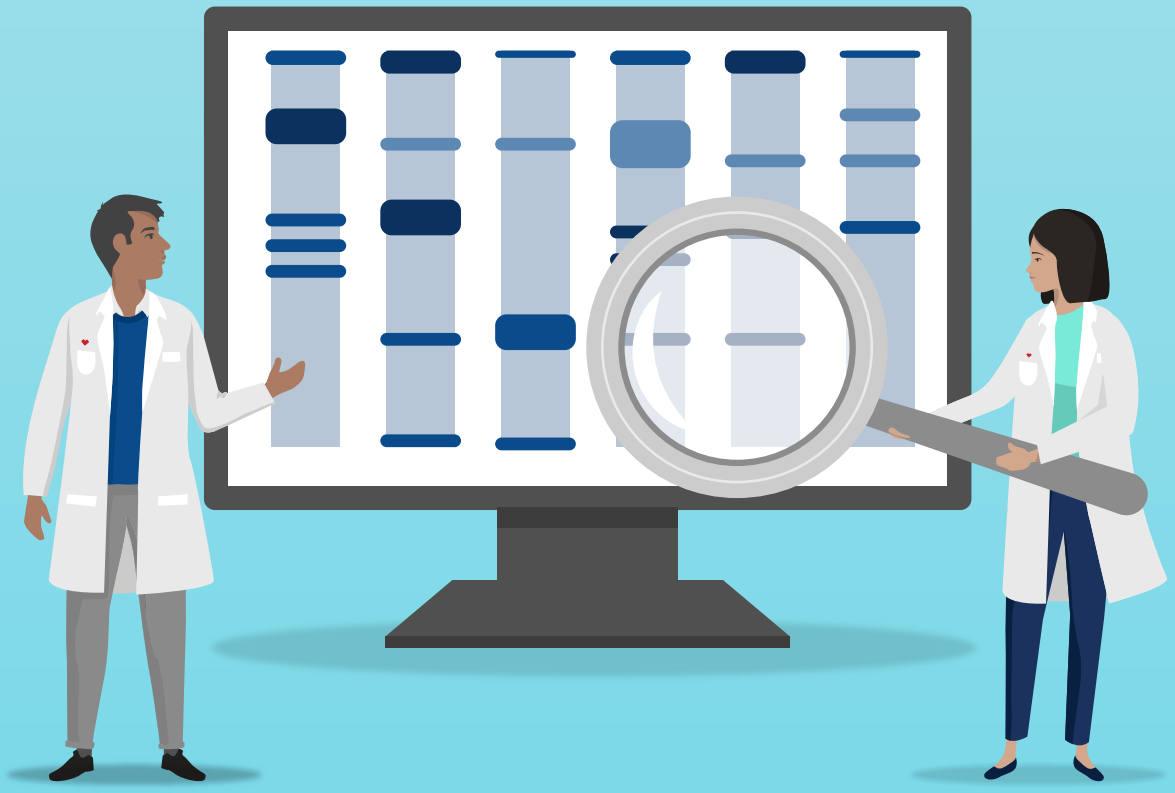
WHITE PAPER

Pharmacogenomic testing in precision medicine

Using evidence-based testing to improve outcomes, lower costs

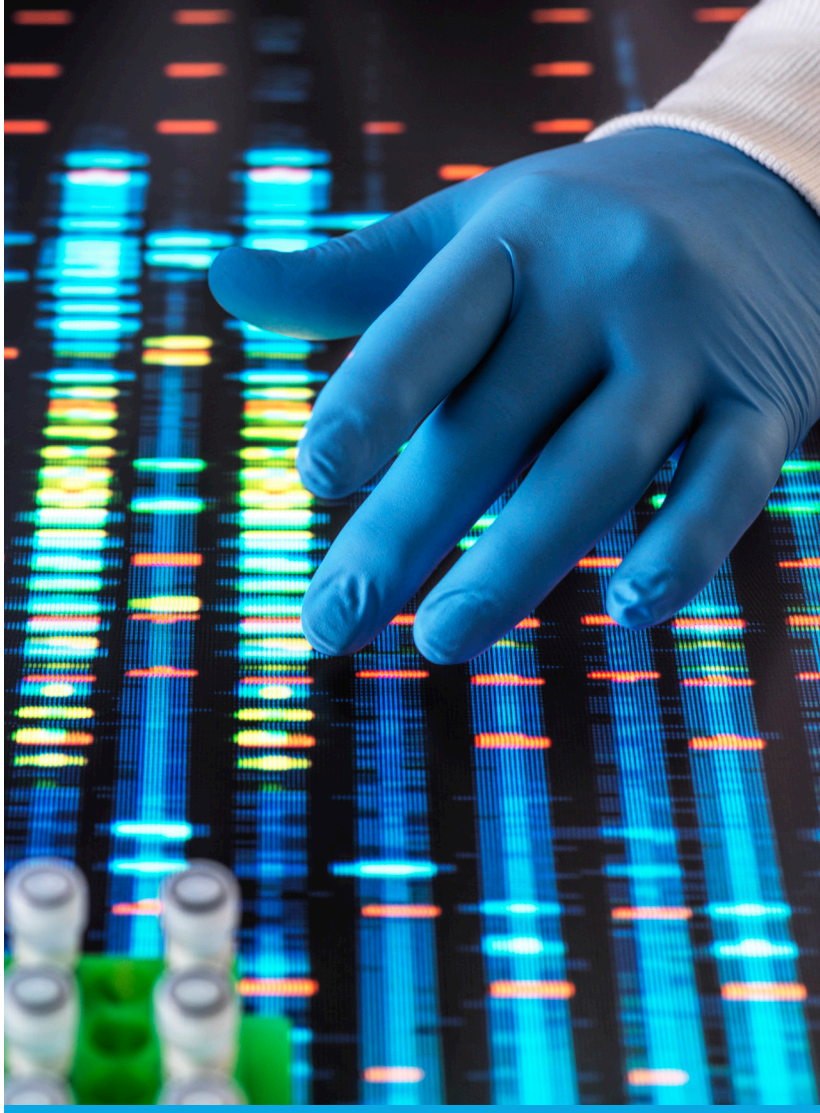


CVS Health®

Precision medicine is an innovative discipline that aims to optimize treatment of individuals or patient subgroups by using disease-specific biomarkers.

The search for acceptable biomarkers to drive precision medicine is at an all-time high.[1] A particularly exciting technology is the identification of biomarkers from genetic or molecular profiling.

Each person responds to a drug differently. Clinicians have long known that whether a treatment works for someone — and how well it works — can vary with factors such as race, gender, and age. Once the human genome was mapped and our understanding of our genetic makeup expanded, it became evident that our genes — and the variability among them — play a key role in both the likelihood of a person developing a certain condition and the way the body absorbs, distributes and clears medicines.



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Gene mutations and the importance of sequencing in treatment selection

Gene mutations

Gene mutations can be somatic — those that happen within a cell and are not inherited — or germline — inherited from a parent to a child.[2] Somatic mutations are the most common cause of cancer. These occur from damage to genes in an individual cell during a person's life. Germline mutations are far less common and may lead to hereditary cancers as well as other conditions with inherited traits like hemophilia, cystic fibrosis and Huntington's disease.

Genetic testing

Genetic testing can identify both somatic and germline mutations.[3] Somatic tissue testing can identify gene mutations that are targets for oncology drugs in cancers. Germline testing can identify mutations that enable prevention, early diagnosis or treatment. Germline testing can also better outline a patient's risk profile. For instance, certain genetic biomarkers can help identify a person's ovarian or breast cancer predisposition and prophylactic treatment can significantly reduce or prevent the onset of disease. Germline mutation testing can help guide targeted therapy in conditions such as cancer as well as identify faulty genes that can be treated by gene therapy.

Next-generation sequencing

Next-generation sequencing is a laboratory technique that allows for rapid, large-scale genetic sequencing at lower costs.[4] It has been particularly important in cancer treatment because it enables identification of multiple biomarkers on a single biopsy specimen, thereby helping determine the best targeted therapy.

Our Transform Oncology Care program is rooted in this predictive and personalized use of genetic information to select the most effective chemo and immune therapies.

Growing prevalence of biomarkers in drug labeling

So far, the U.S. Food and Drug Administration (FDA) has identified more than 400 biomarkers that appear in drug labels across a range of therapeutic areas.*[5] The proportion of drugs with genomic biomarker labeling has increased nearly threefold in the last two decades — comprising 28.2 percent of all treatments in 2020, compared to 10.3 percent in 2000.[6] Of drugs with biomarkers information in the labeling, 24.2 percent contain information on multiple biomarkers. The increased rate of reporting represents both advancements in the underlying biology of disease and a push by the FDA to enable more personalized precision medicine.

It is important to note that because a drug label includes a biomarker, that does not automatically mean that the FDA recommends testing for the biomarker be required prior to using a drug to treat a particular condition. Of the biomarkers that appear in drug labeling, only a minority have been incorporated into the labeling recommendations for dosing and administration.

The clinical utility of a biomarker depends upon the development of reliable evidence that using the biomarker enables better condition management or helps improve outcomes.

Such evidence comes largely from prospective clinical outcome studies that incorporate the biomarker into disease management.

From 2000–2020:

~3X **increase in drugs with genomic biomarker labeling[6]**

2000:

~10% **of all treatments**

2020:

~28% **of all treatments**

Where genetic testing matters

There has been a sea change in our understanding of conditions like cancer and hereditary diseases. New treatments are being developed for conditions that previously had none. Many of these are highly targeted treatments aimed at modifying the activity of a malfunctioning gene or replacing a missing one.

For example, BRAF, a common somatic mutation found in melanoma and other types of cancer cells, causes the cell to make a protein (BRAF kinase) that signals the cell to grow uncontrollably.[7] In tumors with the genetic mutation, the enzyme can get stuck in the "on" position, causing the cell to divide and expand in an uncontrolled fashion. Drugs called BRAF inhibitors can be used in individuals with this genetic marker to slow the growth of metastatic melanoma.[8] Similar mechanisms apply in a range of conditions, including many cancers.

Targeted gene therapies are a new application of genetically guided therapy. Unlike biomarker management, gene therapy involves the introduction of one or more new genes into a cell to compensate for a defective gene. It does not remove or modify the defective gene itself. These new therapies can treat — or possibly cure — diseases caused by a single gene mutation such as inherited forms of retinal blindness, spinal muscular atrophy and Duchenne muscular dystrophy, as well as acquired conditions like cancer. Specific therapies are effective only in individuals with certain genetic mutations. As with biomarker-guided treatment in somatic tumors, gene therapies for germline diseases require genetic testing. Without that personalization, the selected treatment would likely be ineffective.

Since therapies for these conditions are generally very expensive, costing in the tens and hundreds of thousands or even millions of dollars, administering them to a patient for whom a treatment may not work is wasteful. It can also result in poor patient outcomes, including adverse events, side effects, or worsening or progression of their condition — all of which could lead to even greater waste. Ensuring the right patient receives the right treatment for the correct diagnosis is vital for both payors and plan members.

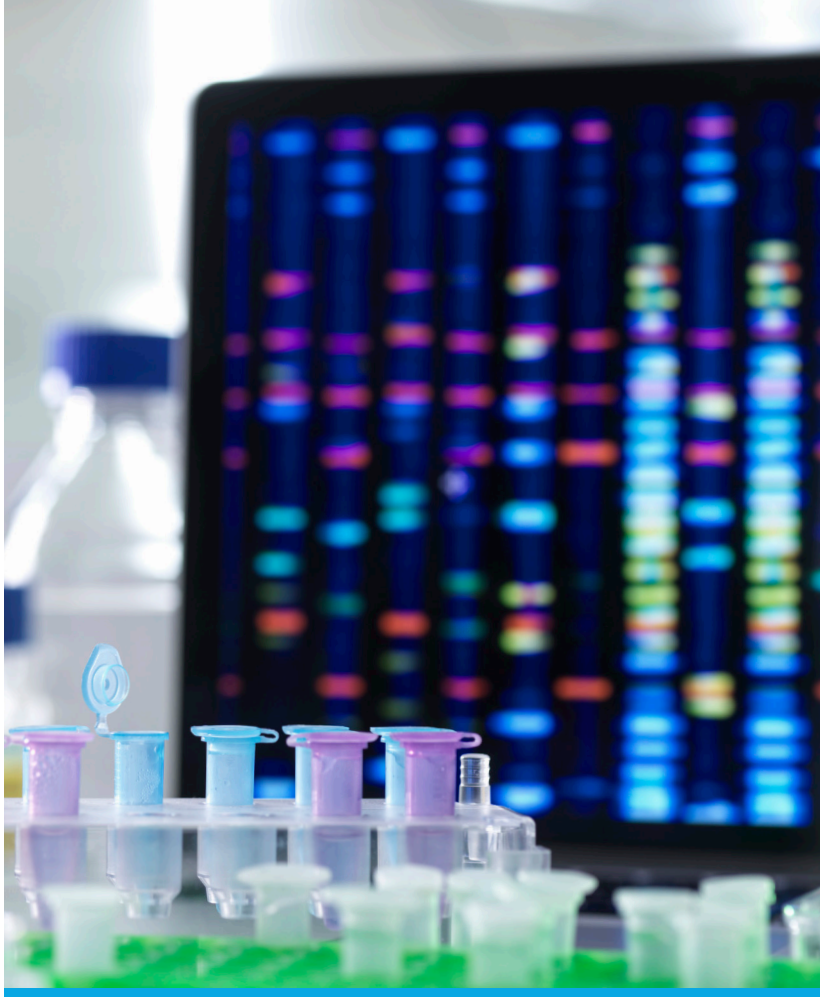
Since gene therapies are very expensive, administering them without appropriate testing to ensure they will work for a patient is wasteful.

What is pharmacogenomics?

There can be significant variability to drug response among individuals. In addition to their genetic makeup, this is also influenced by factors such as age, gender, weight, disease state (e.g., hepatic or renal disease), race, and ethnicity.

Pharmacogenomics is the branch of genetics that studies ways in which an individual's unique genetic makeup influences the response to medications. Pharmacogenomic-based variation can influence either the pharmacokinetic properties of the drug in an individual — such as the rate of absorption, distribution, metabolism, or elimination — or pharmacodynamic properties — such as how well a drug binds to a receptor site thus making the drug available in each individual. For instance, Cytochrome P450 (CYP) is the most prominent gene family influencing pharmacokinetic response by encoding for enzymes important in drug metabolism. There are 58 different human CYP genes which code for various forms of the enzyme.[9] Clinically, just four CYP genes code enzymes involved in the metabolism of as much as 60 to 70 percent of all therapeutic medications used in humans.

In theory, the identification of genetic factors that influence drug metabolism allows for personalization of drug therapy, increasing the likelihood of drug efficacy and minimizing the toxicity profile based on knowledge of each individual's genetic makeup. The potential to increase the safety and efficacy of drugs through targeted savings while also delivering cost savings is significant. CYP enzyme activity can also be affected by genetic and environmental factors, thus limiting the utility of CYP genetic test results to drive clinical decision making.



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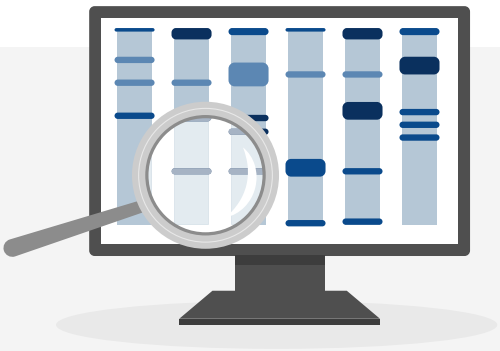
Broad-based pharmacogenomic testing not supported by literature

Currently only a relatively few pharmacogenomic tests are supported by literature and reimbursed compared to the number of tests that are being marketed as having clinical benefit. Tests backed by clinical evidence include genotyping for certain gene variants for drug effectiveness of Plavix (CYP2C19), Xenazine (CYP2D16) and Cerdelga (CYP2D6). Other examples of pharmacogenomic screening tests that are demonstrated to increase drug safety include HLA-B5701 before starting Ziagen and HLA-B1502 prior to the initiation of Tegretol in certain populations.

One area that has generated a great deal of interest in recent years is the use of CYP genetic testing to guide prescribing of SSRIs — a class of anti-depressants — for individuals with anxiety and depression.

Depression affects an estimated eight percent of all U.S. adults.[10] In addition, each individual's response to anti-depressants and the side effects they experience, varies. However, a significant body of research of broad pharmacogenomic testing has repeatedly failed to show clinical benefit in depression therapy.[11] There is some evidence that such testing may offer limited benefit to a narrow patient segment — those who failed multiple antidepressants, whether from side effects or ineffectiveness. Replicability of this finding has been limited. Future research may yield better support for testing a wider patient population. The cost of broad-based testing outweighs the cost of treatment. There cannot be cost effectiveness without clinical effectiveness.

As discussed, not all pharmacogenomic testing is clinically validated and equally relevant in clinical decision making. A large number of biomarkers included in drug labeling in cancer prescribing have been validated and incorporated into clinical care. This is as it should be because it has a clear cost and clinical benefit. And yet, a growing number of individual tests and testing panels without evidence of effectiveness are now being marketed. Further research is required before these enter wide clinical use. Similarly, pharmacogenomics in pharmacokinetics has significant potential to improve drug efficacy, safety and cost. Demonstration of clinical effectiveness is key to deriving value for patients and the health care system.



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The CVS Health perspective

Precision-based, personalized medicine — when evidence-based — has tremendous potential to help improve clinical outcomes and safety, and control overall health care costs. But the rapid expansion of pharmacogenomic testing in both direct-to-consumer and business-to-business environments has outpaced the generation of clinical validation evidence, potentially undermining its value proposition.

We recommend use of genetic testing where it is supported by evidence and incorporate it into our solutions. Our Transform Oncology Care program uses the results of broad-panel next-generation sequencing and the latest National Comprehensive Cancer Network Treatment and Supportive Care Guidelines to help providers select the most precise, appropriate treatment regimen based on the patient's clinical and genetic profile. Our oncology medical directors are available for consultations and can work with community oncology providers to identify optimal, molecular-directed drug therapy. This enables better cancer care management tailored to patient needs and treatment plans, helps enhance quality of care and outcomes, and lowers the overall cost of treating this complex condition. In addition to oncology, a number of examples of pharmacogenomic-based prescribing have been clinically validated and are in use in clinical practice.

Transform Oncology Care enables better cancer care management that:

- ✔ Is tailored to patient needs and treatment plans
- ✔ Helps enhance quality of care and outcomes
- ✔ Lowers overall cost of treatment

Our recommended approach is to prioritize the use of validated biomarkers for targeted therapies as supported by the published, peer-reviewed literature and guidance from medical professionals and health agencies.

For therapy classes where the FDA has recommended incorporating required testing recommendations into drug labels, we incorporate the requirement into our specialty guideline management criteria. Test results and appropriate documentation are required at the time of submitting a prior authorization (PA) request for specific indications and diagnosis for more than 160 treatments. By incorporating it directly into the PA process, we can ensure prescriber adoption so that treatment decisions are based on appropriate diagnosis rather than attestation alone. When test results do not support the use of a particular therapy for an individual, we can work to get the prescriber to change therapy. For all other genetic testing coverage and utilization management decisions, we utilize a systematic, case-by-case approach, based on evidence of clinical effectiveness coupled with a careful cost-benefit analysis.

We believe the future of the role of pharmacogenomic testing in precision medicine testing warrants further exploration. This will help address some of the current challenges and identify additional areas where such testing can deliver better outcomes in a cost-effective manner.

We will continue to monitor the science and economics to identify and make available testing modalities that bring value to our clients and put members on their path to better health.

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5813864/.
2. https://www.seattlechildrens.org/globalassets/documents/for-patients-and-families/pfe/pe2960.pdf.
3. https://medlineplus.gov/genetics/understanding/testing/genetictesting/.
4. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3841808/.
5. https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling.
6. Kim, J.A.; Ceccarelli, R.; Lu, C.Y. Pharmacogenomic Biomarkers in US FDA-Approved Drug Labels (2000–2020). J. Pers. Med. 2021, 11, 179. https://www.mdpi.com/2075-4426/11/3/179.
7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7408709/#:~:text=The%20BRAF%20inhibitors%20vemurafenib%2C%20dabrafenib,and%20survival%20of%20melanoma%20cells.
8. https://www.mskcc.org/cancer-care/types/melanoma/treatment/targeted-therapy-melanoma.
9. https://drnelson.uthsc.edu/cytochromeP450.html.
10. https://www.nami.org/NAMI/media/NAMI-Media/Infographics/NAMI_YouAreNotAlone_2020_FINAL.pdf.
11. Shan X, Zhao W, Qiu Y, Wu H, et. al. Preliminary Clinical Investigation of Combinatorial Pharmacogenomic Testing for the Optimized Treatment of Depression: A Randomized Single-Blind Study. Front Neurosci. 2019 Sep 13;13:960. doi: 10.3389/fnins.2019.00960. eCollection 2019.

*Some drugs have more than one biomarker and some biomarkers may be associated with more than one drug.

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