PHARMACOGENETICS

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Pharmacogenetics Introduction

Pharmacogenetics (PGx)

Pharmacogenetics is the study of how a person's DNA may impact their response (efficacy or safety) to a specific medication. Pharmacogenetics usually only considers one drug-gene pair, whereas pharmacogenomics often includes multiple genes, however these two terms are often used interchangeably.

Pharmacogenetics = **+**

Pharmacogenomics Goals and Importance:
- Provide individualized, safe, and more effective medication recommendations based upon a patient's genomic variants by pharmacogenetic testing.
- Avoid potentially unsafe therapies and decrease adverse effects.
- Current evidence indicates more than 99% of people have at least one actionable pharmacogenetic variant, and about one fifth of commonly prescribed medications having actionable pharmacogenetics. Exposure to a medication with actionable PGx is common, especially within the older population.

Key Terms and Abbreviations

PGx – Shorthand for pharmacogenetics/pharmacogenomics

Actionable – Institution/user-specific criteria that defines which genes/results would be used to change/modify a patient's drug therapy. This Toolkit only considers the following criteria as actionable: (1) a drug-gene pair for which there is a CPIC guideline, (2) on the FDA's Table of Pharmacogenetic Associations Sections 1 or 2, or (3) the potential risk of harm to a patient if the results are not considered (e.g. Factor V and estrogen medications).

Informative – Institution/user-specific criteria that defines which genes/results would NOT be used to change/modify a patient's drug therapy. This Toolkit considers informative results as anything not actionable (as defined above) or a given drug/gene pair for which CPIC recommends "No Recommendation." Note, this information changes constantly, so always check PharmGKB/resources for updates to the recommendations.

Gene – A specific stretch of DNA that usually serves as a template for a protein (e.g., enzyme) product

Single Nucleotide Polymorphism (SNP) – a change in the DNA at a single location.

Allele – one of two or more versions of a gene

Haplotype – same as allele, but each allele contains one or more SNPs that tend to be inherited together in a given pattern

Genotype – A given individual's collection of alleles for a given gene; in humans (which are diploid), there are usually two copies that describe the genotype

Diplotype – Same as genotype, but each allele has a collection of SNPs that tend to be inherited together (rather, haplotype)

Phenotype – An individual's observable traits (e.g., eye or hair color) which are usually a result of their genotype

Metabolizer Phenotypes – An individual's pharmacogenetic phenotype (specific to one gene) that has an effect when exposed to that drug. For example: Ultrarapid Metabolizer (UM), Rapid Metabolizer (RM), Normal (Extensive) Metabolizer (NM), Intermediate Metabolizer (IM), Poor Metabolizer (PM)

Activity Score (AS) – A quantitative method of assigning metabolizer phenotype for a given gene: a numerical value is assigned to a specific allele (e.g., value of 0 = no function, 0.25-0.5 = decreased function, and 1.0 = normal function) for a given gene, and adding the two alleles' values determines a patient's Activity Score; the metabolizer phenotypes are defined by a range of activity scores. Note, this is used for several (but not all) of the drug metabolizing enzymes. For example, CYP2C9*1/*3 genotype: *1 allele = 1.0, *3 allele = 0, CYP2C9 AS = (1.0+0=) 1, which correlates to the CYP2C9 Intermediate Metabolizer phenotype (AS Range of 1.0-1.5) as noted in CPIC Guidelines.

Phenoconversion – Presence of an enzyme inhibitor or inducer that causes the patient to convert from their expected Metabolizer phenotype to a different phenotype (e.g., fluoxetine usually causes phenoconversion from a CYP2D6 Normal to an Intermediate or Poor Metabolizer). Synonymous with phenocopy.

Proteins Impacted by Pharmacogenetics

Table 1. Proteins Impacted by Pharmacogenetics

Proteins	Impact
Drug Metabolizing Enzymes (DMEs)	Responsible for drug metabolism (e.g., CYP2D6, CYP3A4, UGT1A1, etc.)
Transport Proteins	Responsible for absorption, distribution, elimination of medications (e.g., P-glycoprotein, SLCO1B1, etc.)
Drug Receptors/ Targets	Responsible for drug binding and action at therapeutic target (e.g, BCR-ABL fusion protein, HER2 receptor, etc.)
Immune-Related Targets	Responsible for susceptibility to certain adverse reactions (e.g., HLA-A, HLA-B, etc.)

It is important to note that PGx can impact either or both of pharmacodynamics (PD) and pharmacokinetics (PK).

Some Common Medications with Actionable PGx Considerations

Table 2. Some Common Medications with Actionable PGx Considerations

Category	Medications
Anesthesia	Desflurane, enflurane, isoflurane, sevoflurane, succinylcholine
Cardiology/Hematology	Atorvastatin, carvedilol, clopidogrel, fluvastatin, lovastatin, pravastatin, propafenone, rosuvastatin, simvastatin, warfarin
Gastroenterology	Dexlansoprazole, lansoprazole, omeprazole, pantoprazole
Infectious Disease	Abacavir, amikacin, atazanivir, efavirenz, gentamicin, kanamycin, isoniazid, streptomycin, tobramycin, voriconazole
Neurology	Brivaracetam, carbamazepine, clobazam, fosphenytoin, oxcarbazepine, phenytoin, siponimod
Oncology	Azathioprine, belinostat, capecitabine, fluorouracil, irinotecan, mercaptopurine, tamoxifen, thioguanine
Pain and Palliative Care	Celecoxib, codeine, dronabinol, flurbiprofen, hydrocodone, ibuprofen, meloxicam, metoclopramide, ondansetron, piroxicam, tramadol, tropisetron
Psychiatry	Amitriptyline, amphetamine, aripiprazole, atomoxetine, citalopram, clomipramine, clozapine, desipramine, doxepin, escitalopram, fluvoxamine, imipramine, nortriptyline, paroxetine, sertraline, trimipramine
Other	Allopurinol, eliglustat, estrogen-containing contraceptives, rasburicase, tacrolimus, tolterodine

Common Pharmacogenetic Nomenclature

Gene Nomenclature Involving Star (*) Alleles:
Example: CYP2C19*1
- CYP = gene for Cytochrome P450 Superfamily
- 2 = Family
- C = Subfamily
- 19 = Isozyme
- *1 = Allele (Haplotype) Variant

It is important to recognize the nomenclature used in pharmacogenetics, as several systems can be used. The star allele nomenclature and single nucleotide polymorphism (SNP) nomenclature are commonly used in literature, though there are several ways to denote genetic changes. Importantly, star alleles are most often used to describe a pattern/constellation of changes in DNA as opposed to a single nucleotide change in the DNA. Since it is a group of changes that are inherited together, one allele is described as a haplotype, and the combination of two alleles as a diplotype. Of note, for many (but not all) genes the *1 allele/haplotype is considered to be the reference or 'normal' allele/haplotype.

For example, to describe a given patient:
- CYP2C19 *1 = allele (haplotype, the reference allele)
- CYP2C19 *3 = allele (haplotype, a variant allele)
- CYP2C19 *1/*3 = genotype (diplotype, the patient is heterozygous)

Gene Nomenclature Involving Single Nucleotide Polymorphisms (SNPs):
Example: VKORC1 c.-1693 G>A
- VKORC1 = Vitamin K epoxide Reductase Complex
- c.-1693 = cDNA location of the SNP (note: this is sometimes omitted in a given context)
- G = the reference or "normal" nucleotide at this position
- > = denotes nucleotide change
- A = the variant nucleotide

Note the main difference between SNP and star allele nomenclature is the number of points in the DNA that are changed. In SNP nomenclature, you will see a given allele being defined by a single location in the DNA, thus a letter will commonly be used. In both situations, you can identify if a single allele or a genotype is being referenced by looking for a "/" which denotes two alleles.

For example, to describe a given patient:
- VKORC1 G = allele (in this case, this is the reference allele)
- VKORC1 A = allele (in this case, this is the variant allele)
- VKORC1 G/A = genotype (the patient is heterozygous, as the allele is defined at this position in this example)

Pre-Pharmacogenetic Testing Considerations

1. **PGx Test Selection:** Select an appropriate pharmacogenomics test based upon considerations of your patient population, potential medication use, cost, and other pertinent factors. Caution: some direct-to-consumer tests may not be appropriate to use to modify drug therapy.

2. **Benefits/Reasons for Testing:**
   a. To help providers make better choices about medications based upon the patient's DNA (e.g., avoid side effects and help with optimal dosing).
   b. The type of DNA tested in pharmacogenetics does not change over a person's life, so the test results also should not change (though the interpretation may change over time).
   c. This type of testing not only helps guide medication selection, but sometimes can also explain past medication failures, which can be reassuring for patients.

3. **Limitations of Testing:**
   a. Pharmacogenetic testing does not explain all adverse drug reactions or all medication non-response. Other factors (like kidney function, overall health, cigarette smoke, etc.) can also affect how a person responds to medications.
   b. The utility of pharmacogenetic testing may be limited in the setting of a liver transplant, bone marrow transplant, or recent blood transfusion (i.e., within 6 weeks).
   c. Not all Pharmacogenetic tests can be used to adjust medication therapy. Certain direct-to-consumer tests are designed to only identify a potential concern, or are limited to a small area of medication therapy changes, and many require a clinical pharmacogenetic test to determine more specific medication therapy recommendations.

4. **Protection of Results:** The Genetic Information Non-discrimination Act (GINA) prevents discrimination based on genetic results for health insurance and employment. Sometimes there are additional state laws that further protect patient results. Test results are also generally subject to HIPAA privacy and confidentiality protections.

5. **Incidental/Secondary Findings:** While uncommon, some pharmacogenes may predict genetic disease risk (e.g., *DPYD*, *UGT1A1*, etc.).

6. **Appropriate Use of PGx Results:** PGx results are one piece of a larger puzzle in determining the best treatment options. There may be times when not following the PGx recommendation is the best treatment option for the patient. Additionally, many testing companies test for genes with limited guidance, and thus may not be actionable for clinical recommendations. Results should always be considered in the setting of other factors, such as drug-drug interactions, renal and hepatic function and other conditions.

7. **Cost of Testing:** Pharmacogenetic testing cost and insurance coverage vary substantially; patients should be encouraged to check with their insurance and the testing company prior to getting tested. While insurance reimbursement for PGx testing is improving, often it is not covered by insurance companies. Many PGx testing companies have a patient assistance or capitated cost system that may or may not depend upon the patient's insurance coverage. Contact the testing company for details.

Clinical Pharmacogenetic Resources

Table 3. Clinical Pharmacogenetic Resources

Resource	Details
The Clinical Pharmacogenetics Implementation Consortium (CPIC)	• Website: www.cpicpgx.org • Summary: An international consortium of over 500 members creates, curates, and posts freely available, peer-reviewed, evidence-based, and detailed gene/drug clinical practice guidelines. CPIC guidelines are indexed in PubMed as clinical guidelines, endorsed by ASHP and ASCPT, and adhere to the Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines. • How to Use: Access the PDF CPIC Guideline publications and supplemental information including allele definition and frequency tables. View upcoming drug-gene pairs under consideration for guideline development, as well as other PGx resources.
The FDA Table of Pharmacogenetic Associations	• Website: www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations • Summary: The FDA created tables based upon evaluation of current data, and believes there is sufficient scientific evidence to suggest that individuals with certain pharmacogenetic findings (when taking specific medications) may experience altered metabolism or differing therapeutic effects. There are three sections of Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations (Section 1), the Data Indicate a Potential Impact on Safety or Response (Section 2), and the Data Demonstrate a Potential Impact on Pharmacokinetic Properties Only (Section 3). • How to Use: Using Ctrl+F, users are able to quickly identify drugs or genes for which some pharmacogenetic recommendation(s) exist.
The Genetic Testing Registry (GTR)	• Website: www.ncbi.nlm.nih.gov/gtr • Summary: This resource provides a central repository for voluntary submission of available genetic testing offerings. • How to Use: Search for drugs or genes of interest, and find which clinical laboratories test for the item of interest. Learn about the test's purpose, methodology, validity, utility and laboratory contacts and credentials.
The Pharmacogenomics Knowledge Base (PharmGKB)	• Website: www.pharmgkb.org • Summary: PharmGKB is a NIH-funded resource that provides information about how human genetic variation affects response to medications. PharmGKB collects, curates and disseminates knowledge about clinically actionable gene-drug associations and genotype-phenotype relationships. • How to Use: Learn about pharmacogenetics and PharmGKB resources/site features. Use interactive Clinical Guideline Annotations to learn about drug recommendations based upon PGx Guidelines from CPIC, the Dutch Pharmacogenetics Working Group (DPWG), and others. Explore PGx associations for drugs that do not currently have a guideline. Stay current on news from the pharmacogenetics community.
PharmVar	• Website: www.pharmvar.org • Summary: The Pharmacogene Variation Consortium is a central repository for pharmacogenes focusing on haplotype structure and allelic variation. This information is useful for translating between various nomenclature representations of PGx. • How to Use: Use the Genes tab to identify a PGx gene (=pharmacogene) of interest. Learn what SNP(s) define a given haplotype. Translate between different reference sequences for a given allele.

POST-Testing Provider Consultation Pearls:

1. When contacting the provider, provide introductions, purpose for calling, and ask "Is now a good time to discuss the patients' results?"

2. Address clinical questions asked (e.g., specific medication changes, etc.)

3. Address other important clinical concerns
   a. Incidental/Secondary Findings: recommend referral to Genetic Counseling for *DPYD, F2, F5*, X-linked genes (e.g., *G6PD*, *HTR2C*). *UGT1A1* is optional since generally mild/benign. It's important to find out if the patient wants to know this information and respect their wishes.
   b. Other pertinent pharmacy findings (renal dose adjustments, other medication management concerns, etc.)

4. Summarize findings and actions requested

5. Confirm if provider will counsel patient on results or if you will

6. Address any other questions/concerns and thank provider
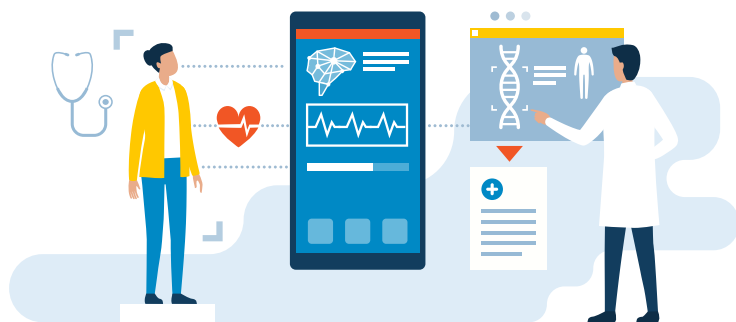
POST-Testing Patient Consultation Pearls (recommend after provider consult):

1. When contacting the patient, provide introductions, purpose for calling and ask, "Is now a good time to discuss your results?"

2. Set expectations for how long the call will take, what will be discussed, and patient preferences.
   a. Timeframe of call: 15 to 60 minutes, depending upon various factors
   b. Establish what and how much the patient is interested in learning (e.g., only changes to meds versus if they want to know more/everything).
   c. Define incidental/secondary findings and confirm if they want to know this information before you tell them about findings

3. Address pressing patient questions

4. Tailored patient consult should primarily focus on the main concept that changes in DNA can impact medication response (this is the key point that patients should remember). However, more in-depth consultations may include the following:
   a. DNA → Protein → Proteins can interact with their medicine
   b. Definitions as needed (e.g., gene = chunk of DNA that makes a protein; variant = change in DNA; metabolism = how drugs are activated or broken down in our body, etc.)
   c. Focus on actionable findings – results that may warrant medicine changes now or later
   d. Share incidental findings if patient wants to know them, and referral for Genetic Counseling
   e. Patient access to reports (advise patient on how to get copies and share their results)

5. If applicable, share any changes you and their healthcare provider decided upon and rationale, and/or advise the patient to not make any changes to their medications without first talking to their healthcare provider

6. Encourage patient to share results with other healthcare providers that prescribe medicines

7. Use teach-back to evaluate understanding of important points

8. Provide contact information for follow-up questions

9. "What questions do you have for me?"

PGx General Testing Pearls:
- While the *1 allele is usually the 'reference' or 'normal' allele (and thus highest allele frequency within a population), that is not always the case.
- Star allele function is not defined by the star allele number (e.g., *2 for *CYP2D6* is normal function whereas *2 for *CYP2C19* is reduced function).
- Since most PGx testing is genotyping (not sequencing), the *1 (or reference) allele is a default designation assigned in the absence of detection of other star alleles. This means that a patient could be incorrectly identified as having a normal function allele if they have an allele that the company does not test for or a variant of unknown significance/novel SNP.
- More is not better – instead of selecting a PGx Test based upon the number of genes, evaluate based upon the presence of actionable genes and alleles pertinent to your patient population.

Very Important Pharmacogene (VIP) Pearls:
- *CYP2C19* – The *17 allele is an increased function allele due to upregulation of the gene. It is in linkage disequilibrium with the *4 allele (a relatively uncommon nonfunctional allele), thus the only way to ensure correct phenotype assignment is to ensure the testing laboratory is querying for both *4 and *17. Always verify the company's phenotype against CPIC guidelines, as many companies deviate from CPIC genotype/phenotype definitions.
- *CYP2C9* – This gene is important for several medications and is often part of a multigene guideline (e.g., warfarin/*CYP2C9,VKORC1*; phenytoin/*CYP2C9*, HLA-B). This gene uses the Activity Score (AS) system to help determine the Metabolizer Phenotype from the genotype (see Key Terms and Abbreviations for more details).
- *CYP2D6* – *CYP2D6* is the most polymorphic CYP enzyme, and there are a wide variety of phenotypes in part due to the presence of two non-functional similar genes, *CYP2D7* and *CYP2D8P*. Ensure the PGx test you are using can distinguish *CYP2D6* from *2D7* and *2D8P*, as well as determine the copy number of the *CYP2D6* gene since this will identify Ultrarapid Metabolizers. This gene uses the Activity Score system. Always verify the company's phenotype against CPIC guidelines, as many companies deviate from CPIC genotype/phenotype definitions.
- *CYP3A4* – This gene is responsible for the metabolism of about 30% of commonly prescribed medications, and has thus far not had strong pharmacogenetic associations owing to substantial intra- and interindividual expression and function not explained by genetics. This is because *CYP3A4* is largely influenced by many factors including phenoconversion, physiological/pathological factors, environmental exposures, and has complex regulation. The *22 allele appears to have consistent evidence for reduced function, however its low frequency limits the clinical utility.
- *CYP3A5* – Many populations will be Poor Metabolizers (*3/*3) for this gene, especially as their ethnicity increases in distance from the equator. As many clinical trials are done in populations who also happen to be Poor Metabolizers, generally speaking dose adjustments are not required for Poor Metabolizers. Note Intermediate (*1/*3) or Normal (*1/*1) Metabolizers actually warrant a dose increase for tacrolimus.

Implementation of Pharmacogenetics

There are many barriers to implementation of pharmacogenetics, however many settings have successfully addressed these barriers. Please see below for pharmacogenomics stakeholders and roles, as well as suggested readings.

Table 4. Recommended Stakeholders and Collaborators

Stakeholder/ Collaborator	Description
Clinician Champion (MD, DO, NP, PA, etc.)	Help garner support for initiative, as well as financial support. Sometimes lead pharmacogenetic initiatives.
Informatics Personnel	Help with integration of pharmacogenetic results into electronic medical record (EMR), which is the most high-leverage method of ensuring consistent pharmacogenetic recommendations.
Pharmacists	Help provide interpretation, education and consultation on pharmacogenetic results. Can help design implementation and lead pharmacogenetic initiatives.
Genetic Counselors	Help with laboratory selection considerations, educational/consultation initiatives, guidance on incidental/secondary findings, program design/consideration advisement.
Research Scientists	Often pharmacogenetic implementation starts as a research initiative, thus these individuals often have a wealth of experience and considerations that greatly assist with implementation.
Laboratory Personnel	Help with laboratory and testing considerations, as well as reporting of results.

Suggested Implementation Readings

- Arwood et al. "Implementing pharmacogenomics at your institution: establishment and overcoming implementation challenges." *Clin Transl Sci*. 2016;9(5):233-245. PMID 27214750
- Bates et al. "Ten commandments for effective clinical decision support: making the practice of evidence-based medicine a reality" *J Am Med Inform Assoc*.2003;10(6):523-530. PMID 12925543
- Caraballo et al. "Electronic medical record-integrated pharmacogenomics and related clinical decision support concepts" *Clin Pharmacol Ther.* 2017;102(2):254-264. PMID 28390138
- Duarte et al. "Multisite investigation of strategies for the clinical implementation of pre-emptive pharmacogenetic testing" *Genet Med.* 2021:23(12):2335-2341. PMID 34282303
- Dunnenberger et al. "Implementation of a multidisciplinary pharmacogenomics clinic in a community health system" *Am J Health Syst Pharm.* 2016:73(23):1956-1966. PMID 27864203
- Gammal et al. "Documenting pharmacogenomics test results in electronic health records: practical considerations for primary care teams" *J Pers Med.* 2021:11(12):1296. PMID 34945768
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Acknowledgements

Pharmacogenetic Research Initiatives and Collaboratives

- **All Of Us** – This NIH-funded research is an effort to collect and study data from one million plus people living in the United States to advance areas of precision medicine, including pharmacogenetics. Learn more at www.joinallofus.org
- **eMERGE PGx** – This partnership of the electronic MEdical Records and GEnomics Network and the Pharmacogenomics Research Network advanced pharmacogenetic implementation by providing funding and guidance for early PGx implementation efforts with many healthcare institutions across the United States. Learn more at www.genome.gov/Funded-Programs-Projects/Electronic-Medical-Records-and-Genomics-Network-eMERGE
- **IGNITE** – The Implementing GeNomics In pracTicE also advanced pharmacogenetic implementation by providing funding and guidance for early PGx implementation efforts with many healthcare institutions across the US. Learn more at www.genome.gov/Funded-Programs-Projects/Implementing-Genomics-in-Practice-IGNITE-Pragmatic-Clinical-Trials-Network

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