# Pharmacogenomics Revolution

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# Pharmacogenomics (PGx) uses a patient's genetic profile to optimize drug safety, efficacy and enables drug choice

## Why is PGx important?


Most medications don't work for everyone

**Up to 70%**

Up to 70% of patients treated with top-selling medications*

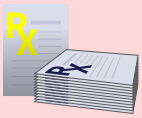
**82%**

82% of American adults take at least one medication

**3 million**

Adverse drug reactions affect nearly 3 million people and are the 4th leading cause of death in the US [2,3]

**5 billion**




More than 5 billion prescriptions are written every year [4]

## What can PGx testing do?

Enables precise prescribing decisions

Reduces trial and error

Helps predict effective, safe medications and doses

Lowers health care costs [5,6]

Helps reduce health disparities [7]

## PGx research can impact:

Psychiatry and mental health

Cardiology

Oncology


Pain management

Perioperative care and post-operative care



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# PHARMACOGENOMICS

## FINDING THE RIGHT DRUG FOR THE RIGHT PERSON

**Patient requiring medication**

**Standard approach**

The patient is **prescribed a medicine** for their health problem often at a set dose – a one-size-fits-all approach

The patient's genes affect how they **respond to the medicine** and whether they have side effects

The **prescription is changed or adjusted** to suit the person

**Medication stopped**

**Dose lowered**

**Dose increased**

**Pharmacogenomic approach**

The patient has a **pharmacogenomic test** – a blood test carried out once in a person's lifetime

The patient is given **the right medicine at the right dose** for them

# WHAT IS PHARMACOGENOMICS?

Pharmacogenomics refers to the interface between drugs and genomics, using a patient's genetic information to improve therapeutic effect and decrease inadvertent harm by giving a drug and dose that are optimal. It may also inform more targeted therapeutic drug or clinical monitoring.

The word "pharmacogenomics" is combined from the words pharmacology and genomics.

- Pharmacology deals with the uses and effects of medications.
- Genomics deals with understanding genes and their roles.

Genes carry information that you inherit from your parents. Genes determine which characteristics you have, such as your eye color and blood type.

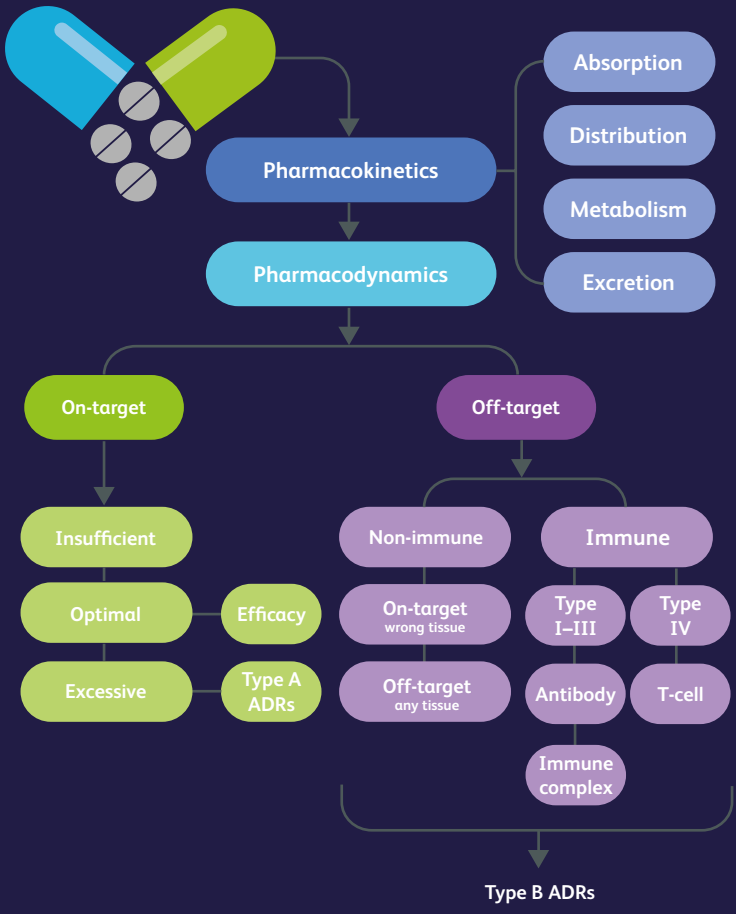
Your genes influence how your body responds to medications.

As everyone has a unique genetic makeup, this can affect how you will respond or react to certain medications.

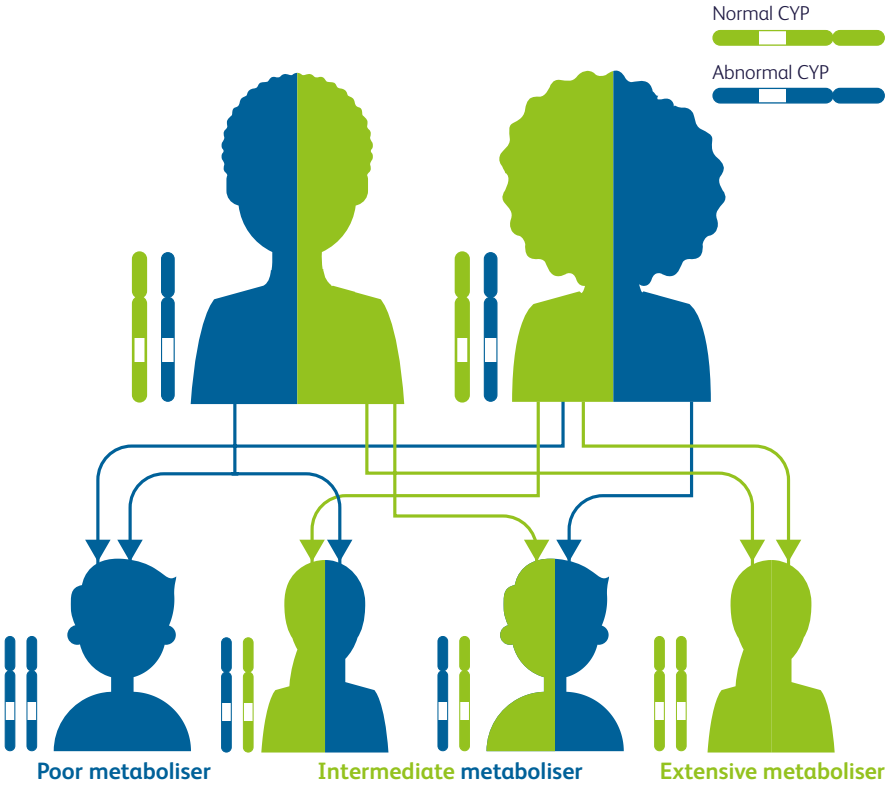
A medication or dose that works for one person may be ineffective or cause harmful side effects in another.

Through pharmacogenomics testing, personalized medicine treatment plans can be developed based on each patient's genetic makeup, to determine optimal drugs and dosages, and limit harmful side effects.

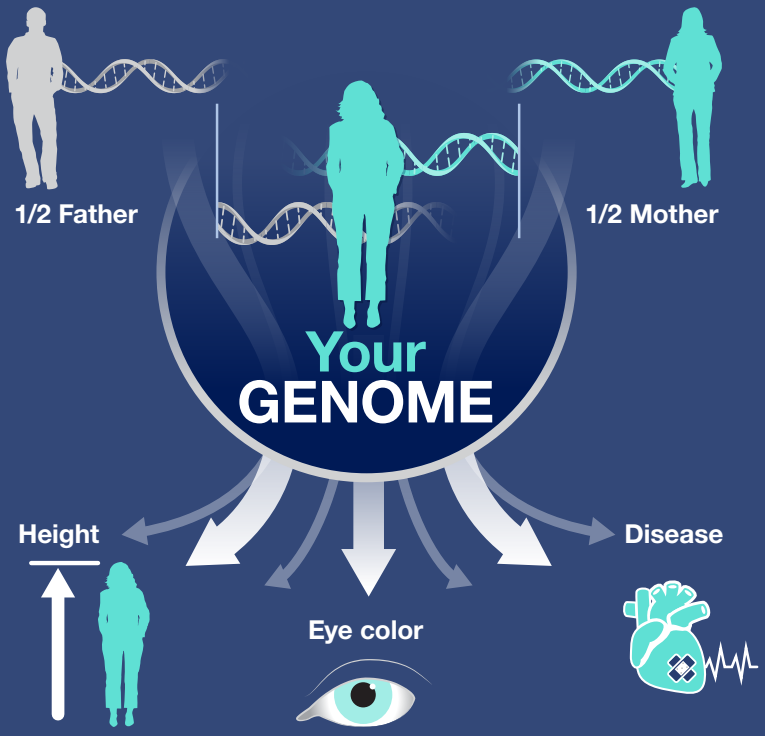
This is based on an understanding of how genetic variants affect drug absorption, metabolism, distribution and excretion (pharmacokinetics), as well as drug targets such as receptors, enzymes and ion channels (pharmacodynamics).



Cytochrome P450 enzymes (CYPs) commonly impact drug metabolism, and are coded by genes (sometimes called pharmacogenes) that vary in the population. Differential metabolism by such enzymes can lead to diverse metabolizer phenotypes, ranging from ultrarapid (able to metabolize a drug at a much greater rate than the population mean) to poor (complete lack of metabolism or lower rate of metabolism than the population mean) metabolizers.



Humans have a germline (nuclear) and a mitochondrial genome present in most cells of the body. The nuclear genome is transmitted from both parents (germline DNA) and follows Mendelian inheritance, while the mitochondrial genome is exclusively maternally inherited. Sequence variations within these genomes can affect the pharmacokinetics and pharmacodynamics of drugs. The focus of this report is on germline and mitochondrial DNA variation. It does not cover somatic genetic mutations, which are alterations that occur after conception or arise in a clonal manner in a malignancy. In oncology, knowledge of somatic gene driver mutations is now successfully used in targeted therapies for cancer.



## WHY SHOULD I HAVE PHARMACOGENOMIC TESTING?

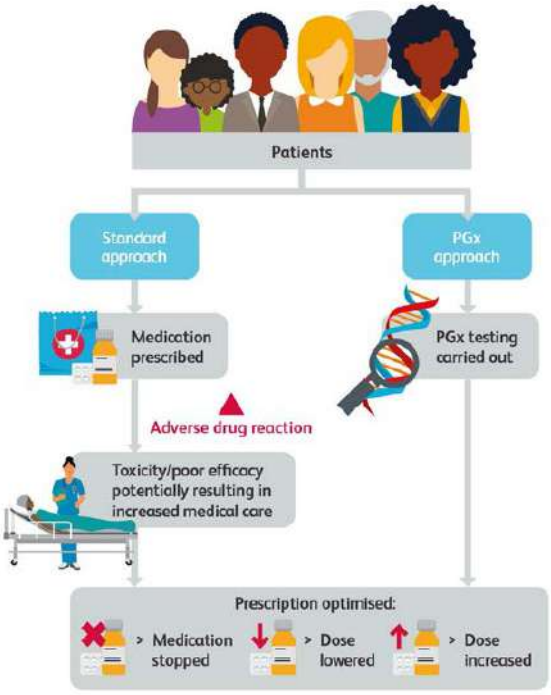
The purpose of pharmacogenomic testing is to find out if a medication is right for you.

- Pharmacogenomic testing can help to determine:
- How likely a medication is to work for you
- The best dose of a medication
- If you could have serious side effects from a medication

Testing patients prior to beginning treatment may help determine their response to certain drug classes and help avoid drugs that may be ineffective or cause harmful side effects. For patients currently on treatment, it may identify new treatment options or identify why current treatments aren't working.

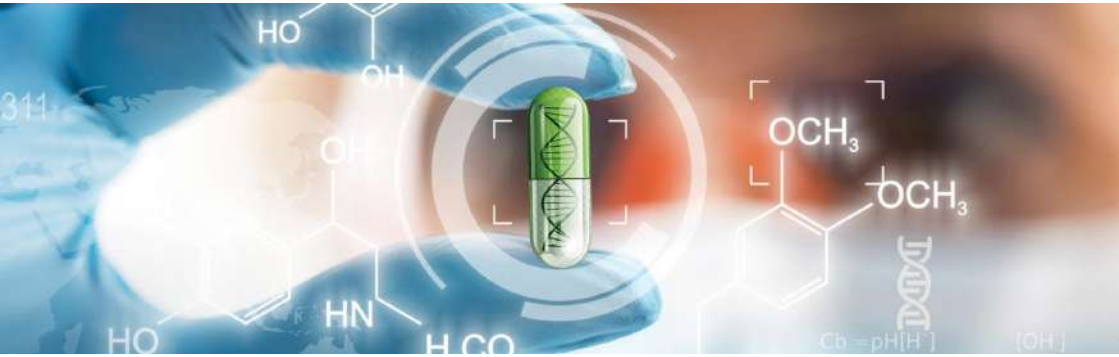
### Advantages of PGx testing may include:

- Decreasing and potentially eliminating the need for a "trial and error" approach to find effective therapy and dosages
- Decreasing the number of adverse drug reactions a patient experiences
- Saving patients time and money on ineffective medications
- Decreasing the amount of time patients are on medication
- Improving patient quality of life by finding effect treatments faster



## HOW LONG DOES IT TAKE TO GET THE RESULTS BACK?

Results for most pharmacogenomic tests are available within a week or two.




## WHAT SHOULD I DO WITH MY TEST RESULTS?

Talk to your physician about the results. They may recommend that you:

Keep taking a medication, Change the dose of a medication, Stop taking a medication, or Take a different medication.

## HOW IS PHARMACOGENOMICS RELATED TO PERSONALIZED MEDICINE?

Pharmacogenomics is part of an expanding area of health care called precision, or personalized, medicine. In personalized medicine, health care is tailored to the patient's unique needs. The goal of personalized medicine is to better predict, prevent, diagnose, and treat diseases to help patients live longer and healthier lives.

# WHAT WILL THE RESULTS FROM PGx TELL ME?

## How you process different types of drugs

- Variations in genes influence how quickly or how thoroughly individuals metabolize specific drugs. Individuals may be classed as a poor, intermediate, normal or ultra-rapid metabolizer for certain drugs.
- More than 75 % of people have variations in drug metabolism that fall outside of what is regarded as "normal" metabolizers. In some cases, these differences can cause significant side effects or mean the medication is ineffective. In severe cases, side effects may be life threatening.

## Likelihood to respond to a given medication

- In a patient classified as a "poor" metabolizer, some drugs will not be processed effectively by the body, resulting in no response or minimal response which may require the selection of alternative medication.
- In patients who are classified as an "ultra-rapid" metabolizer, the drug is processed and removed from the body rapidly. This may mean that the drug is less effective at the standard dose, requiring a higher dose to be effective.

## Risk of an adverse drug reaction (ADR)

- In a patient classified as a "poor" metabolizer, drugs may be eliminated slowly and accumulate in the body, requiring a lower than normal dose to avoid adverse reactions.
- For patients who are classified as an "ultra-rapid" metabolizer, some drugs may be processed quickly leading to rapid onset of the drug's effect and increased side effects, requiring a reduction in the drug dosage to achieve the desired outcome.

## WHO SHOULD HAVE PGx TESTING DONE?

PGx testing is available to everyone but may be most useful for patients who are currently on or about to begin taking medications for any of the conditions covered. It may also be useful for people who have tried numerous drugs to find one that may effectively treat their symptoms.

PGx is particularly relevant in psychiatry where antidepressants are essential components in treatment. 30-50 % of patients do not respond to their first antidepressant, and lengthy trials are often required before the optimal treatment type and dose is identified.

Patients who have had genetically-guided prescribing may have a greater chance of remission compared to patients without genetic prescribing.

Our PGx panel also covers over 100 common drugs. For patients who are about to commence treatment, this may help identify which drugs are likely to be effective. For patients who are currently on treatment, PGx testing may identify new treatment options, or identify if or why current medications aren't effective.

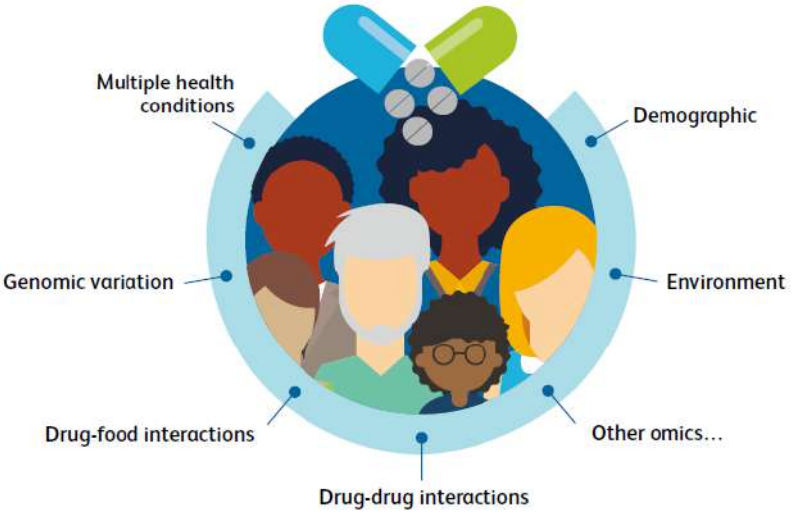
## WHAT ARE ADVERSE DRUG REACTIONS?

We all have some unique differences in our genes, which means that some medicines might work well for us, while others may not. Some people react badly to certain medications. This is what doctors call an adverse drug reaction (ADR). Adverse drug reactions can range from mild to severe, and can even be life-threatening. When this occurs, the offending medication needs to be identified, stopped, and replaced with a different medication which is safer or better tolerated. Pharmacogenomic testing has been shown to reduce the risk of developing an ADR.

## WHICH OTHER FACTORS COULD AFFECT MY RESPONSE TO A MEDICATION?

Apart from your unique genetic makeup, other factors that can affect how you respond to medication include:

- Age
- Weight,
- Height




## HOW MANY TIMES DO I HAVE TO DO MY PHARMACOGENOMICS TEST?

Pharmacogenomic testing only needs to be done once in a lifetime as your genetic makeup never changes. You will always be able to refer back to your test results when you need to take a new medication. Your test results can be used as a reference each time that your doctor or pharmacist needs to decide on the most appropriate medication for a particular ailment.

## DO I HAVE TO BE TAKING ANY MEDICATION TO DO THE TEST?

No, the test measures how your genes influence your response to certain medications. It is not affected by the actual medicine you are taking.

## WHO SHOULD HAVE THIS TEST?

Any person of any age can benefit from having pharmacogenomic testing done. In elderly patients with chronic disorders, pharmacogenomic testing can help to reduce the number of medication prescribed and reduce unwanted side-effects. Pharmacogenomic testing has also been used in the management of pediatric patients with cancer and rare/complex diseases. Any person on chronic medications such as psychiatric medications, antidepressants, statins or anti-coagulants (to name but a few) could benefit from having this test done.

## WHAT MEDICATIONS ARE COVERED BY PGx TESTING?

| Conditions | Drug Classes | Common Drugs |
|---|---|---|
| Pain Management | Anti-inflammatory, Analgesic, Antipyretic, Opioids, Gout, Anti-rheumatic | Ibuprofen, Codeine, Morphine, meloxi-cam,metamizole, nabumetone, naproxen<br>Piroxicam, alfentanil<br>Buprenorphine,codeine<br>Fentanyl,hydrocodone<br>Hydromorphone, levomethadone, metha-done, morphine, naltrexone oxycodone |
| Cardiovascular Medications | Antiarrhythmic, Anti-hypertensive, Cardiac Stimulant, Vasodilator, Angina medications, Dyslipidemia, Antico-agulant, Antiplatelet | Warfarin, Aspirin, Amiodarone, Captopril , Atorvastatin , Fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin |
| Internal Medicine | Respiratory Function, Antiemetic, Peptic Ulcer disease, Obesity, Diabetes, Migraine, Antihistamine, Hy-perparathyroidism, Dermatology | Ivacaftor, Dexlansoprazole, esomeprazole, Lansoprazole, omeprazole, pantoprazole, rabeprazole, allopurinol |
| Psychiatry | Antidepressants, Anti-psychotics | Atomoxetine, amitriptyline, clomip-ramine,desipramine, doxepin,imipramine, nortriptyline, trimipramine, citalopram, desvenlafaxine<br>Duloxetine, escitalopram<br>Fluoxetine, fluvoxamine<br>Levomilnacipran, milnacipran<br>Paroxetine, sertraline, venlafaxine |
| Neurology | ADHD related drugs, Eplilepy, Sedatives, An-ticonvulsants, Muscle relaxants, Alzheimer's and Parkinson's relat-ed drugs | Phenytoin, carbamazepine<br>oxcarbazepine |
| Oncology, Hema-tology | Antineoplastic, Anti-neoplastic Targeted Therapy | Ondansetron, tamoxifen<br>Tropisetron, capecitabine<br>Fluorouracil, tegafur,<br>azathioprine<br>mercaptopurine<br>thioguanine |

| Conditions | Drug Classes | Common Drugs |
|---|---|---|
| Infectiology | Antibiotics, Antifungal, Antiviral, Antiretrovira | Voriconazole, efavirenz, abacavir, ribavirin, amikacin dibekacin gentamicin kanamycin, atazanavir |
| Anaesthesiology | Anaesthetic, Muscle Relaxant | desflurane enflurane halothane isoflurane methoxyflurane sevoflurane succinylcholine |
| Organ Transplantation | Immunosuppressive, Immunomodulation | tacrolimus |

## PRACTICAL PGx FINDINGS

**Oncology**
PGx-guided therapies improved safety outcomes and saved money—Risk of grade ≥ 3 toxicity was reduced from 73% (control group) to 28% (PGx-guided group) for *DPYD*2A* allele carriers

**Behavioral health**
PGx-guided treatment helped patients experience greater improvement from baseline depression scores compared with unguided patients suffering from major depression

**Cardiovascular**
PGx-guided dosing of warfarin was a cost-effective strategy, improving outcomes of patients with atrial fibrillation in the United Kingdom and Sweden

**Pain management**
PGx testing for specific variants could help reduce opioid addiction, saving up to $14,000 USD per patient each year in addiction treatment

## PGx VALUE FOR PHYSICIANS

**20-30%**
**of ADRs prevented**
with PGx testing

**Up to 99%**
**of patients**
**have at least one actionable gene variant** that predisposes them to increased drug metabolism risk

**7.6%**
**improvement in medication adherence**
using PGx testing to guide treatment

## PGx VALUE FOR PATIENTS

**Save money on medications**

**Reduced medical trial and error,**
especially for mental health therapies

## Limitations of Testing

The PGx report provides information on how your body will metabolize drugs, which may be helpful in choosing medications. It is however, only one component of how a person may react to any particular drug. Drug reactions may be caused by other mechanisms apart from the known effect of the drug itself. These include hypersensitivity reactions (allergies), intolerance and drug interactions. The PGx report can be used as an aid in choosing medications but must be used in conjunction with previous medical history and other medical information available to your health care practitioner.

# References


1. Schork NJ (2015) Personalized medicine: Time for one-person trials. Nature 520(7549):609-11.
2. https://health.gov/our-work/health-care-quality/adverse-drug-events
3. FDA (2021) https://www.fda.gov/drugs/drug-interactions-labeling/preventable- adverse-drug-reactions-focus-drug-interactions
4. IQVIA Institute for Human Data Science. Medicine Use and Spending in the U.S. (2019) https://www.iqvia.com/insights/the-iqvia-institute/reports/medicine-use-and-spending-in-the-us-a-review-of-2018-and-outlook-to-2023
5. Maciel A, Cullers A, Lukowiak AA, Garces J (2018) Estimating cost savings of pharmacogenetic testing for depression in real-world clinical settings. Neuropsychiatric disease and treatment 14: 225–230. https://doi. org/10.2147/NDT.S145046
6. An-Economic-Evaluation-of-Pharmacogenomic-Testing.pdf (pro-genex.com)
7. https://www.frontiersin.org/articles/10.3389/fgene.2023.1233045/full
8. Harper AR, Topol EJ. Pharmacogenomics in clinical practice and drug development [published correction appears in Nat Biotechnol. 2012 Dec;30(12):1249]. Nat Biotechnol. 2012;30(11):1117-1124.doi:10.1038/nbt.2424
9. Dong D, Ozdemir S, Mong Bee Y, Toh SA, Bilger M, Finkelstein E. Measuring High-Risk Patients' Preferences for Pharmacogenetic Testing to Reduce Severe Adverse Drug Reaction: A Discrete Choice Experiment. Value Health. 2016;19(6):767-775. doi:10.1016/j.jval.2016.03.1837
10. Chan SL, Ng HY, Sung C, et al. Economic burden of adverse drug reactions and potential for pharmacogenomic testing in Singaporean adults. Pharmacogenomics J. 2019;19(4):401-410. doi:10.1038/s41397-018-0053-1
11. Alfirevic A, Pirmohamed M. Genomics of Adverse Drug Reactions. Trends Pharmacol Sci. 2017;38(1):100-109. doi:10.1016/j.tips.2016.11.003
12. Ji Y, Skierka JM, Blommel JH, et al. Preemptive Pharmacogenomic Testing for Precision Medicine: A Comprehensive Analysis of Five Actionable Pharmacogenomic Genes Using Next-Generation DNA Sequencing and a Customized CYP2D6 Genotyping Cascade. J Mol Diagn. 2016;18(3):438-445. doi:10.1016/j.jmoldx.2016.01.003.
13. Winner JG, Carhart JM, Altar CA, et al. Combinatorial pharmacogenomic guidance for psychiatric medications reduces overall pharmacy costs in a 1 year prospective evaluation. Curr Med Res Opin. 2015;31(9):1633-1643. doi:10.1185/03007995.2015.1063483
14. Dong OM, Wheeler SB, Cruden G, et al. Cost-Effectiveness of Multigene Pharmacogenetic Testing in Patients With Acute Coronary Syndrome After Percutaneous Coronary Intervention. Value Health. 2020;23(1):61-73. doi:10.1016/j.jval.2019.08.002
15. Deenen MJ, Meulendijks D, Cats A, et al. Upfront Genotyping of DPYD*2A to Individualize Fluoropyrimidine Therapy: A Safety and Cost Analysis. J Clin Oncol. 2016;34(3):227-234. doi:10.1200/JCO.2015.63.1325
16. Hall-Flavin DK, Winner JG, Allen JD, et al. Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. Pharmacogenet Genomics. 2013;23(10):535-548. doi:10.1097/FPC.0b013e3283649b9a
17. Verhoef TI, Redekop WK, Langenskiold S, et al. Cost-effectiveness of pharmacogenetic-guided dosing of warfarin in the United Kingdom and Sweden. Pharmacogenomics J. 2016;16(5):478-484. doi:10.1038/tpj.2016.4
18. J Marcalus S, Bristow-Marcalus S. Combating opioid addiction and abuse-2 ways to effectively intervene in the cycle of addiction through pharmacogenomics. J Am Pharm Assoc (2003). 2019;59(4):469-473. doi:10.1016/j.japh.2019.04.016

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