Advisory Board

Pharmacogenomics Glossary

Enhance stakeholder conversations through a shared vocabulary

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What is pharmacogenomics?

Pharmacogenomics (PGx) is the science of understanding the influence of a person's genome on drug treatment outcomes. Provider-based PGx programs are not currently widespread—they mostly exist in large academic medical centers and in some community hospitals with strong use cases (e.g., those with large oncology or mental health patient populations). As the PGx field evolves and becomes more prevalent in the health care industry, a concise glossary that fosters a common understanding among stakeholders is more important than ever.

Why do we need a pharmacogenomics glossary?

A wide variety of health care companies are involved in the PGx process. As a result, cross-stakeholder collaboration is inherent and vital to the PGx workflow. Stakeholders include health systems (e.g., pharmacists, clinicians, IT leaders), lab vendors, clinical decision support (CDS) vendors, electronic health record (EHR) vendors, life sciences companies, and payers. Many of these groups, however, use different vocabularies to discuss PGx, creating barriers to essential cross-industry collaboration.

Additionally, language barriers can exist within a given organization. For example, clinicians often use terms interchangeably that, in reality, have different meanings. For stakeholders who are not currently involved in PGx, the knowledge gap becomes even wider. Many providers are unfamiliar with pharmacogenomics itself, let alone how to implement the process into clinical practice.

This glossary addresses these challenges by:

1. Clarifying commonly confused terms to ensure that stakeholders across the health care industry use a shared language to collaborate on the topic of PGx.
2. Supporting broader education efforts to use on an individual basis, to use within an organization, or to share with partners outside of an organization.

What should I consider as I use this glossary?

Out of the many PGx-related terms, this glossary focuses on 20 terms that stakeholders most often confuse or use differently, as well as terms that are essential to understand the PGx workflow.

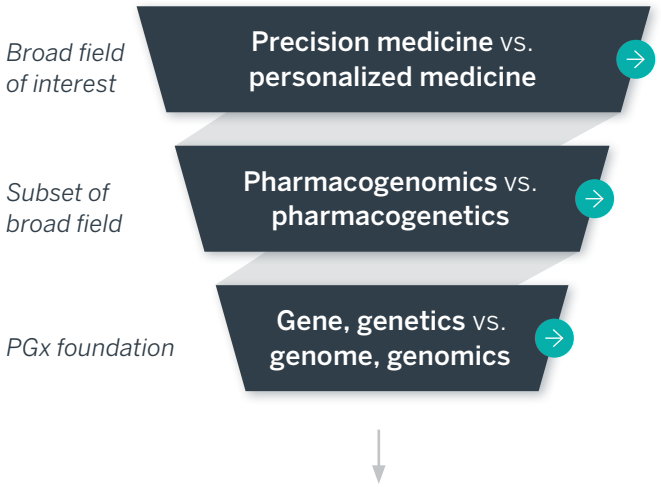
This glossary focuses on definitions outside of cancer care (i.e., germline mutations). PGx testing can analyze two types of mutations: germline and somatic. Germline mutations occur in the body's germ cells (i.e., egg or sperm), can be passed on from one generation to the next, and affect the DNA in all cells of the offspring. Somatic mutations can occur in any cells of the body except for the germ cells, and therefore are not hereditary. Somatic mutations can cause cancer and other diseases.

To date, researchers and clinicians have largely focused PGx testing on oncology use cases, mostly for somatic mutations (although providers can test for germline mutations in the case of hereditary cancers). The reason for this prioritization is that the oncology space has a deeper set of related PGx evidence, technologies, and resources. Some of the terms detailed in this glossary have different connotations in oncology use cases, but this glossary provides clarification for, and insight into, the emerging field of non-oncology PGx.

How to use this glossary

Unlike a typical glossary, this resource is not in alphabetical order. Instead, we've structured the terms based on their place in the PGx process writ large—starting with an understanding of the broader topic and moving down to granular steps in the PGx clinical workflow. We've grouped the terms that stakeholders commonly confuse or use interchangeably on the same page. Click the links for more details about each term.

DEFINING THE BROADER CONTEXT



HIGH-LEVEL PGx WORKFLOW AND RELATED TERMS

1

Establish clinical efficacy of drug-gene pairs; create testing guidelines; disseminate prescribing recommendations; educate providers

- Clinical Pharmacogenetics Implementation Consortium (CPIC)

2

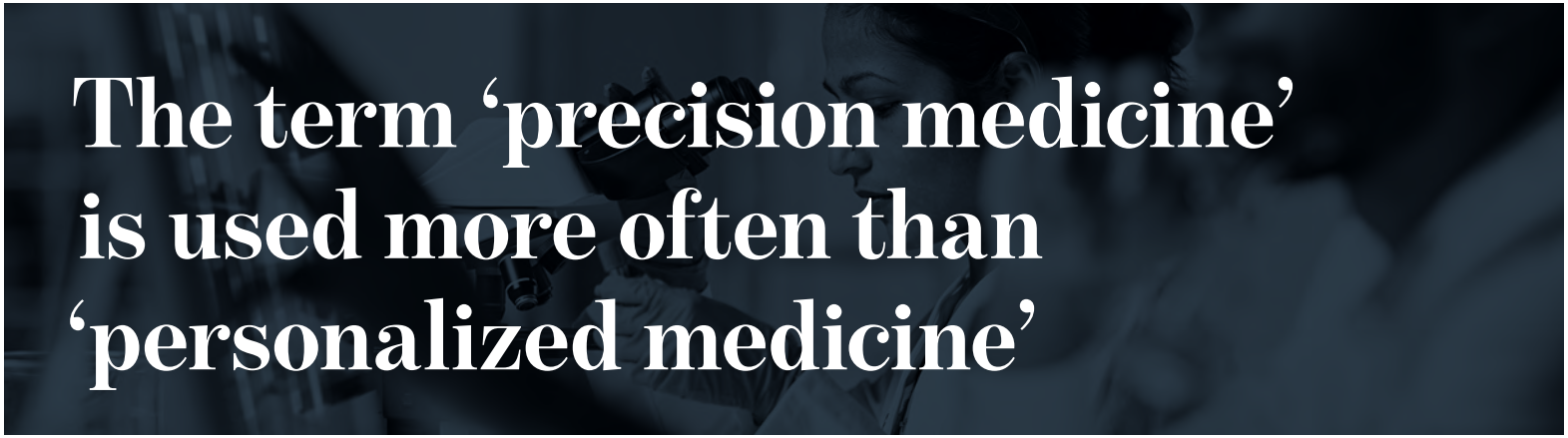
Identify and test appropriate patients

- Genetic test, gene test, gene panel
- Molecular diagnostic, in vitro diagnostic (IVD), laboratory-developed test (LDT)
- Biomarker, companion diagnostic

3

Interpret results and **implement** into practice

- Genotype, phenotype
- Clinical decision support (CDS)



The term ‘precision medicine’ is used more often than ‘personalized medicine’

Precision medicine uses genomic, epigenomic, exposure, and other data to define individual patterns of disease, potentially leading to better individual treatment. It refers to the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or in their response to a specific treatment.

Many health care stakeholders favor the term precision medicine over **personalized medicine**, since the term “personalized” makes it seem like pharmaceutical companies and clinicians will tailor each treatment and prevention effort to every individual patient.

The journey to precision medicine

TRADITIONAL MEDICINE

- Predates personalized medicine
- Provides generalized treatments for populations with the same disease (e.g., diabetes)
- Reacts to symptoms and diagnoses
- Example: Group patients based on metrics like high vs. normal blood pressure

PERSONALIZED MEDICINE

- Suggests treatments and preventions developed for an individual
- Relies on available data sources to determine appropriate treatment plans for patients
- Popular term up until 2015, when President Obama announced the Precision Medicine Initiative
- Example: Use genetic test results to recommend lifestyle changes

PRECISION MEDICINE

- Uses genetic data and other data sets to treat patients proactively
- Incorporates algorithms to inform care recommendations
- Categorizes subpopulations using common genetic patterns, lifestyles, drug responses, and environmental and cultural factors
- Preferred term since 2015, with providers and other health care stakeholders using the term in program branding
- Example: Categorize patients based on genetic phenotype

1900s
First drugs are produced and regulated under the FDA

1999
First publication includes term "personalized medicine"

2015
President Obama gives precision medicine speech

Source: "What is the difference between precision medicine and personalized medicine? What about pharmacogenomics?" U.S. National Library of Medicine; Bresnick J, "What are precision medicine and personalized medicine?" *Health IT Analytics*, January 11, 2018; "Toward precision medicine: building a knowledge network for biomedical research and a new taxonomy of disease," National Research Council; "Advancing precision medicine with gene and cell therapies," Covance, 2019; "What is modern medicine?" *Medical News Today*; Caulfield T, "The limits of personalized medicine," *The Atlantic*, March 16, 2016; Pharmacy Executive Forum interviews and analysis.

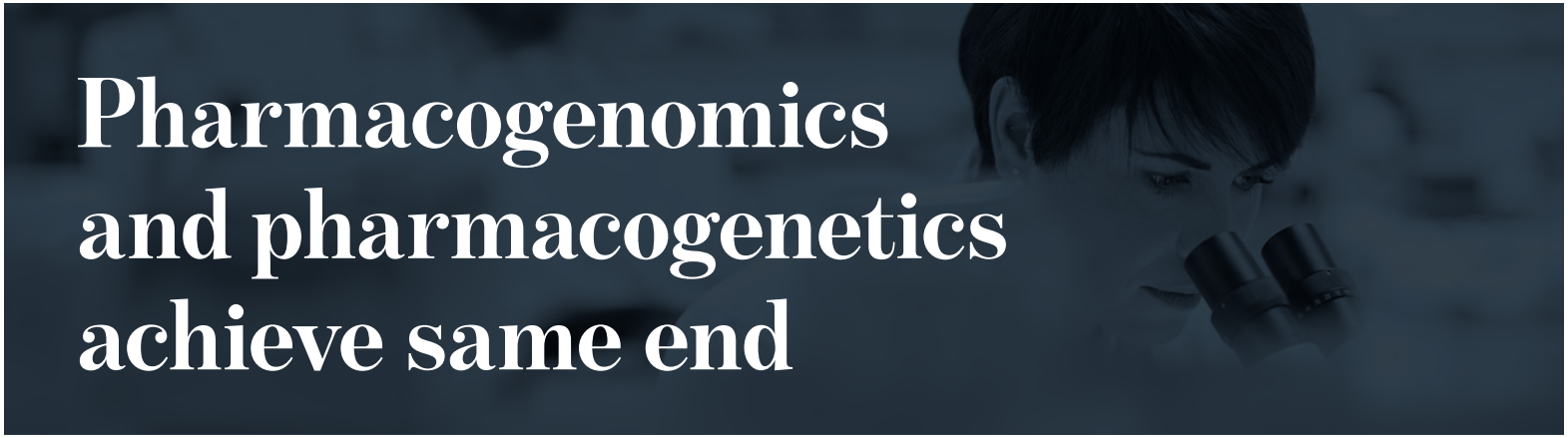
Did you know...

- Most provider organizations use the terms **precision medicine**, **personalized medicine**, and **individualized medicine** interchangeably. While precision medicine is the more common term, word choice is based on preference rather than clinical aim.
- Health systems may include the words **precision**, **personalized**, **or both**, in their program name.
- Broadly, precision medicine includes **pharmacogenomics**, **pharmacogenetics**, **cell therapy**, and **gene therapy**, and includes interventions like CAR-T immunotherapy.
- Precision medicine **does not literally mean** the creation of drugs or medical devices that are unique to a patient.

Precision medicine myth busting

HYPE	REALITY
Precision medicine is solely focused on individuals.	Precision medicine focuses on treating populations with similar characteristics (e.g., disease state or genetic mutation).
Precision medicine is relevant for all disease states and care settings.	Primary care, cardiovascular, and oncology have the most scientific evidence and are major focus areas of most precision medicine programs.
Life sciences companies develop drugs on an individual patient basis.	Drug development is driven by identifiable genetic variability across populations.

Source: Leopold J, et al., "Emerging role of precision medicine in cardiovascular disease," *Circulation Research*, 2018; "What is the difference between precision medicine and personalized medicine? What about pharmacogenomics?" U.S. National Library of Medicine; Gameiro G, et al., "Precision medicine: changing the way we think about healthcare," *Clinics* (Sao Paulo), 2018; "Remarks by the president on precision medicine," The White House, January 30, 2015; Krzyszczyk P, et al., "The growing role of precision and personalized medicine for cancer treatment," *Technology*, 2018; Pucheril D, et al., "The history and future of personalized medicine," *Managed Care*, November 6, 2011; Pharmacy Executive Forum interviews and analysis.



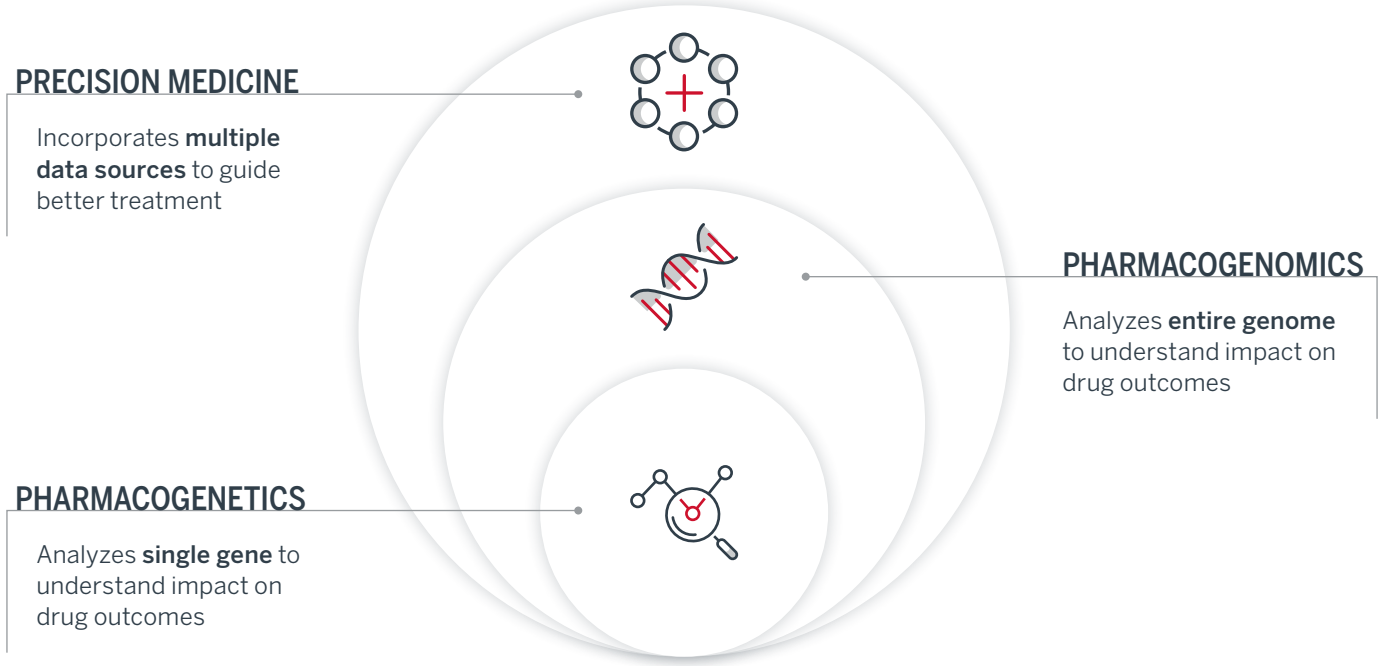
Pharmacogenomics and pharmacogenetics achieve same end

Pharmacogenomics (PGx) is the science of understanding the influence of the entire genome on drug treatment outcomes. **Pharmacogenetics (PGt)** describes the influence of a single gene on drug treatment outcomes. Pharmacogenomics is a subset of precision medicine, and pharmacogenetics is a subset of pharmacogenomics.

Even though PGx denotes looking at the entire genome, most PGx tests investigate single genes or multiple genes simultaneously.

Relationship between precision medicine and PGx

PGx makes up one component of precision medicine

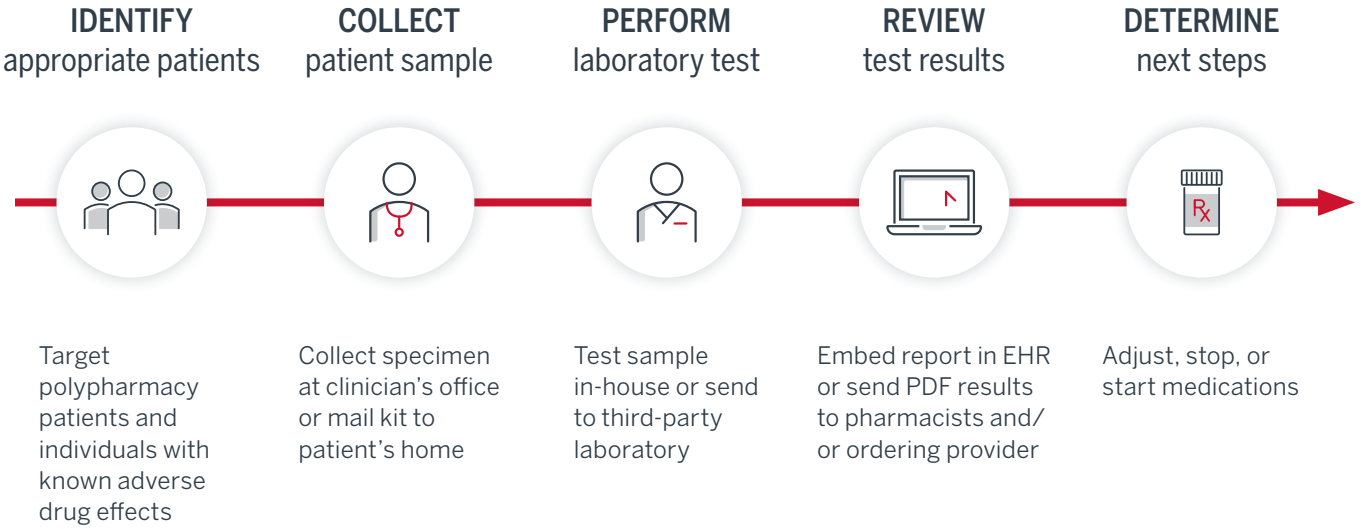


Source: "Pharmacogenomics," Science Direct; "PharmGKB FAQs," PharmGKB; Pharmacy Executive Forum interviews and analysis.

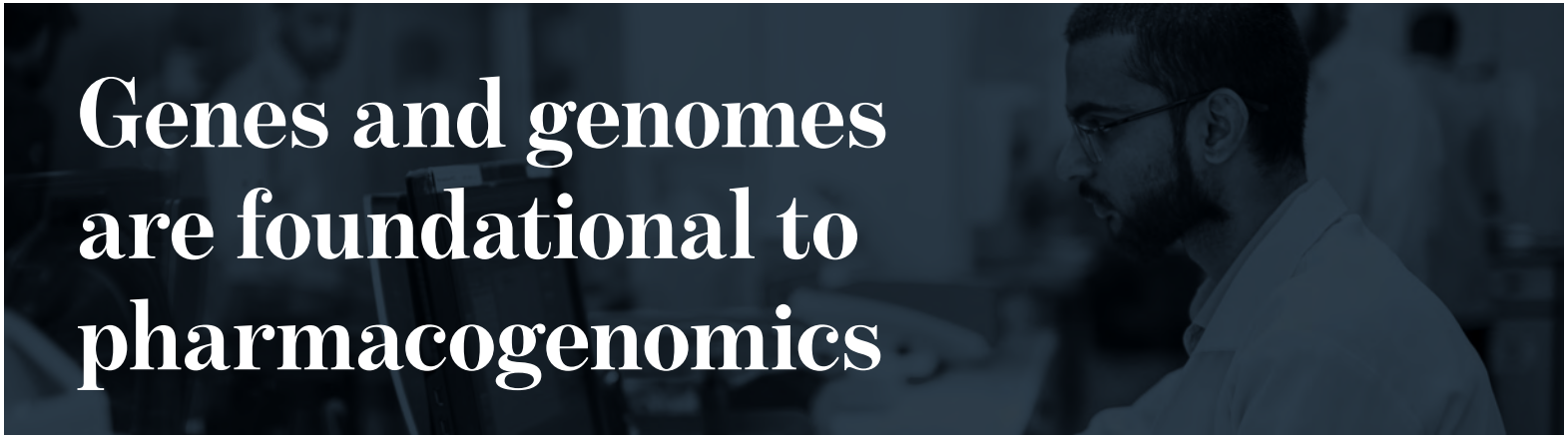
Did you know...

- While clinicians typically use the terms pharmacogenomics and pharmacogenetics interchangeably, **most provider organizations** use the term pharmacogenomics.
- Both PGx and PGt help clinicians understand **how patients respond to drugs** based on their genetic differences.
- A variety of organizations offer PGx, including academic medical centers (AMCs), cancer hospitals, community hospitals, and community clinics. But at present, health system **PGx programs** are not widespread and **exist primarily in large AMCs.**
- **In oncology, PGx testing is less common** than genomic and genetic tests. Practitioners use genomic testing on tumors to determine which drugs work best against the tumor. They use genetic tests on patients to assess hereditary cancer risk.

High-level view of pharmacogenomics workflow



Source: "Pharmacogenomics," Science Direct; "PharmGKB FAQs," PharmGKB; Pharmacy Executive Forum interviews and analysis.

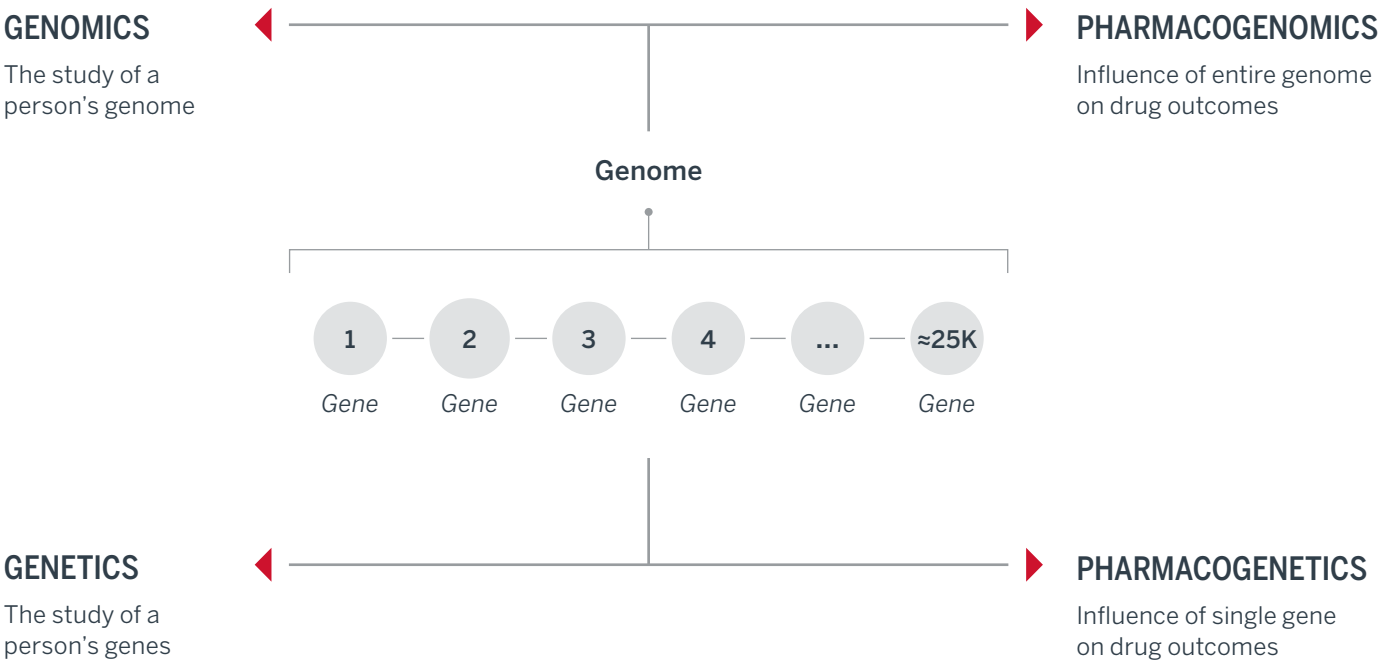


Genes and genomes are foundational to pharmacogenomics

A **gene** is the basic physical and functional unit of heredity and consists of DNA. Humans have between 20,000 and 25,000 genes. The study of a person's genes is called **genetics**. A **genome** is an organism's complete set of DNA, including all of its genes. The study of a person's genome is called **genomics**, and includes interactions between genes and the person's environment.

Researchers have discovered that specific genes—and their relevant mutations—can impact drug response, leading to the practice of pharmacogenomics.

Increased gene-level understanding informs appropriate prescribing



Source: "Table of pharmacogenetic associations," U.S. Food and Drug Administration; Pharmacy Executive Forum interviews and analysis.

Did you know...

- In **pharmacogenomics**, a patient receives single- or multi-gene testing to determine which drugs are safe and effective for prescribing.
- PGx enables providers to have a greater understanding of gene-drug interactions, genetic mutations, and genetic responses to therapeutics. As a result, **PGx can help inform the way providers prescribe medications**, the way life sciences companies develop drugs, and the way the federal government ensures safe prescribing through labeling.
- The FDA broadly categorizes drugs with gene-drug interactions into three categories: drugs that need **therapeutic management**, drugs with **potential impact** on patients, and drugs that do not have **sufficient evidence** to show impact.

Example populations affected by gene-drug interactions




DRUG	AFFECTED POPULATION	GENE-DRUG DETAILS	PGx CONSIDERATIONS
Clopidogrel	May affect individuals with East Asian ancestry	Clopidogrel, or Plavix, is correlated with an increased risk of stroke for individual carriers of the CYP2C19 gene with *2, *3, or *8 mutations	Individuals with East Asian ancestry have a heightened prevalence of these alleles[1] and may require PGx testing before taking clopidogrel
Codeine	May impact breastfeeding infants with Ethiopian ancestry	Women who are CYP2D6 ultra-rapid metabolizers can pass elevated amounts of morphine through breast milk to their newborns	Individuals with Ethiopian ancestry have greater percentages of this mutation and may require PGx testing for safe prescribing if breastfeeding

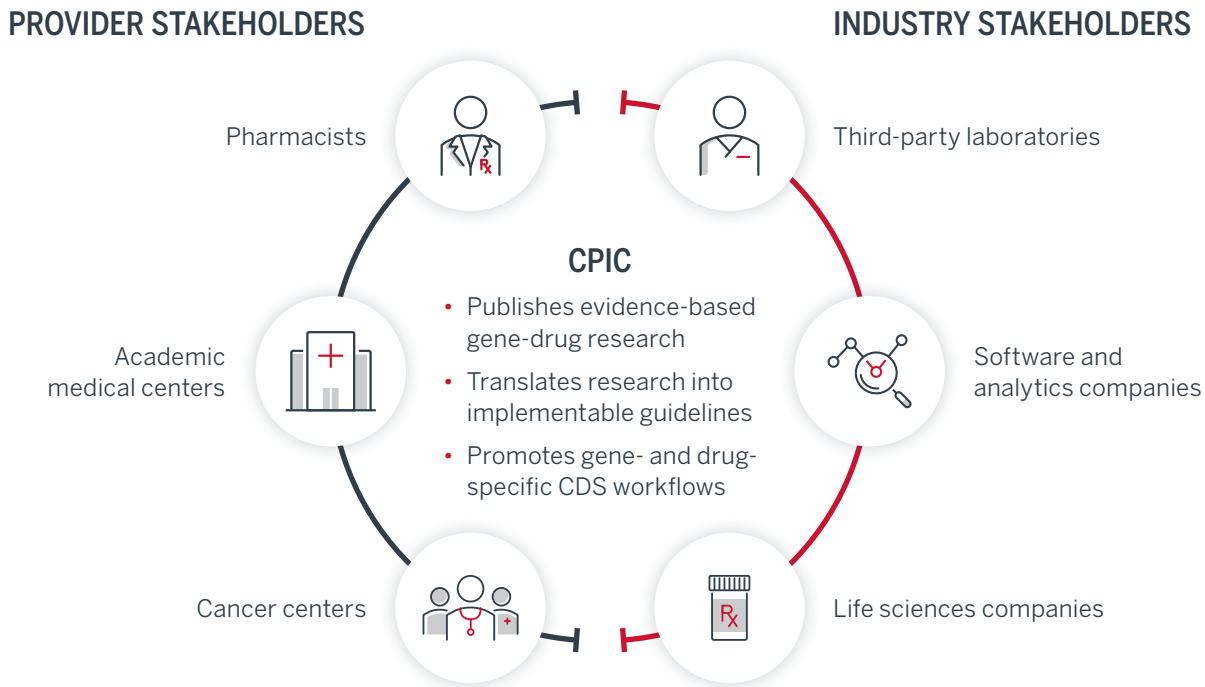
1. The alternate form or version of a gene; sometimes referred to as a genetic mutation or genetic variant.

Source: Pan Y, et al., "Genetic polymorphisms and Clopidogrel efficacy for acute ischemic stroke or transient ischemic attack," *Circulation*, 2017; Madadi P, et al., "Safety of codeine during breastfeeding: Fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine," *Canadian Family Physician*, 2007; "Allele," National Human Genome Research Institute; Pharmacy Executive Forum interviews and analysis.

Clinical Pharmacogenetics Implementation Consortium

The Clinical Pharmacogenetics Implementation Consortium (CPIC) is a leading **international body of individual volunteers** interested in **facilitating the use of pharmacogenetic tests** for patient care. CPIC's cross-industry members include pharmacists, pharmacogeneticists, academic researchers, laboratories, life sciences organizations, and software companies. CPIC publishes evidence-based, peer-reviewed gene/drug clinical practice guidelines. Vendors and provider organizations widely use CPIC guidelines, which consist of clinical decision support recommendations, drug resource mapping, and gene resource mapping.

CPIC stakeholders



Did you know...

- In addition to CPIC, **there are several other organizations** that disseminate clinical PGx evidence and recommendations, such as the Dutch Pharmacogenetics Working Group (DPWG). The U.S. Food and Drug Administration maintains a list of PGx biomarkers used in drug labeling. Other organizations, like the Pharmacogenomics Knowledge Base (PharmGKB), collate this PGx-related data.

- Since CPIC is volunteer-based, it is a **neutral third party in its research** and guideline recommendations. However, that volunteer-based leadership can also delay the amount of time it takes to produce and release new publications.

CPIC guidelines' impact on health systems and industry stakeholders

CPIC	HEALTH SYSTEM BENEFIT	INDUSTRY BENEFIT
Updates PGx evidence and makes research freely available	Saves pharmacists and clinicians time reviewing large amounts of journals and research articles	Informs PGx software vendors, labs, and payers of what is deemed scientifically relevant
Illustrates CDS[1] workflows	Assists IT and informatics staff with building new clinical pathways	Incorporates CPIC-recommended algorithms for customer use

1. Clinical decision support is software that provides clinicians with filtered knowledge and person-specific information, typically at the point of care, to enhance patient health through informed decision-making.

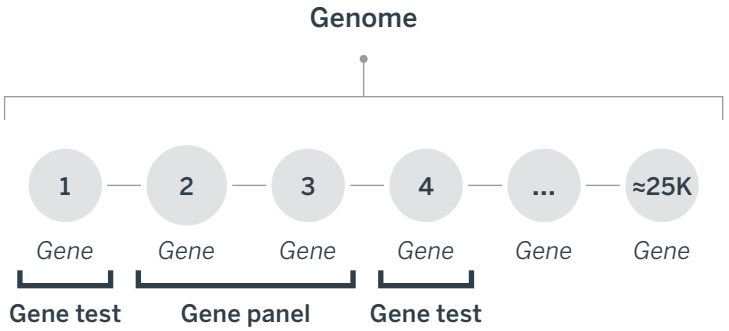
Source: "What is CPIC?" Clinical Pharmacogenetics Implementation Consortium; "Members," Clinical Pharmacogenetics Implementation Consortium; Pharmacy Executive Forum interviews and analysis.

Providers may choose from multiple genetic test types

A **genetic test** identifies changes in chromosomes, genes, or proteins in people suspected of having, or are at risk of developing, a particular disease or condition. A **gene test** looks for changes within one gene. A **gene panel** analyzes several genes at once that could cause the same or a similar medical condition to help identify targeted therapies. When a provider orders PGx testing, a lab runs a genetic test to identify a patient's genetic mutations, which are ultimately sent back to the ordering provider.

Genetic test types

Common tests look at single gene or multi-gene mutations



Example

SINGLE GENE TEST

Patient has a heart attack and experiences chest pains

Clinician considers prescribing clopidogrel, which is affected by the CYP2C19 gene

Clinician orders a single gene test for CYP2C19

Lab tests the CYP2C19 gene exclusively

GENE PANEL TEST

Patient has epilepsy and experiences depressive episodes

Clinician considers prescribing phenytoin and imipramine, which are affected by the CYP2C9, HLA-B, CYP2C19, and CYP2D6 genes

Clinician orders a gene panel test, which include these four genes

Lab tests the CYP2C9, HLA-B, CYP2C19, and CYP2D6 genes, and potentially others in the panel

Source: "What is genetic testing?" U.S. National Library of Medicine; "Genetic testing," Centers for Disease Control and Prevention; "Genetic testing panels," Kaiser Permanente; Ji Y, et al., "Moving beyond single gene-drug pairs in clinical pharmacogenomics testing," *ARUP Laboratories*; "Personalized medicine investment playbook," Advisory Board Oncology Roundtable, 2015; Pharmacy Executive Forum interviews and analysis.

Did you know...

- Gene panel tests are also called **multi-gene tests, multi-gene panels,** and **multiple-gene tests.**
- Gene tests and gene panel tests are both types of **genetic tests.**
- A gene test is for a **single gene** whereas gene panels test **multiple genes** at once.
- Insurers are more likely to cover **single gene tests** than gene panel tests, but some do cover multi-gene tests.

Payer coverage requirements for PGx testing

UNITEDHEALTHCARE[1]

Behavioral health

Approved PGt multi-gene panel for prescribing antidepressants and antipsychotics if:

- Patient has major depressive disorder or anxiety disorder diagnosis
- Patient failed prior medication
- Multi-gene panel has 15 or fewer genes

MEDICARE

Warfarin

Approved PGx testing of CYP2C9[2] or VKORC1[2] alleles if:

- Patient has not been previously tested
- Patient received fewer than five days of warfarin in the anticoagulation regimen
- Patient is enrolled in a prospective, randomized, controlled clinical study

AETNA

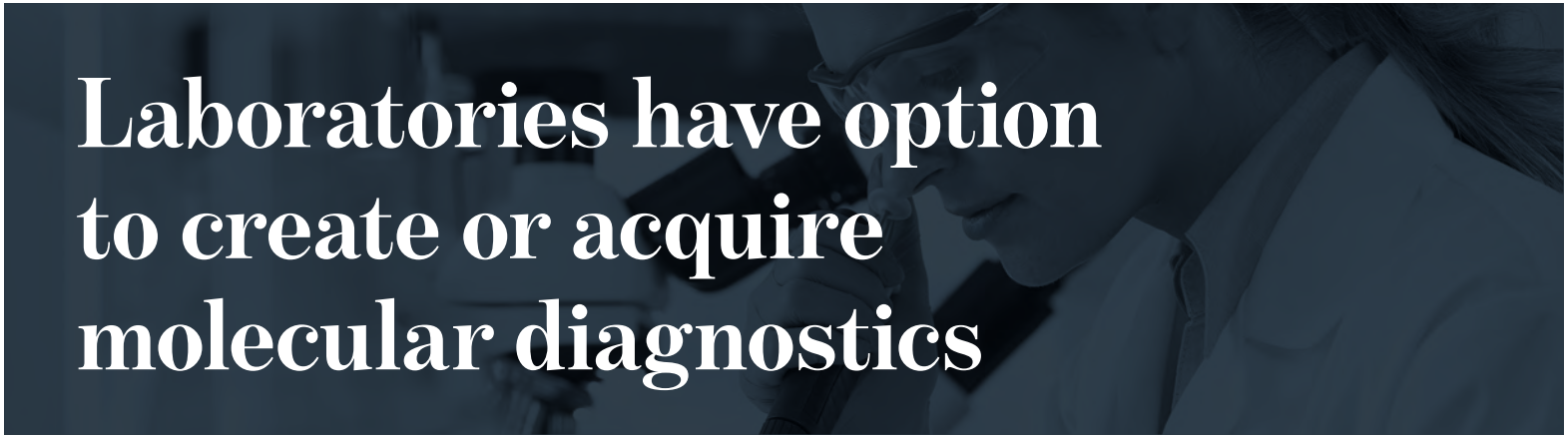
Carbamazepine

Aetna considers PGt genotyping for HLA-B*1502[3] medically necessary for persons of Asian ancestry if:

- Tested before commencing treatment with carbamazepine

1. Advisory Board is a subsidiary of UnitedHealth Group, the parent company of UnitedHealthcare. All Advisory Board research, expert perspectives, and recommendations remain independent.
2. The FDA cites genetic variation in the CYP2C9 and/or VKORC1 genes can, in concert with clinical factors, predict how each individual responds to warfarin.
3. Aetna cites a strong association between the HLA-B*1502 variant and certain serious skin reactions, found almost exclusively in people of Asian descent.

Source: "Pharmacogenetic testing," UnitedHealthcare, February 1, 2020; "Pharmacogenetic testing for warfarin response," CMS; "Decision memo for pharmacogenomic testing for Warfarin response (CAG-00400N)," CMS; "Pharmacogenetic and pharmacodynamics testing," Aetna, February 17, 2020; Pharmacy Executive Forum interviews and analysis.



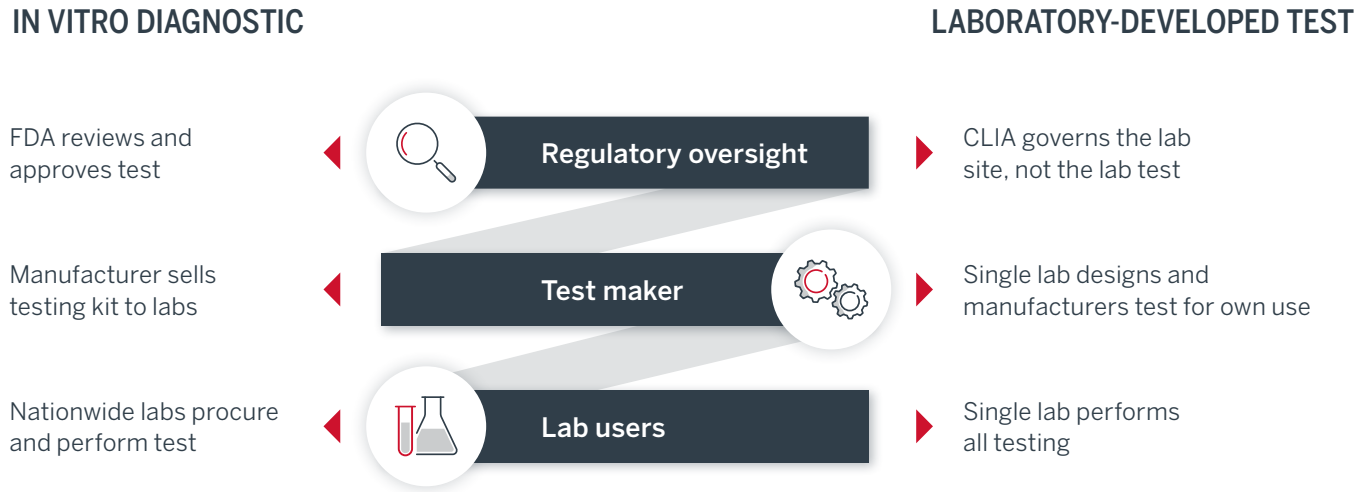
Laboratories have option to create or acquire molecular diagnostics

A **molecular diagnostic** is a test that determines genetic predispositions to a disease or a person's likely response to a drug. Two examples of molecular diagnostics are the **in vitro diagnostic (IVD)** and **laboratory-developed test (LDT)**. Both use human specimens to identify which patients will likely benefit from a specific therapeutic. An IVD is an FDA-approved test that can be sold to laboratories, whereas an LDT does not require FDA approval and must be designed, manufactured, and used within a single laboratory.

When a provider orders PGx testing—such as a gene test or gene panel—the lab may use an IVD or LDT to perform the test.

From a regulatory standpoint, IVDs and LDTs face different levels of scrutiny, even though they may test for the same genetic mutations. IVDs must receive FDA approval, while the lab that creates and uses the LDT must receive certification in accordance with the Clinical Laboratory Improvement Amendments (CLIA) Act.

In vitro diagnostics versus laboratory-developed tests



Source: "Introduction to molecular diagnostics: the essentials of diagnostic series," AdvaMedDx; "In vitro diagnostics," U.S. Food and Drug Administration; "Laboratory developed tests," U.S. Food and Drug Administration; Mamuszka H, "The neverending LDT vs IVD debate," *Journal of Precision Medicine*, 2019; "Personalized medicine investment playbook," Advisory Board Oncology Roundtable, 2015; Pharmacy Executive Forum interviews and analysis.

Did you know...

- Hospital-owned laboratories performing PGx testing can use **IVDs or LDTs depending on resource availability.** Because LDT creation requires a significant amount of investment and specific expertise, many hospital-based labs opt to purchase IVDs or outsource their lab testing.

- LDTs have evolved from fairly simple tests, like vitamin D measurements, to more complex tests, like PGx testing. The **FDA is reconsidering oversight policies and regulations** since, historically, LDTs have not needed pre-market approval for use.

- In PGx, hospital-owned and commercial labs **typically use low-cost IVDs, LDTs,** and other testing methods, like mass arrays, far more frequently than expensive sequencing-based tests (e.g., next-generation sequencing and whole exome sequencing).

Examples of IVDs and LDTs in practice

Diagnostic types differ by manufacturing location and regulations

IN VITRO DIAGNOSTIC

Manufacturer
- Manufacturer makes FDA-approved ready-to-use IVD for commercial use

Laboratory
- Laboratory buys IVD test kit for own use

Provider
- Provider orders PGx testing
- Sends patient sample to lab

Laboratory
- Laboratory performs PGx test with IVD
- Sends results to provider

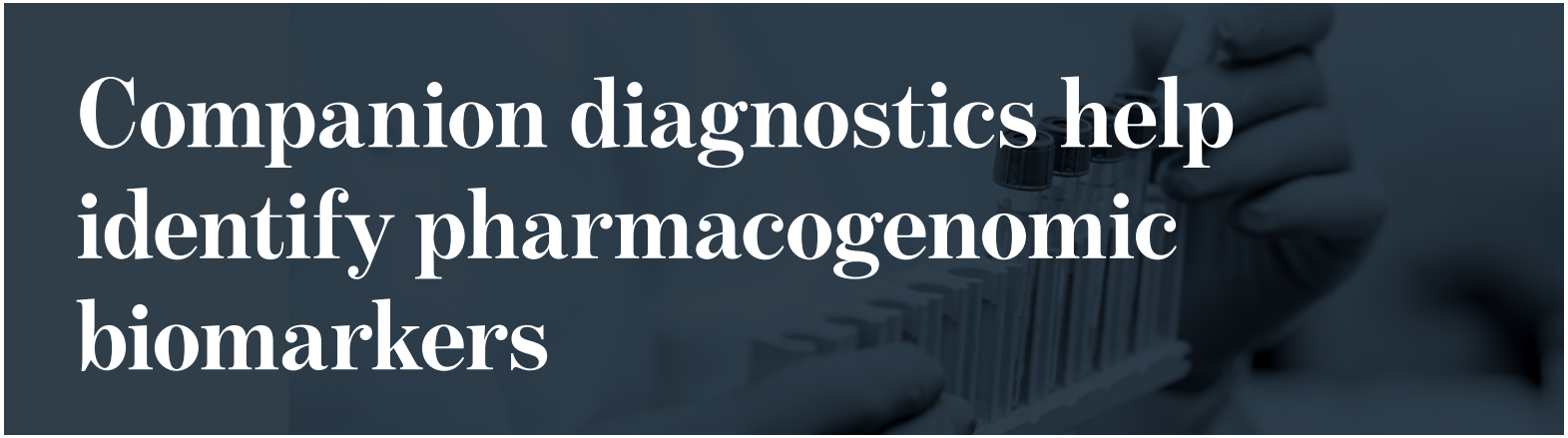
LABORATORY-DEVELOPED TEST

Laboratory
- CLIA-certified laboratory designs and makes LDT for own use

Provider
- Provider orders PGx testing
- Sends patient sample to lab

Laboratory
- Laboratory performs PGx test with LDT
- Sends results to provider

Companion diagnostics help identify pharmacogenomic biomarkers



A **biomarker** is a characteristic that can be scientifically measured or evaluated as an indicator of normal biologic processes, disease, or response to therapeutic intervention. In germline PGx testing, in vitro diagnostic tests measure genetic biomarkers. In oncology PGx testing, in vitro diagnostics and molecular imaging diagnostics measure genetic biomarkers or tumor sites, respectively.

In instances when a therapeutic has a known gene-drug interaction, life sciences companies can include a **companion diagnostic** to classify responders and non-responders for the drug. A companion diagnostic is typically an in vitro diagnostic that detects a predictive biomarker to determine the likely efficacy of a drug. Clinicians should order the corresponding companion diagnostic to ensure safety and efficacy before prescribing the therapeutic, when applicable.

Role of companion diagnostics in care delivery

Companion diagnostics add steps before prescribing

Oncologist recommends drug with companion diagnostic and known PGx interactions

Oncologist orders corresponding companion diagnostic to determine gene-drug safety and efficacy

Companion diagnostic tests patient for predictive biomarkers using genetic sample

Oncologist receives diagnostic test results

Oncologist prescribes drug if predictive biomarkers found; considers alternative drugs if biomarkers absent

Source: "Definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories," European Medicines Agency, November 2007; "Companion diagnostics," U.S. Food and Drug Administration; Taylor C, "Predictive biomarkers and companion diagnostics. The future of immunohistochemistry," *Applied Immunohistochemistry & Molecular Morphology*, 2014; Khoury J, et al., "Next-generation companion diagnostics: promises, challenges, and solutions," *Archives of Pathology & Laboratory Medicine*, 2015; "Table of pharmacogenomic biomarkers in drug labeling," U.S. Food and Drug Administration; "List of cleared or approved companion diagnostic devices (in vitro and imaging tools)," U.S. Food and Drug Administration; "Foundation Medicine expands indication for FoundationOne®CDx as a companion diagnostic for Piqray® (alpelisib)," Foundation Medicine, December 4, 2019; Mendes E, "FDA approves Idhifa (enasidenib) for acute myeloid leukemia," American Cancer Society, 2017; "Abbott RealTime IDH2," Abbott; "Lynparza approved in the US as a 1st-line maintenance treatment of germline BRCA-mutated metastatic pancreatic cancer," AstraZeneca, 2019; "BRACAnalysis CDx," BRACAnalysis CDx; Pharmacy Executive Forum interviews and analysis.

Did you know...

- The vast majority of **FDA-approved** companion diagnostics apply to various cancer types.
- In addition to IVDs, companion diagnostics can be **laboratory-developed tests.**
- 250+ FDA-approved therapeutics have **biomarker information included** on their drug labels.
- The FDA requires that IVD companion diagnostics used with therapeutics **must explicitly mention** this on the labels of the diagnostic and the therapeutic.
- If a therapeutic requires a companion diagnostic for safe use and prescribing, the test helps determine which patients **should and should not** receive a particular drug.
- Companion diagnostic tests also **monitor ongoing treatments** for safety and efficacy.

Therapeutics and companion diagnostic examples

Drug name	**Piqray®**	**Idhifa®**	**Talzenna®**
Drug maker	Novartis	Celgene[3]	Pfizer
Clinical use	Breast cancer	Acute myeloid leukemia	Breast cancer
Companion diagnostic	**FoundationOne®CDx**	**Abbott RealTime IDH2**	**BRACAnalysis CDx®**
Testing information	Tests patients for the PIK3CA[1] mutation in HR+/HER2-[2] advanced breast cancer	Tests patients for the IDH2[4] mutation	Tests patients for the BRCA1 or BRCA2[5] mutation
Details	≈40% of patients living with HR+/HER2- breast cancer have the PIK3CA mutation	In vitro diagnostic detects nine different IDH2 mutations	In vitro diagnostic detects germline BRCA1 and BRCA2 mutations from whole blood specimen

1. According to the Cancer Genome Atlas Network, PIK3CA is the most commonly mutated gene in HR+/HER2- breast cancer. Approximately 40% of patients living with HR+/HER2- breast cancer have this mutation.
2. Hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative.
3. In 2017, the FDA granted approval of Celgene's Idhifa along with Abbott Laboratories' RealTime IDH2 Assay companion diagnostic. In 2019, Celgene became a wholly owned subsidiary of Bristol-Myers Squibb.
4. Isocitrate dehydrogenase-2 (IDH2).
5. When either the BRCA1 or BRCA2 gene is altered or mutated, cells are more likely to develop additional genetic alterations that can lead to cancer

Source: "Definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories," *European Medicines Agency*, November 2007; "Companion diagnostics," U.S. Food and Drug Administration; Taylor C, "Predictive biomarkers and companion diagnostics. The future of immunohistochemistry," *Applied Immunohistochemistry & Molecular Morphology*, 2014; Khoury J, et al., "Next-generation companion diagnostics: promises, challenges, and solutions," *Archives of Pathology & Laboratory Medicine*, 2015; "Table of pharmacogenomic biomarkers in drug labeling," U.S. Food and Drug Administration; "List of cleared or approved companion diagnostic devices (in vitro and imaging tools)," U.S. Food and Drug Administration; "Foundation Medicine expands indication for FoundationOne®CDx as a companion diagnostic for Piqray® (alpelisib)," *Foundation Medicine*, 2019; Mendes E, "FDA approves Idhifa (enasidenib) for acute myeloid leukemia," *American Cancer Society*, 2017; "Abbott RealTime IDH2," Abbott; "FDA approves companion diagnostic for Pfizer's Talzenna," *CLP Mag*, November 27, 2018; "BRACAnalysis CDx," BRACAnalysis CDx; Pharmacy Executive Forum interviews and analysis.

Genotype and phenotype research supports care recommendations

A **genotype** is the collection of genes that provides instructions to make proteins. The genotype consists of pairs of alleles, which are gene pairs that determine hereditary characteristics. A **phenotype** is the observable characteristics of an individual's traits, such as metabolic activity or blood type. Genotypes may affect phenotypes, but environmental and epigenetic[1] factors can also affect them.

In pharmacogenomics, genetic mutations serve as genotypes, while the phenotype represents how an individual will likely metabolize a specific therapeutic (e.g., normal metabolizer or low metabolizer) based on the genotype information.

1. According to the National Human Genome Research Institute, epigenetics is an emerging field of science that studies heritable changes caused by the activation and deactivation of genes without any change in the underlying DNA sequence of the organism.

CPIC genotypes and phenotypes for sample drugs

Drug	Genotype	Associated phenotype	Recommendation classification[1]	CPIC provider considerations
Clopidogrel	CYP2C19*1/*1	Normal metabolizer	Strong	Use label recommendations
	CYP2C19*1/*2	Intermediate metabolizer	Moderate	Increased risk of adverse cardiovascular events; consider alternative antiplatelet therapy
	CYP2C19*1/*17	Ultra-rapid metabolizer	Strong	Use label recommendations
Codeine	CYP2D6*1/*1	Normal metabolizer	Strong	Use label recommendations
	CYP2D6*4/*10	Intermediate metabolizer	Moderate	Monitor use for response
	CYP2D6*4/*4	Poor metabolizer	Strong	Avoid codeine; consider morphine and nonopioid analgesics

1. CPIC has three levels of therapeutic recommendations: strong, moderate, and weak. They are defined as strong "evidence is high quality and the desirable effects clearly outweigh the undesirable effects"; moderate, in which "there is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects; and optional, for recommendations in between strong and weak where there is room for differences in opinion as to the need for the recommended course of action.

Source: "Epigenetics," National Human Genome Research Institute; "The genotype/phenotype distinction," *Stanford Encyclopedia of Philosophy*, 2017; "Phenotype," National Human Genome Research Institute; Mukerjee G, et al., "User considerations in assessing pharmacogenomic tests and their clinical support tools," *NPJ Genomic Medicine*, 2018; "Caudle K, et al., "Standardizing terms for clinical pharmacogenomic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium," *Genetics in Medicine*, 2016; Scott S, et al., "Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy: 2013 update," CPIC, 2013; Krews KR, et al., "Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update," CPIC, 2014; Krews KR, et al., "Supplemental material: Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for cytochrome P450 2D6 (CYP2D6) genotype and codeine therapy," CPIC, 2012; Pharmacy Executive Forum interviews and analysis.

Did you know...

- The use of genotypes and phenotypes is **most relevant in germline PGx** (i.e., hereditary genetic mutations).
- Drug metabolizing enzymes are typically grouped into five categories: **poor** metabolizer, **intermediate** metabolizer, **normal** metabolizer (previously known as extensive metabolizer), **rapid** metabolizer, and **ultra-rapid** metabolizer.
- **Phenotypes lack standard definitions** when it comes to prescribing therapeutics based on PGx results and recommendations. While CPIC has established definitions for metabolism categories, some third parties offer slightly different definitions, **which can cause variance** in PGx recommendations.

Example of genotype translation in clinical care

1 Lab tests specific genotypes

2 Lab sends discrete data to third-party software company for PGx analysis

3 Analytics software translates genotype data into phenotypes

4 Vendor inputs phenotypic data into provider EHR

5 EHR uses phenotype to flag gene-drug interactions

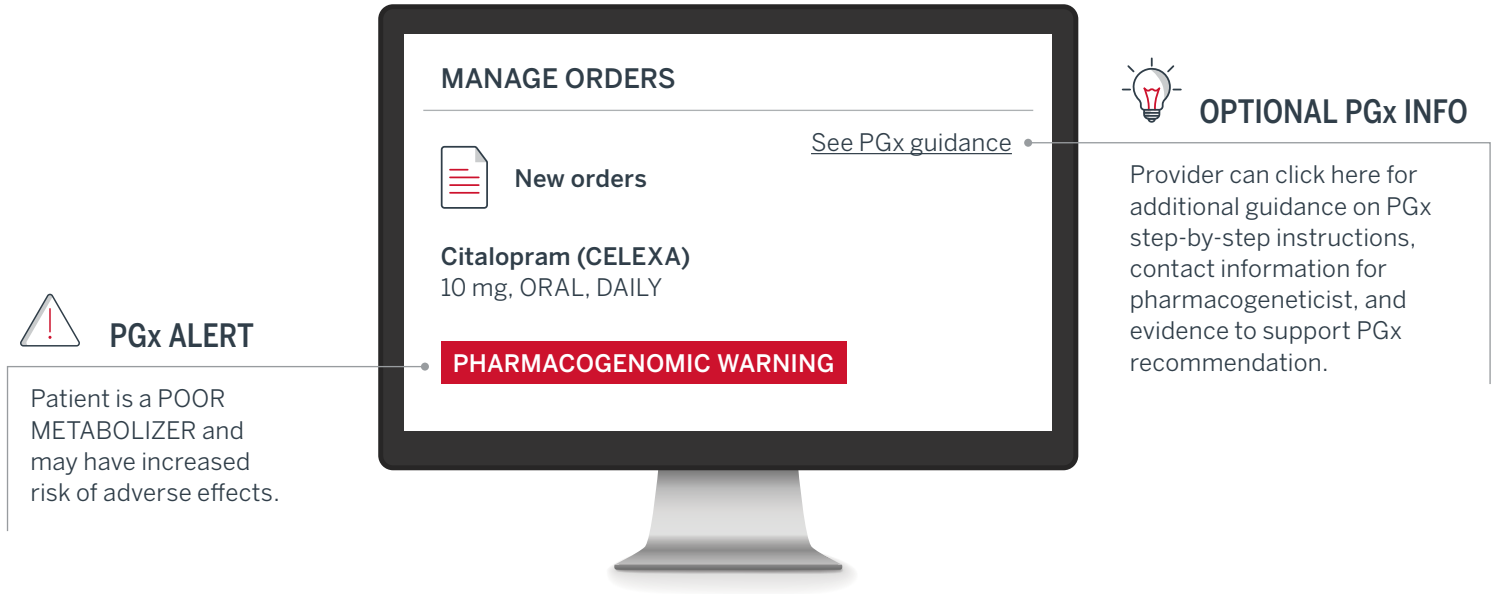
6 Provider prescribes appropriate drugs

Clinical decision support arms clinicians with actionable information

Clinical decision support (CDS) software provides clinicians with filtered knowledge and person-specific information, typically at the point of care, to enhance patient health through informed decision-making. CDS can include warnings or suggestions for the care team to consider when ordering or prescribing medications in the clinical workflow.

A number of CDS vendors offer PGx tools and software that incorporate an individual's genetic test results to help providers make evidence-based prescribing decisions. To implement PGx, providers must integrate patients' genetic information into their EHRs; otherwise, the provider cannot use CDS for PGx purposes.

Example of clinical decision support in action

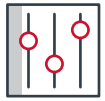


Source: "Clinical decision support," HealthIT.gov; "Clinical decision support," Agency for Healthcare Research and Quality; Pharmacy Executive Forum interviews and analysis.

Did you know...

- Many provider organizations **embed CDS** in their electronic health records to flag providers and pharmacists of known drug-gene interactions.
- CDS software **cross-references** a patient's pharmacogenomics test results with prescription ordering and available therapies **to limit adverse drug events.**
- Provider organizations with resource constraints may not be able to use PGx CDS. Instead, they will receive the test results in **PDF format** that clinicians must review manually.

Advantages of clinical decision support



REAL-TIME RECOMMENDATIONS

Incorporate evidence-based drug-gene interaction rules to inform appropriate prescribing at point-of-care

EMBEDDED LEARNING

Insert PGx how-to guides at point-of-care; add phone numbers of PGx leaders or pharmacists for providers if they have implementation questions

TRACKABLE ALERTS AND ADHERENCE

Analyze number of PGx-prompted alerts and track providers' adherence to recommendations

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