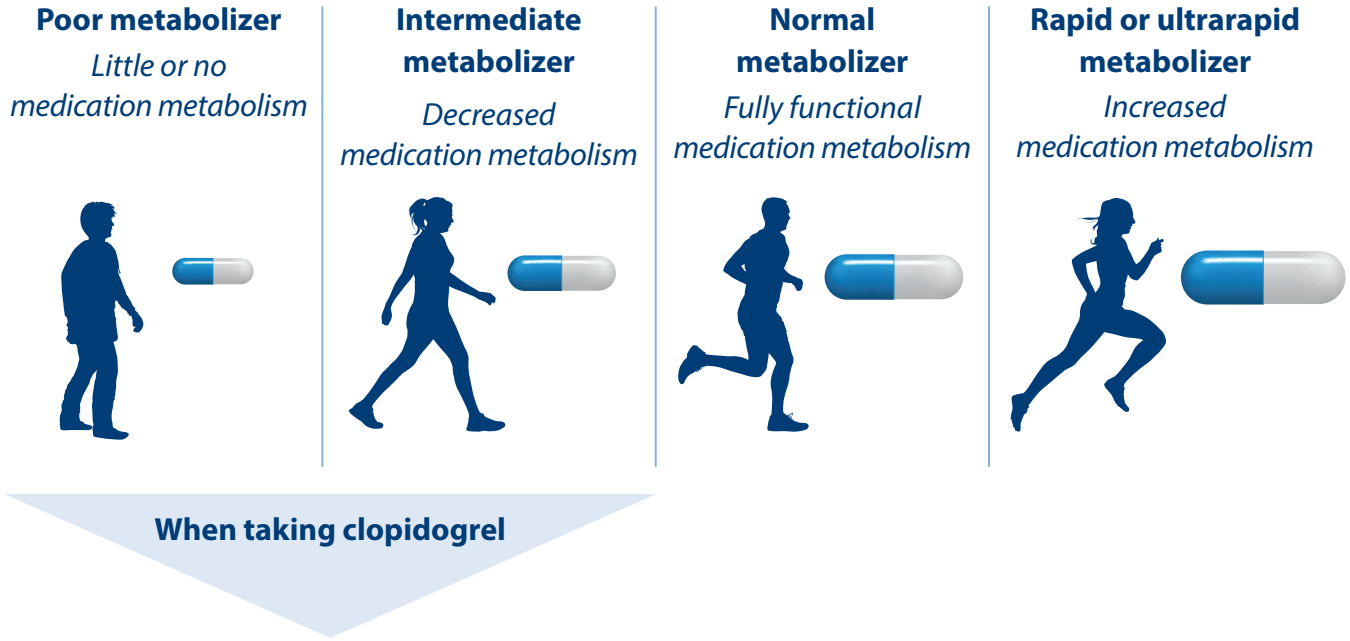
Abacavir (*57:01)	Allopurinol (*58:01)
• Hypersensitivity reaction (e.g., fever, rash, respiratory symptoms) • **Black Box Warning** for HLA testing prior to initiation for all patients	• Maculopapular eruption • Severe cutaneous adverse reactions • Warning for HLA testing prior to initiation for patients in genetically at-risk populations
Carbamazepine (*15:02)	**Phenytoin/Fosphenytoin (*15:02)**
• Stevens-Johnson Syndrome • Toxic epidermal necrolysis • **Black Box Warning** for HLA testing prior to initiation for patients in genetically at-risk populations	• Stevens-Johnson Syndrome • Toxic epidermal necrolysis • Warning for HLA testing prior to initiation for patients in genetically at-risk populations

The above medications should be avoided in carriers of identified HLA variants.

2 Efficacy

One example of the efficacy implications of PGx testing includes polymorphisms in the primary metabolism pathway of clopidogrel. The prodrug clopidogrel is an antiplatelet agent that is metabolized to active components by *CYP2C19*.[11] Polymorphisms in medication metabolism can result in an increased risk of therapeutic failure in patients undergoing coronary stenting due to insufficient platelet inhibition.

Figure 3. *CYP2C19* intermediate and poor metabolizers prescribed clopidogrel may be at risk for subsequent cardiovascular events.[11]



- Decreased efficacy
- Could result in increased cardiovascular events
- Recommend using alternative antiplatelet therapy[+]

[+]Data strongest in patients prescribed clopidogrel for percutaneous coronary intervention (PCI).

Order PGx testing as a proactive, precision medicine approach to improve medication safety and efficacy in select patients.

Considerations for timing of PGx testing

Pre-emptive testing

- Performed strictly for future use without a target medication or indication
- Pre-emptive testing will no longer be offered starting January 1, 2026

Reactive testing

- Recommended for patients who are newly prescribed select medications impacted by PGx testing
- Targets patients with high-risk diagnoses (cancer) or starting high-risk medications (e.g., antiplatelets, antidepressants, chemotherapy, medications impacted by HLA)
- Consider prior to prescribing when a first dose of a medication could be fatal (e.g., certain chemotherapeutics)

Diagnostic testing

May benefit patients with sub-optimal response to medicine still requiring pharmacotherapy. Examples:

- Lack of therapeutic response (e.g., depression symptoms, recurrent cardiovascular events on clopidogrel)
- Treatment-limiting side effects (e.g., myopathy with statins)

Common medication classes impacted by PGx

The medication classes most commonly impacted by PGx are those used for mental health, pain, cardiovascular, auto-immune, gastrointestinal, neurologic, and oncologic disorders. These medications are commonly prescribed to Veterans.

Even though the indication for PGx testing may be relevant to only one medication the Veteran is currently prescribed at the time of testing, **results from a multi-gene panel often have clinical utility for future medications the Veteran may take.**

Table 1. Example PGx panel for over 40 medications

Category	Medication class	Medication	Gene
Oncology/ autoimmune	Fluoropyrimidines	Capecitabine, Fluorouracil	*DPYD*
	Thiopurines	Azathioprine, Mercaptopurine, Thioguanine	*TPMT, NUDT15*
	Selective estrogen receptor modulator	Tamoxifen	*CYP2D6*
Cardiovascular	Anticoagulants	Warfarin	*CYP2C9, VKORC1, CYP4F2, CYP2C*
	Antiplatelets	Clopidogrel	*CYP2C19*
	Statins	Atorvastatin, Fluvastatin, Lovastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin	*SLCO1B1*
Gastrointestinal	Antiemetics	Ondansetron	*CYP2D6*
	Proton pump inhibitors	Dexlansoprazole, Lansoprazole, Omeprazole, Pantoprazole	*CYP2C19*
Infectious diseases	Antifungals	Voriconazole	*CYP2C19*
Pain	NSAIDs	Celecoxib, Flurbiprofen, Ibuprofen, Meloxicam, Piroxicam	*CYP2C9*
	Opioids	Codeine, Tramadol	*CYP2D6*
Psychotropic	ADHD Agents	Atomoxetine	*CYP2D6*
	Anticonvulsants	Fosphenytoin, Phenytoin	*CYP2C9*
	Antidepressants	Amitriptyline, Clomipramine, Doxepin, Imipramine, Trimipramine	*CYP2C19, CYP2D6*
		Citalopram, Escitalopram, Sertraline	*CYP2C19*
		Desipramine, Fluvoxamine, Nortriptyline, Paroxetine	*CYP2D6*
Transplant	Immunosuppressants	Tacrolimus	*CYP3A5*

Explaining PGx testing to Veterans

Obtaining oral consent prior to PGx testing is a required part of the ordering process. Documentation of oral informed consent is necessary due to VA regulations on germline genetic testing and is required by VA ethics.

Education should include the following:

What is PGx testing?	**Pharmacogenomics (PGx) refers to genetic testing** that helps inform us **how your body processes medicines.** Each person may have some differences in their genes that explain why we may react differently to the same medicine. These genes can affect how well a medicine may work for you or if you are at risk of having certain side effects. This information can be used to help plan your care and the medicines you receive.
How is PGx testing done?	**PGx testing can be done with blood or saliva.** Results take 10-20 days to return and will be stored in the medical record. Your sample will be destroyed once data is collected.
Will healthcare coverage be impacted by PGx testing?	Federal law **protects patients from genetic discrimination** by insurance or employers. This law is called GINA or the "Genetic Information Nondiscrimination Act." VHA also has rules that forbid discrimination based on protected genetic information.
What are the risks with PGx testing?	Some pharmacogenomic gene panels will include genes that have **implications beyond medicine management.** This may identify if a Veteran and potentially their family members are at increased risk for certain health conditions. You would be notified if such conditions are identified and provided appropriate resources for managing any implications.

Inform Veterans of PGx testing benefits and limitations prior to placing a pharmacogenomics order.

Interpreting PGx test results

The CPIC (Clinical Pharmacogenetics Implementation Consortium) has standardized the terminology describing a genetic variant's impact on enzyme function or predicted phenotype.[12]

Table 2. Standardized terms for clinical PGx test results[12]

Gene category	Standardized term	Functional definition
Pharmacokinetics: Drug-metabolizing enzymes *(CYP2C19, 2D6, 3A5, 2C9, TPMT, DPYD, UGT1A1)*	Ultrarapid metabolizer	Increased enzyme activity
	Rapid metabolizer	Increased enzyme activity (less than ultrarapid)
	Normal metabolizer	Fully functional enzyme activity
	Intermediate metabolizer	Decreased enzyme activity
	Poor metabolizer	Little to no enzyme activity
Pharmacokinetics: Transporters *(SLCO1B1)*	Increased function	Increased transporter function
	Normal function	Fully functional transporter function
	Decreased function	Decreased transporter function
	Poor function	Little to no transporter function
Off-target: Immune-mediated drug reactions *(HLA-B)*	Positive	Detection of high-risk allele
	Negative	High-risk allele not detected
Pharmacodynamic: Vitamin K-epoxide reductase protein *(VKORC1)*	High	High warfarin sensitivity
	Intermediate	Intermediate warfarin sensitivity
	Low	Low warfarin sensitivity

Clinicians can utilize PGx test results to assist with evidence-based adjustments **in medication selection and dosing. This is expected to augment the safety and efficacy** of medications prescribed.

The CPIC provides peer-reviewed guidelines on how to utilize pharmacogenomic information. They translate genetic laboratory test results into actionable prescribing recommendations for affected medications. In addition, VHA will be reviewing and recommending how to utilize PGx testing in clinical care based on additional published guidelines, FDA guidance, and peer-reviewed literature.

Incorporate PGx test results with patient-specific factors to optimize pharmacotherapy safety and efficacy.

Sample PGx reports

When interpreting a PGx report, remember that **PGx helps supplement clinical decision-making associated with prescribing** by providing an additional variable for consideration.

The ordering provider will be notified of the availability of PGx results in the electronic medical record.

Most PGx reports provide the following:

- **Identified drug-gene interactions, a summary of how the Veteran may respond to a medication, and a recommendation for adjustment**
  - *Dosing guidance and recommendations are based ONLY on PGx test results. They do not consider age, organ function, comorbidities, drug allergies, or other medications the Veteran may be receiving.*
- Complete overview of the Veteran's test results by **genes, genotype, phenotype, and alleles tested**

Figure 4. The role of PGX testing

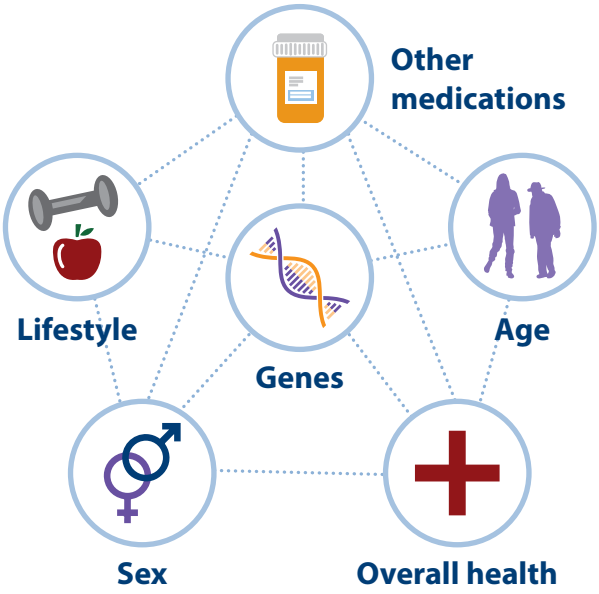


Table 3. Sample PGx report: drug-gene interactions

Category	Medication class	No change needed	May need change
Anticancer agents	Fluoropyrimidines	Capecitabine, Fluorouracil	—
	Thiopurines	Azathioprine, Mercaptopurine, Thioguanine	—
Cardiovascular	Anticoagulants	—	Warfarin
	Antiplatelets	Clopidogrel	—
	Statins	Atorvastatin, Fluvastatin, Lovastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin	—
Gastrointestinal	Antiemetics	—	Ondansetron
	Proton pump inhibitors	—	Dexlansoprazole Lansoprazole Omeprazole Pantoprazole

Table 4. Sample PGx report: dosing recommendations

Medication	Response	Dosing recommendation
Ondansetron 	**Non-response to ondansetron (CYP2D6:** Ultrarapid metabolizer)	A substantially decreased antiemetic effect has been reported in *CYP2D6* ultrarapid metabolizers when taking standard doses of this medication. Consider prescribing an alternative medication not metabolized by *CYP2D6*, such as granisetron.
Paroxetine 	**Reduced response to paroxetine (CYP2D6:** Ultrarapid metabolizer)	There is a risk for decreased efficacy at a standard dosage. If a standard dose is prescribed to a *CYP2D6* ultrarapid metabolizer, suboptimal plasma concentrations of the medication are likely. Consider an alternative medication.

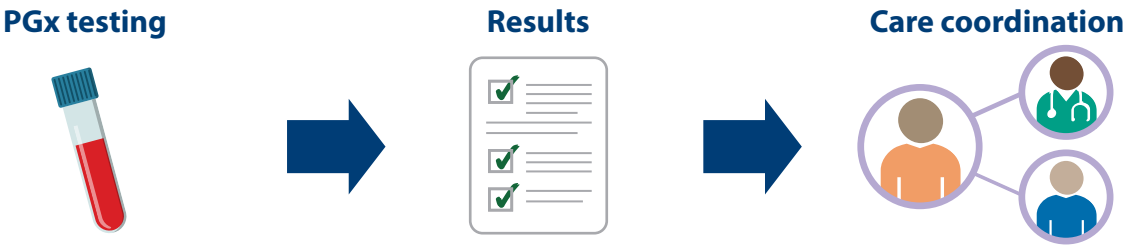
Table 5. Sample PGx report: overview of test by genes, genotype, phenotype, and alleles tested

Gene	Genotype	Phenotype	Alleles tested
CYP2C	g.96405502G>A G/G	Low sensitivity	g.96405502G>A
CYP2C19	*1/*1	Normal metabolizer	*2, *3, *4A, *4B, *5, *6, *7, *8, *17
CYP2C9	*1/*1	Normal metabolizer	*2, *3, *5, *6, *8, *11
CYP2D6	*1/*5	Intermediate metabolizer	*2, *3, *4, *4M, *6, *9, *10, *41, *5 (gene deletion), XN (gene duplication)
CYP3A5	*1/*1	Normal metabolizer	*3, *6, *7
CYP4F2	c.1297G>A G/G	Normal activity	c.1297G>A
DPYD	Activity score: 2	Normal metabolizer	1905 + 1G>A, 1679T>G, 2846A>T
SLCO1B1	*1/*5	Decreased function	388A>G, 521T>C
TPMT	*1/*1	Normal metabolizer	*2, *3A, *3B, *3C, *4

Care coordination

Communicating across medical specialties and settings of care is a critical component of pharmacogenomics. The healthcare team must work together to ensure results are evaluated and reviewed with the Veteran.

Figure 5. Examples of care coordination



Due to transitions of care		
Inpatient: PCI procedural team orders PGx test for clopidogrel	***Patient discharged:*** Results come back and PGx CPP reviews	***Outpatient:*** PGx CPP communicates with outpatient cardiologist and Veteran about changes
Due to incidental findings		
Primary care: PGx test ordered for patient with statin intolerance	***Primary care:*** Results come back and show the patient's SSRI may be impacted	***Mental health:*** PGx CPP reviews and communicates with SSRI prescriber and Veteran about changes

CPP: clinical pharmacy practitioner; PCI: percutaneous coronary intervention; SSRI: selective serotonin reuptake inhibitor

Clinical pharmacy practitioners can help

- ☑ The **National Pharmacogneomics Program (NPP)** program has broadened PGx testing and CPP presence across VA to bridge knowledge gaps.
- ☑ **PGx CPPs** function as Advanced Practice Providers on the healthcare team.
- ☑ **Your PGx CPP** can order PGx testing, review results and provide recommendations, review dashboards and alert you to actionable results, provide comprehensive medication management for patients impacted by PGx test results, and support the training of other clinicians.

  Visit the **National Pharmacogenomics Program SharePoint** for more information.

Support continuity during transitions of care, address incidental findings with the healthcare team, and communicate changes with the Veteran.

There may be a national or regional interfacility consult (IFC) service to assist if you do not have a local PGx CPP.

Provider request for information	Provider request for CPP intervention
• Specific pharmacotherapy recommendations based on PGx test results • Comprehensive review of pharmacotherapy once PGx test results come back • Guidance on additional PGx testing	• CPP can contact the patient for education regarding their results and recommended changes • CPP may initiate, modify, and discontinue medication. In addition, the CPP may place additional consults to optimize care

Additional resources

- **National Pharmacogenomics Program SharePoint:** http://tinyurl.com/bdft5zd8
- **Clinical Pharmacogenomics Implementation Consortium (CPIC guidelines):** https://cpicpgx.org/
  Explains how available genetic test results should be used to optimize pharmacotherapy
- **PharmGKB:** www.pharmgkb.org
  Information about how human genetic variation affects response to medications

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Acknowledgments

THIS GUIDE WAS WRITTEN BY:

Sarah J. Popish, PharmD, BCPP
Amanda D. McQuillan, PharmD, BCPS, BCPP
Johanna Peragine, MBA, PharmD
Jill Bates, PharmD, MS, BCOP, DipACLM, FASHP
Deepak Voora, MD

WE THANK OUR EXPERT REVIEWERS:

Mark Geraci, PharmD
Rebecca Graham, PharmD, BCPP
Roshankumar Patel, MD
Scott Pawlikowski, MD
Jennie Piccolo, PharmD
Sarah Providence, PharmD, BCPS, BCCCP
Yelizaveta Russ, PharmD

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This reference guide was created to be used as a tool for VA providers and is available from the Academic Detailing SharePoint.

These are general recommendations only; specific clinical decisions should be made by the treating provider based on an individual patient's clinical condition.

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PharmacyAcademicDetailingProgram@va.gov

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