

# Pharmacogenomic Testing in Community Pharmacy

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## Abstract:

Pharmacogenomic testing, also known as personalized medicine, has gained significant attention in recent years due to its potential to optimize drug therapy by tailoring treatments to an individual genetic make up. Community pharmacies play a crucial role in patient care, and integrating pharmacogenomic testing into their practices could lead to improved medication safety, efficacy, and patient outcomes. This review aims to provide a comprehensive assessment of the current state of pharmacogenomics testing in community pharmacy settings exploring its benefits, challenges, and practical implementation strategies.

**Keywords:** Pharmacogenomic testing, community pharmacy, genetic variation.

## Introduction:

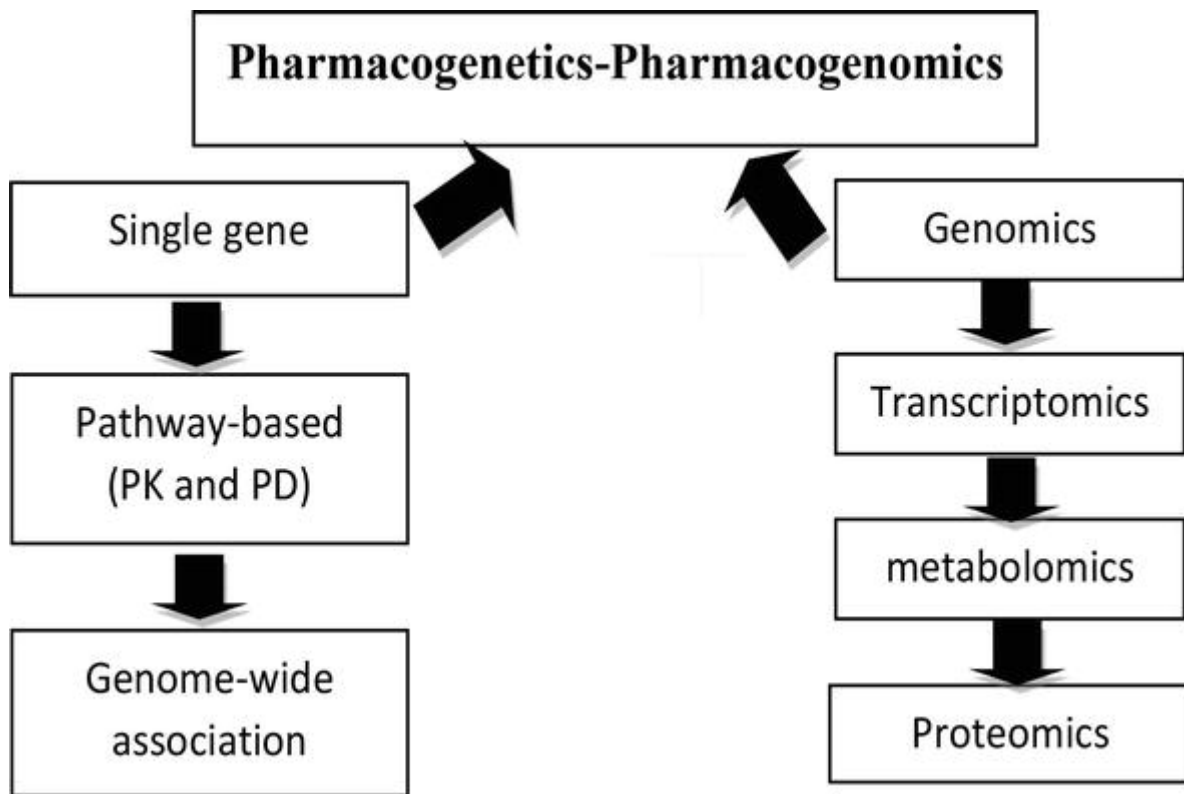
Pharmacogenomics (PGx) can help predict which medication will be most effective and safe in individual patients while potentially reducing healthcare costs. Ideally, an individual's PGx profile would be known before drug prescription – an approach known as pre-emptive PGx testing or PGx screening – rather than being determined after observing low therapeutic response or adverse drug reactions (ADRs). Potential benefits of introducing PGx screening into a routine healthcare setting include reduced hospitalizations and cost, and improved safety, adherence and efficacy. Dutch national guidelines on practical application of PGx for drug prescription developed by the Dutch Pharmacogenetics Working Group (DPWG) are available through the Dutch drug database, referred to as the G-standard. Based on these DPWG guidelines, it is estimated that an alternative dosage or drug would be recommended for 1 in 20 drug prescriptions in primary care if PGx screening became the standard-of-care in the Netherlands. Nevertheless, PGx is rarely applied in current clinical practice.

A number of barriers to PGx implementation have been identified so far. These include unclear procedures, insufficient evidence, inefficient infrastructure, lack of a standardized format for reporting results, lack of ICT support tools, and lack of knowledge, training and experience among healthcare practitioners (HCPs).

Reported facilitators include recognition of clinical utility, pharmacist’s feelings of responsibility for delivering PGx to patients, and the availability of professional guidelines for interpreting test results. To the best of our knowledge, no study has identified barriers and facilitators from the perspective of all the relevant stakeholders in an actual implementation setting. Therefore, we carried out an explorative pilot study to identify such barriers and facilitators while offering PGx screening in two outpatient clinics of the University Medical Center of Groningen (UMCG) in the Netherlands.

**Basics of pharmacogenomics:**

In pharmacogenomic, genomic information is used to study individual responses to drugs. When a gene variant is associated with a particular drug response in a patient, there is the potential for making clinical decisions based on genetics by adjusting the dosage or choosing a different drug, for example. Scientists assess gene variants affecting an individual's drug.



**Fig:1 Pharmacogenetics-pharmacogenomics.**

response the same way they assess gene variants associated with diseases: by identifying genetic loci associated with known drug responses, and then testing individuals whose response is unknown. Modern approaches include multigene analysis or whole-genome single nucleotide polymorphism (SNP) profiles, and these approaches are just coming into clinical use for drug discovery and development.

When studying drug action in individuals, researchers focus on two major determinants: how much of a drug is needed to reach its target in the body, and how well the target cells, such as heart tissue or neurons, respond to the drug. The scientific terms for these two determinants are pharmacokinetics and pharmacodynamics, and both are critical considerations in the field of pharmacogenomics<sup>(1)</sup>

**Pharmacogenomics individualised prescribing:**

There is a relatively small number of genes for which there is a high level of evidence that genetic analysis should inform individualised prescribing. Many of these genes regulate the absorption, distribution, metabolism and excretion (ADME) of medications. The ADME processes determine what level of ‘exposure’ a patient will have to a medication. The speed of biochemical pathways involved in the metabolism of medications – for example, by the cytochrome P450 (CYP) class of enzymes – differs between individuals, resulting in an up to 100-fold variation in exposure to medications. This often explains why patients can respond differently to the same medication at the same dose.<sup>(2)</sup> Genetic differences in the ADME genes presumably reflect evolutionary responses to different environmental toxins in the distant past. Testing a patient for gene variants that cause extremes of medication exposure (too high or too low) can provide insight into why a patient is responding to a medication in a certain way, or perhaps not responding at all.

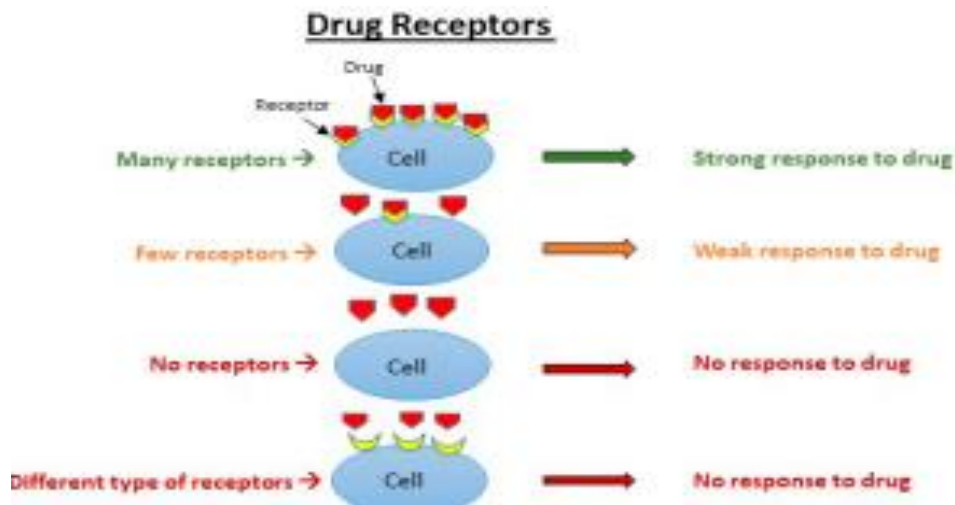
There is another group of genes that are not involved in ADME but influence medication responses directly. Some of these genes are predictive of severe and potentially life-threatening immune-mediated toxicities. Knowledge of whether a patient is susceptible to such reactions means that particular medications can be avoided; for example, carbamazepine should not be prescribed to patients with certain human leucocyte antigen (HLA) genotypes because of an increased risk of Stevens-Johnson syndrome and toxic epidermal necrolysis. The potential for immune-mediated toxicities is probably specific for each medication rather than being generalised to a class of medications. Knowledge of the gene variants influencing exposure or response (ie pharmacogenomics) allows prescribers to move from the general to the particular, and provide a scientific basis for individualised prescribing. The goal is more effective and safer choices of medication and dose (refer to Case studies).<sup>(3)</sup>

**Process of the pharmacogenomic testing:**

Pharmacogenomic tests use a sample of saliva, blood, or a buccal (cheek) swab as a source of genetic material. Once collected, the sample is processed through a series of steps that result in DNA extraction, purification, and genotyping. The results of genotyping are then relayed to the care provider.<sup>(6)</sup> Pharmacogenomic tests can be performed on single genes or can provide an analysis of multiple genes at once. Using proprietary algorithms, many pharmacogenomic tests that include multigene panels provide colour-coded assessments of the suitability of medications based on results of testing. For example, medications categorized as green can be prescribed as directed and yellow-coded drugs have the potential for moderate gene-drug interactions.<sup>(7)</sup>

**Work of pharmacogenomic testing:**

Drugs interact with your body in numerous ways, depending both on how you take the drug and where the drug acts in your body. After you take a drug, your body needs to break it down and get it to the intended area. Your DNA can affect multiple steps in this process to influence how you respond to the drug. Some examples of these interactions include

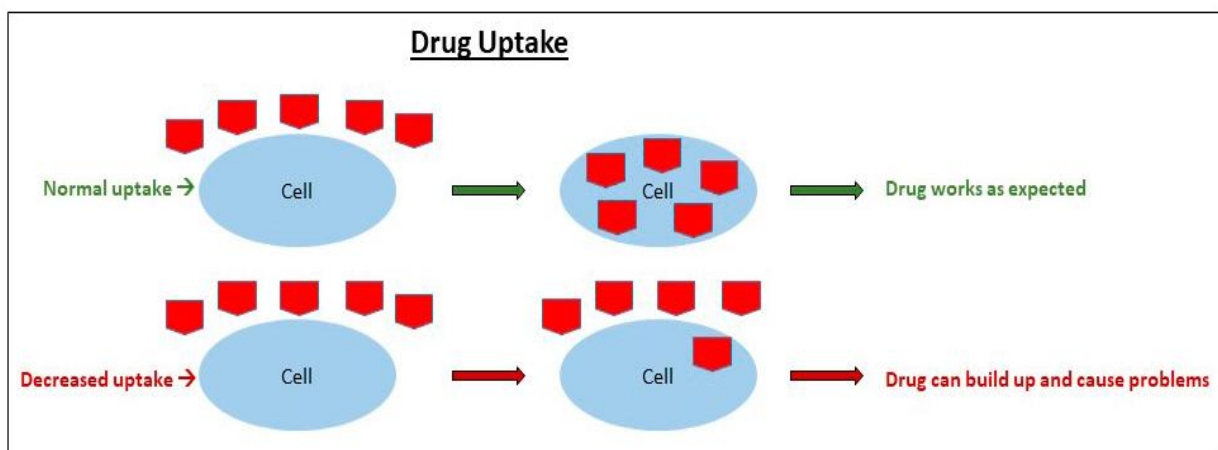


**Fig:2 Drug receptors.**

**Drug Receptors.** Some drugs need to attach to proteins on the surface of cells called receptors in order to work properly. Your DNA determines what type of receptors you have and how many, which can affect your response to the drug. You might need a higher or lower amount of the drug than most people or a different drug.

**Example: Breast Cancer and T-DM1.** Some breast cancers make too much HER2, a receptor, and this extra HER2 helps the cancer develop and spread. The drug T-DM1 can be used to treat this type of breast cancer and works by attaching to HER2 on cancerous cells and killing them. If you have breast cancer, your doctor may test a sample of your tumor to determine if T-DM1 is the right treatment for you. If your tumor has a high amount of HER2 (HER2 positive), your doctor may prescribe T-DM1. If your tumor does not have enough HER2 (HER2 negative), T-DM1 will not work for you.

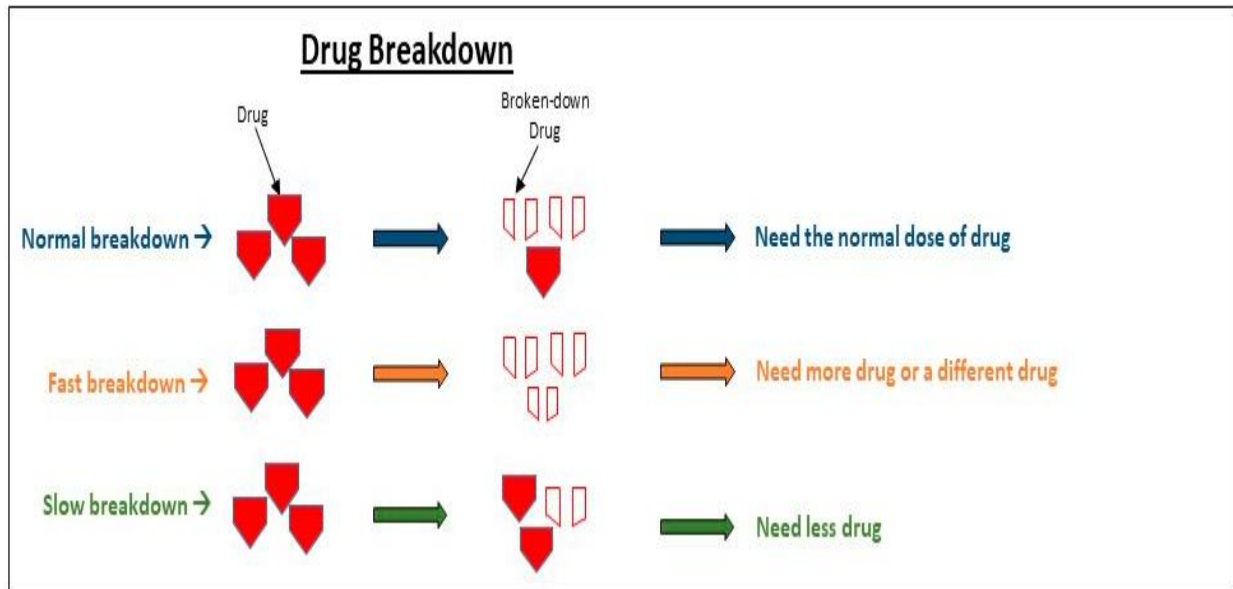
**Drug Uptake.** Some drugs need to be actively taken into the tissues and cells in which they act. Your DNA can affect uptake of certain drugs. Decreased uptake can mean that the drug does not work as well and can cause it to build up in other parts of your body, which can cause problems. Your DNA can also affect how quickly some drugs are removed from the cells in which they act. If drugs are removed from the cell too quickly, they might not have time to act.



**Fig:3 Drug uptake.**

**Example: Statins and Muscle Problems.** Statins are a type of drug that act in the liver to help lower cholesterol. In order for statins to work correctly, they must first be taken into the liver. Statins are transported into the liver by a protein made by the *SLCO1B1* gene. Some people have a specific change in this gene that causes less of a statin called simvastatin to be taken into the liver. When taken at high doses, simvastatin can build up in the blood, causing muscle problems, including weakness and pain. Before prescribing simvastatin, your doctor may recommend genetic testing for the *SLCO1B1* gene to check if simvastatin is the best statin for you or to determine what dose would work best.

**Drug Breakdown.** Your DNA can affect how quickly your body breaks down a drug. If you break the drug down more quickly than most people, your body gets rid of the drug faster and you might need more of the drug or a different drug. If your body breaks the drug down more slowly, you might need less of the drug.



**Fig:4 Drug breakdown.**

**Example: Depression and Amitriptyline.** The breakdown of the antidepressant drug amitriptyline is influenced by two genes called *CYP2D6* and *CYP2C19*. If your doctor prescribes amitriptyline, he or she might recommend genetic testing for the *CYP2D6* and *CYP2C19* genes to help decide what dose of the drug you need. If you breakdown amitriptyline too fast, you will need a higher dose for it to work, or you may need to use a different drug. If you breakdown amitriptyline very slowly, you will need to take a smaller dose or will need to take a different drug to avoid a bad reaction.

**Targeted Drug Development.** Pharmacogenomic approaches to drug development target the underlying problem rather than just treating symptoms. Some diseases are caused by specific changes (mutations) in a gene. The same gene can have different types of mutations, which have different effects. Some mutations may result in a protein that does not work correctly, while others may mean that the protein is not made at all. Drugs can be created based on how the mutation affects the protein, and these drugs will only work for a specific type of mutation.

**Example: Cystic Fibrosis and Ivacaftor.** Cystic fibrosis is caused by mutations in the *CFTR* gene which affect the CFTR protein. The CFTR protein forms a channel, which acts as a passageway to move particles across the cells in your body. For most people the protein is made correctly, and the channel can open and close. Some mutations that cause cystic fibrosis result in a channel that is closed. The drug ivacaftor acts on this type of mutation by forcing the channel open. Ivacaftor would not be expected to work for people with cystic fibrosis whose mutations cause the channel not to be made at all. **Example: Cystic Fibrosis**

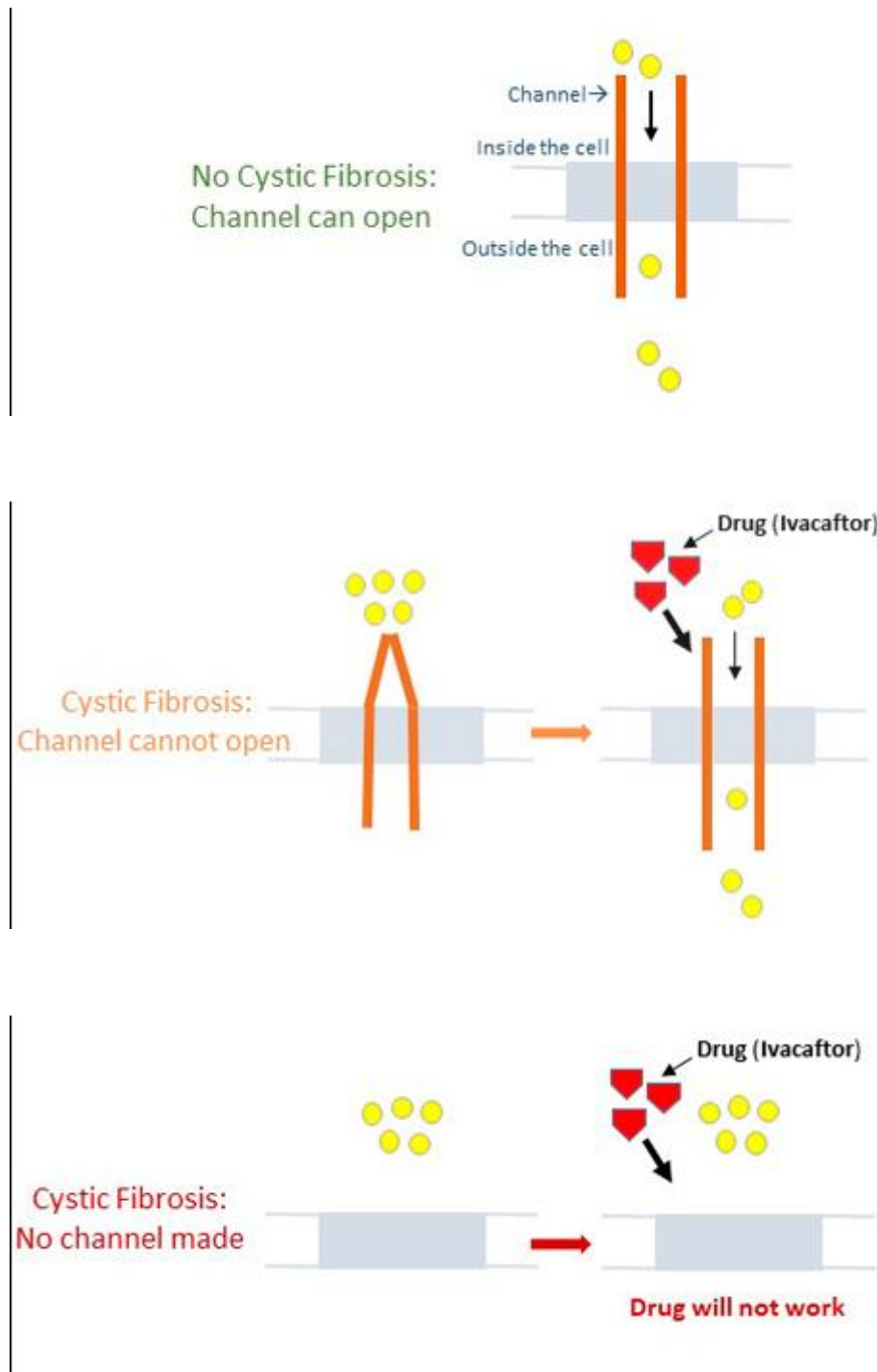


Fig:5 Examples of cystic fibers.



**The future role of pharmacy in pharmacogenomics:**

Pharmacists are key professionals working on the frontline of healthcare and are the experts in medicines. Their unique training in science and healthcare enables pharmacists to articulate complex medicines issues in a patient-friendly way. International evidence demonstrates diverse opportunities for pharmacists 'and pharmacy teams' in PGx across all sectors of pharmacy.<sup>(4)</sup>

Pharmacists and pharmacy teams increasingly lead and support the development and delivery of new services, utilising their clinical expertise to advise on when and where PGx testing could be piloted. They have the fundamental pharmacological understanding to optimise the use of PGx test results for better patient outcomes. PGx is a natural expansion of the role of the pharmacist and the pharmacy team when it becomes part of everyday practice.<sup>(5)</sup>

**Benefits of pharmacogenomic:**

Pharmacogenomics (PGx) is the study of how variations in the human genome dictate a person's response to medications. In one study, more than 99% of people assessed had a genotype associated with a higher risk to at least one medication.<sup>1</sup> Findings from pharmacogenomics research can lead to better future outcomes for both individuals and healthcare providers through improved medication safety and efficacy and lowered medical costs.<sup>(5)</sup>

**Need pharmacogenetic testing:**

Your provider may order these tests before you start a certain medicine. You may also need a pharmacogenetic test if you are taking a medicine that's not working and/or causing serious side effects. Pharmacogenetic tests are not available for all medicines. Examples of common medicines that have pharmacogenetic tests include:

- Abacavir, an HIV treatment.
- Carbamazepine, a epilepsy treatment.
- Tamoxifen, a breast cancer treatment.
- Warfarin and clopidogrel, blood thinners.

**Applications:**

Pharmacogenomic testing has applications in many fields of medicine, including:

- Cardiology.
- endocrinology.
- gastroenterology.
- hematology.
- immunology.
- neurology.
- oncology.
- psychiatry.<sup>(8)</sup>

**Pharmacogenomic testing for psychotic disorders:****Moods disorders:**

Relative to other psychiatric disorders, the clinical effectiveness of pharmacogenomic testing for mood disorders, including major depressive disorder, bipolar disorder, and other depressive disorders, appears to have the largest volume of clinical studies published to date.

**Schizophrenia:**

In a single-blind RCT, 311 people aged 18 years or older who were diagnosed within the schizophrenia spectrum were randomized to receive antipsychotic drug treatment guided by pharmacogenomic testing, antipsychotic drug treatment guided by structured clinical monitoring, or treatment as usual. Within the pharmacogenomic testing group, attending psychiatrists were provided information on patients' cytochrome P450 2D6 and 2C19 (*CYP2D6* and *CYP2C19*) genotype, which could be used to inform prescription decisions based on the CYP guidelines.

Participants within the structured clinical monitoring group were assessed for treatment effects, adverse effects, and attitudinal and behavioural factors influencing patient adherence routinely, which could be used to adjust treatment selection or dosing if deemed appropriate. Participants in the control group received standard care, assessment of symptoms at fixed time points was not required, and the CYP test results were concealed. The study found that there was no significant difference in antipsychotic drug persistence (i.e., the time in days to the first modification of the initial antipsychotic treatment) between the pharmacogenomic-guided group and the control group, suggesting the prescribing that was guided by pharmacogenomic testing did not improve tolerability or effectiveness.<sup>(9)</sup>

**Autism spectrum disorders:**

An observational cohort study by Arranz and colleagues examined the effectiveness of a pharmacogenomic intervention that evaluated genetic variants in *CYP1A2*, *CYP2C19*, *CYP2D6*, and *SLC6A4* genes in people with autism spectrum disorders. A total of 42 individuals with treatment-resistant autism spectrum disorders were included in the intervention group, while 62 individuals with autism spectrum disorders were included in the control group that received no pharmacogenomic intervention. Of the 42 individuals in the pharmacogenomic testing group, 39 (93%) experienced improvement in their Clinical Global Impression (CGI) scores, and 37 (88%) experienced improvement in their Children's Global Assessment Scale (CGAS) scores. The proportion of people who experienced treatment response was higher in the intervention group than in the control group, in which 41 individuals (66%) were classified as responders (i.e., they had improvements in CGI and CGAS scores after treatment).<sup>(10)</sup>

**Pharmacogenomic in heart failure:**

Heart failure has reached epidemic proportions. Approximately 5 million adults have heart failure in the United States with recent projections suggesting that by 2030, the prevalence of this syndrome will increase another 25%. Thus, heart failure has tremendous impact on the health care system and constitutes a major medical and societal burden. Heart failure is characterized by insufficient cardiac performance to meet metabolic requirements or accommodate systemic venous return. The body's neurohormonal system including the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS) is activated in order to compensate for these deficiencies but activation of these systems contribute to



worsening heart failure, worsened quality of life, and poor outcomes such as the need for a heart transplant, or sudden cardiac death.<sup>(11)</sup>

Evidence-based medical therapies that suppress these responses can substantially reduce the progression of this syndrome. Accordingly, comprehensive heart failure management guidelines from both the American College of Cardiology (ACC)/American Heart Association (AHA) and the Heart Failure Society of America (HFSA) recommend specific pharmacological management, mostly focused on neurohormonal suppression, to improve outcomes in all patients with heart failure and reduced ejection fraction.  $\beta$  blockers and angiotensin converting enzyme (ACE)-inhibitors are considered the foundation, but evidence has shown important roles for other therapies which help delay progression of heart failure and reduce mortality including angiotensin receptor blockers (ARB)s, aldosterone antagonists, hydralazine/isosorbide combination, and even device therapies such as implanted defibrillators and cardiac resynchronization therapy (CRT).

In addition, while there is no evidence for mortality benefits with loop diuretics and digoxin, these agents are indispensable, improving symptoms and possibly reducing hospitalizations. It is thus evident that heart failure patients are currently subjected to a multiplicity of medications to achieve maximum benefit and optimized outcomes.

This polypharmacy in heart failure patients is associated with increased risk of toxicity, drug interactions, and poor compliance. Current guidelines do offer some advice regarding tailoring of therapy on clinical grounds; for example, the HFSA guidelines recommend that factors such as age, ethnicity, heart failure severity, renal function, and serum potassium should be used to choose which of the many agents a heart failure patient should receive in his or her regimen. However, even in patients who appear to have similar clinical factors, a great deal of variability exists in response to treatment.

Genetic variability in response to heart failure treatment exists and genetic information may complement conventional clinical information in tailoring therapy to an individual patient, ultimately improving outcomes. The present review focuses on available data from pharmacogenomic studies in heart failure medications, particularly focusing on new developments over the past 2 years (earlier literature has been nicely described elsewhere summarized by medication class).

Proof-of-principle findings are presented that are important to be aware of, but actionable genetic testing to guide therapeutic choices in heart failure remains limited to date. Thus, the review also shows that further work in this area is needed before the clinical implementation of heart failure pharmacogenomics becomes a reality, and we provide a glimpse of the future needs and directions.

### **Uses of pharmacogenomics:**

Pharmacogenetic testing may be used to:

- Find out whether a certain medicine could be effective for you.
- Find out how much of the medicine you need.
- Predict whether you will have a serious side effect from a medicine.

### **Methods:**

Clinicians and research scientists can use various technologies for genotyping for pharmacogenomics.

One method is:

**Quantitative polymerase chain reaction (qPCR):**

which “is ideal for routine testing of samples up to about 120 genetic targets because it enables a low cost per sample and a fast time-to-results,” Fonseca says. “

**Real-Time PCR Solutions for Pharmacogenomics:**

featuring TaqMan Assays and QuantStudio instruments, is a good example of this technology.” Thermo Fisher Scientific’s Digital Science offering includes cloud-based data analysis apps for genotyping, which Fonseca says, “enable users to maximize the value of their data, through features such as improved visuals and integrated traces of allelic discrimination plots that allow thorough quality control of SNP assays to accurately reflect the true signals versus background noise.

**Microarrays:**

On the other hand, can test thousands of genetic targets. “This is the best choice when you want the maximum amount of data available, such as in translational research applications or preemptive screening of participants in pharmaceutical clinical trials,” Fonseca notes. The Applied Biosystems PharmacoScan Solution is a good example of this technology. Combining this with Thermo Fisher Scientific’s “Precision Medicine Diversity Array with the Axiom Plus workflow can characterize both SNP variants and copy-number variation with a single assay,” Fonseca says.<sup>(12)</sup>

**Conclusion:**

Pharmacists believe pharmacogenomics knowledge is important to the profession, but they lack the knowledge and self-confidence to act on the results of pharmacogenomics testing and may benefit from pharmacogenomics education.

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