Guide to Pharmacogenetics & Introduction to TreatGx<sup>plus</sup>
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Pharmacogenetics (PGx)
1. Definition & role in personalized medicine

**Pharmacogenetics**: how a single genetic variant influences medication response  
**Pharmacogenomic**: how all genes (the genome) influence medication response

Personalized or ‘precision’ medicine involves using patient-specific information to tailor therapy, and incorporates many different patient factors, but usually refers to the use of genetic information.

Pharmacogenetic information can help clinicians optimize medication selection, dose, treatment duration and avoid adverse drug reactions (Figure 1). In addition, pharmacogenetics can provide new insights into mechanisms of drug action and contribute to the development of new therapeutic agents.³

It has been suggested that pharmacogenetics should be integrated into clinical pharmacy practice through medication therapy management to improve the quality and safety of patient care.²

**Figure 1.** Effects of pharmacotherapy with and without pharmacogenetics³
2. Types of genetic variations

Single Nucleotide Polymorphisms

Single nucleotide polymorphisms (SNPs) are the most common genetic variations in human DNA, occurring once approximately every 300 base pairs. More than 20 million SNPs have been mapped in the human genome. SNPs occur when one nucleotide base pair replaces another. If a SNP changes the amount or function of a protein that contributes to pharmacokinetics or pharmacodynamics, it may alter the patient’s response to a medication. SNPs are what make everyone’s DNA sequence unique to them.

Copy Number Variants

Copy number variants (CNVs) are DNA segments over one kilobase in size that have been duplicated, deleted, or rearranged, so that certain genetic regions have more or less than two copies of alleles. Although the contribution of CNVs to the development of common conditions is questionable, CNVs in some pharmacogenetic genes play a clear role in drug efficacy and toxicity.

One of the most widely recognized genes affected by CNVs is CYP2D6. For example, more than two copies of CYP2D6 normal alleles have been shown to increase CYP2D6 enzyme activity above that of “normal.” Associations between CYP2D6 CNVs and therapeutic response to drugs have been found in a wide range of drug classes including antidepressants, endocrine therapy agents, and beta-blockers.

Human Leukocyte Antigens

Human leukocyte antigens (HLAs) gene testing can help identify those who are at risk of potentially fatal adverse drug reactions when taking specific medications such as allopurinol or carbamazepine. The HLA gene family codes for the HLA complex, which is involved in immune system mediation.

Adverse drug reactions (ADRs) are divided into type A and type B reactions. Type A reactions are based on a drug’s known pharmacological action, for example, drowsiness caused by dimenhydrinate. Type B reactions are considered idiosyncratic and are often non-predictable and dose-independent. Type B reactions are thought to be drug-induced immune responses, and can include serious ADRs such as Stevens-Johnson syndrome and toxic epidermal necrolysis. HLA surface proteins are highly polymorphic, and have been found to be associated with risk of these idiosyncratic drug hypersensitivity reactions.
3. Pharmacokinetic vs pharmacodynamic effects

Two of the main ways in which pharmacogenetics can affect drug response is through changes in drug pharmacokinetics and pharmacodynamics.

Pharmacokinetics

Pharmacokinetics involves absorption, distribution, metabolism, and excretion of medications in the body. Currently, pharmacogenetic testing for pharmacokinetic changes mostly involves genetic variants in drug metabolizing enzymes and drug transporters.

Pro-drug and active drugs can be affected differently by changes in metabolism status. A pro-drug is a medication or compound that, after administration, is metabolized (i.e. converted within the body) into a pharmacologically active drug. Clopidogrel is an example of a pro-drug that is metabolized by CYP2C19 to its active form. Patients who are poor CYP2C19 metabolizers may be more likely to have an adverse cardiovascular outcome because of the reduced antiplatelet action caused by the reduced effectiveness of the clopidogrel. Conversely, medications like citalopram are inactivated by CYP2C19, so CYP2C19 poor metabolizers are recommended to take a lower starting dose of citalopram to avoid adverse effects.

Pharmacodynamics

Pharmacodynamics describes the effect of a medication at its therapeutic target and at other non-target sites. Genetic polymorphisms in drug target proteins, such as receptors, enzymes, ion channels, or signaling proteins, can contribute to overall drug response. Compared to pharmacokinetics, there are relatively few pharmacogenetic associations related to pharmacodynamics, for a number of reasons. Drug target pathways are fairly complex compared to the more straightforward pathways of drug metabolism and drug transport, where there is generally one main enzyme involved in each drug’s metabolism. In addition, the variability in drug metabolism is much greater in magnitude than variability in drug target binding, making it easier to detect differences in drug metabolism in studies.
4. Commonly prescribed medications affected by PGx

The most commonly prescribed medications affected by pharmacogenetics are those metabolized by four enzymes found in the cytochrome P450 system. These four CYP enzymes (CYP2C9, CYP2C19, CYP2D6, CYP3A4) are responsible for the metabolism of 60-70% of all medications. Some well-studied HLAs are also associated with drug-induced hypersensitivity reactions to commonly used medications such as allopurinol. In figure 5, some of these commonly prescribed medications are categorized under the pharmacogenetic marker that is associated with variability in response with their use.

Figure 5. Pharmacogenetic markers associated with variability in response to commonly prescribed medications

Numerous medications now have pharmacogenetic information included in their labelling. In some cases, the labelling also specifies actions to be taken based on the genetic variant information. The FDA has compiled a “Table of Pharmacogenetic Biomarkers in Drug Labelling” that is available online and updated regularly (https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm).

- **CYP2C19**
  - Clopidogrel
  - SSRIs (citalopram, sertraline)
  - PPIs (lansoprazole, omeprazole, pantoprazole)
  - TCA (amitriptyline)

- **CYP2D6**
  - Opioids (codeine, oxycodone, tramadol)
  - SSRIs (paroxetine, fluvoxamine)
  - SNRI (venlafaxine)
  - TCAs (amitriptyline, nortriptyline)
  - Antipsychotics (aripiprazole, haloperidol, risperidone)
  - Beta-blocker (metoprolol)

- **HLA**
  - HLA-A*31:01 carbamazepine
  - HLA-B*15:02 carbamazepine lamotrigine
  - HLA-B*58:01 allopurinol lamotrigine
5. Who can benefit from pharmacogenetic testing?

While understanding the impact that genetics variants may have on a person’s health or treatment plan, pharmacogenetic testing is not right for everyone. Those who have already trialled all the drugs typically used to treat their condition, or are taking an effective drug with no side effects, should be advised that a pharmacogenetic test may not be of benefit to them for this condition.

People who might get a more immediate benefit from pharmacogenetic testing include those who are:

- Starting a new treatment regime
- Taking multiple medications
- Experiencing multiple medical conditions
- Experiencing or have experienced serious adverse effects
- Reluctant to take medication due to concerns about safety or efficacy
- Not responding to their medication
- Requiring very high or very low medication doses
- In high-risk ethnic groups for certain severe adverse drug reactions: (e.g. Han Chinese and considering initiating allopurinol)

Below you can find examples of how TreatGxplus can improve specific patient cases.

For more patient case examples, please see the link below in the product resources section of the website. https://www.lifelabsgenetics.com/product/treatgxplus-service/
6. Implementation in pharmaceutical care

Pharmacogenetic testing is not diagnostic, but is one more piece of the personalized medicine puzzle that can be used in combination with renal function, co-morbidities, drug-drug interactions and other patient-specific factors to improve the efficacy and safety of a medication plan.

In the US, the American Society of Health-System Pharmacists (ASHP) statement on the Pharmacist’s Role in Clinical Pharmacogenetics outlines that pharmacists should be able to:9

- Recommend pharmacogenomic testing to aid in the process of drug and dosage selection.
- Design a patient-specific drug and dosage regimen based on a patient’s pharmacogenetic profile and personal health information.
- Educate patients, and other healthcare professionals about pharmacogenomic principles and appropriate indications for clinical pharmacogenomic testing.
- Communicate pharmacogenomics-specific drug therapy recommendations to the healthcare team, including documentation of interpretation of results in the patient’s health record.

In Canada, there are differences by province/territory for which healthcare provider can requisition pharmacogentic testing.

Pharmacists receive pharmacogenetic education during their degree programs, and are well equipped to discuss the benefits of pharmacogenetics with their patients.

Physicians should be included as certain results require review or changes to a medication prescription.
6.1 Benefits

Pharmacogenetic testing has the potential to greatly improve drug adherence and treatment outcomes in several ways:

1. More effective drug therapy
2. Reduced adverse drug reactions (ADRs)
3. Long-term cost savings

1. More effective drug therapy

Incorporating pharmacogenetics into patient care may help bring an end to the trial-and-error approach to drug prescribing. Clinicians will be able to use genetic information to match the right drug, to the right patient, at the right dose while minimizing adverse effects. This precision medicine approach may speed recovery or improvement in symptoms, and is invaluable for patients with many conditions.

Figure 8 illustrates the large percentage of patients who do not respond to commonly used and expensive medications.

2. Adverse drug reactions

Adverse drug reactions (ADRs) are a major burden for the healthcare system. Pharmacogenetic testing can contribute to avoidance of ADRs by predicting who should avoid or use lower doses of a particular medication, and by identifying those at higher risk for drug hypersensitivity reactions.

ADRs are divided into type A and type B reactions. Type A reactions are based on a drug’s known pharmacological action, for example, drowsiness caused by dimenhydrinate. Type B reactions are considered idiosyncratic and are often non-predictable and dose-independent. Type B reactions are thought to be drug-induced immune responses, and can include serious ADRs such as Stevens-Johnson syndrome and toxic epidermal necrolysis.

3. Long-term cost saving

A recent review on the cost-effectiveness of pharmacogenetic testing found that testing has a positive impact on healthcare quality and costs.

Pharmacogenetic testing has the potential to save healthcare expenditure through fewer adverse drug reactions, decreasing the number of failed medication trials, limiting the duration of therapy, and decreasing the number of medications taken by individual patients.

Imprecision Medicine

For every person they do help (blue), the ten highest-grossing drugs in the United States fail to improve the conditions of between 3 and 24 people (red)

1. Abilify (aripiprazole) Schizophrenia /5
2. Nexium (esomeprazole) Heartburn /25
3. Humira (adalimumab) Arthritis /4
4. Crestor (rosuvastatin) High cholesterol /20
5. Cymbalta (duloxetine) Depression /9
6. Advair Diskus (fluticasone propionate) Asthma /20
7. Remicade (infliximab) Crohn’s disease /4
8. Enbrel (etanercept) Psoriasis /4
9. Copaxone (glatiramer acetate) Multiple sclerosis /16
10. Neulasta (pegfilgrastim) Neutropenia /13

Based on published number needed to treat (NNT) figures. For a full list of references see Supplementary information at go.nature.com/4dr78f
6.2 Barriers

Potential barriers, as well as patient concerns, to the implementation of pharmacogenetic testing in routine clinical practice include:

1. Evidence and clinical utility
2. Limited healthcare provider & patient knowledge
3. Cost
4. Genetic non-discrimination legislation
5. Patient privacy

1. Evidence and clinical utility

Case-control studies are the most common study design in pharmacogenetics. In these studies, cases are defined as those who have had a specific adverse drug event or a poor therapy outcome, and the genetic variant frequencies in the cases are compared with the controls who have a comparable level of drug exposure but are also free of the study outcome. These studies are able to investigate associations between the gene and the drug-therapy outcome, but results are prone to bias due to the retrospective design and lack of randomization.19

For many medications, variations in genes affecting both pharmacokinetic and pharmacodynamic drug properties may interact to determine the ultimate effects from drug therapy. It is therefore challenging to identify the combination of gene variations that best predicts response for these medications.3

Over the past decade, the number of pharmacogenetic studies published has increased exponentially and as the evidence base for implementation of pharmacogenetics testing increases, the acceptance of pharmacogenetic testing in routine care will also increase.20

2. Limited healthcare provider & patient knowledge

Genetics is a relatively new field of medicine. In order to recommend and implement pharmacogenetic testing, healthcare providers should be familiar with test characteristics and implementation strategies. Clinical decision support tools are essential to help interpret and utilize the pharmacogenetic test results effectively and in combination with other patient-specific factors.1

3. Cost

The cost of pharmacogenetic testing can be prohibitive for some patients. There is also limited coverage of this testing by insurance companies as there is still emerging evidence that supports the cost effectiveness of pharmacogenetic testing.22 Another potential cost of pharmacogenetic testing may arise when a safer or more effective alternative medication is more expensive than the generally accepted first-line therapy.14

Comprehensive pharmacogenetics testing provides results that are relevant for a patient’s lifetime. This information has the potential to prevent an ADR and/or allow for a more rapid return to health - both being invaluable for many patients.
4. Genetic Non-Discrimination Legislation

On May 4, 2017, the Genetic Non-Discrimination Act (GNA) was passed in Canada. Formerly known as Bill S-201, the act protects individuals from the use of genetic test results in areas outside medical care and medical research, such as insurance and employment. GNA prohibits insurance providers (and other providers of goods and services) from requiring or requesting genetic testing or the disclosure of previous or future genetic test results. Federally regulated employers also cannot request or require genetic test results of an employee or use genetic test results in decisions about hiring, firing, job assignments, or promotions. GNA does not prevent insurers from using information about a current condition, even if it has a genetic basis, or from using family medical history.

More information regarding GNA can be found here: http://laws-lois.justice.gc.ca/eng/acts/G-2.5/index.html

5. Patient privacy

Before submitting a DNA sample, patients should be informed as to what the pharmacogenetic test will uncover, the risks and benefits of the information sought, whether their DNA will be stored or discarded, and how the privacy of their sample and test results will be maintained.29 Ensuring the privacy and confidentiality of DNA samples and test results is essential to reassure patients that undergoing pharmacogenetic testing will not adversely affect them in other ways.29 DNA from samples sent to the TreatGx\textsuperscript{plus} service may be used for future research and/or test development unless the patient checks the box that says they do not consent to this.

The TreatGx\textsuperscript{plus} team is committed to ensuring the security of the user’s personal information in order to protect it from unauthorized access, collection, use, disclosure, copying, modification or disposal or similar risks. The following security measures are followed to ensure that the user’s personal information is appropriately protected:

- Physically securing offices where personal information is held
- The use of user ids, passwords, encryption, firewalls
- Restricting employee access to personal information as appropriate (i.e., only those that need to know will have access)
- Contractually requiring any service providers to provide comparable security measures
7. Literature and guidelines

Listed below are samples of some conclusions from recent pharmacogenetic outcome studies:

- Maciel et. al., examines the use of PGx in patients with depression. “Assuming a test cost of USD$2,000 for pharmacogenetic testing, the (economic) model predicts a savings of USD$3,962 annually per patient with pharmacogenetic-guided medication management.”

- Olsen et. al., 2017: Incorporating pharmacogenetic information reduced ADRs from 53% to 28%. More than half (53%) of patients in the control group reported at least 1 adverse drug event compared to 28% of patients with PGx-guided medication management (P = .001).

- Blasco-Fonticilla, 2017: Pharmacogenetic testing helped to improve the clinical outcome, and to reduce polypharmacy and the number of drugs used in children and adolescents with severe mental disorders.

- Peterson et. al., 2017: Certain pharmacogenomics tools show promise of improving short-term depression remission rates in women in their mid-40s with little comorbidity.

- Kaufman et. al., 2017: Considerable clinically actionable pharmacogenomic information for cardiovascular drugs exists, supporting the idea that consideration of such information when prescribing is warranted.

There are now several groups that publish pharmacogenetic-based drug dosing guidelines, including the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Royal Dutch Association for the Advancement of Pharmacy - Pharmacogenetics Working Group (DPWG), and the Canadian Pharmacogenomics Network for Drug Safety (CPNDS). In addition, some professional societies, such as the American College of Rheumatology, include statements about pharmacogenetic testing. The FDA-mandated incorporation of pharmacogenomic information in drug labelling also offers some guidance on potential clinical implementation.

- PharmGKB: Pharmacogenetics Knowledgebase
  - Funded by National Institutes of Health (NIH)
  - Guidelines & primary literature

- CPIC: Clinical Pharmacogenetics Implementation Consortium
  - Funded by the National Institutes of Health (NIH)
  - Open membership, international non-profit group
  - Evidence-based, peer-reviewed and publicly available

- DPWG: Dutch Pharmacogenetics Working Group
  - Funded by Royal Dutch Pharmacist’s Association
  - Membership by invitation

- CPNDS: Canadian Pharmacogenomics Network for Drug Safety
  - Funded by several provincial and federal agencies including Canadian Institutes of Health Research, Genome Canada, Genome British Columbia, Michael Smith Foundation for Health Research, Canada Foundation for Innovation, and Provincial Health Service Authority

Published recommendations for gene-drug pairs by CPIC and the DPWG groups show a high rate of concordance, but differences in the guidelines exist due to different guideline development methods.
Guide to TreatGxplus
1. TreatGx\textsuperscript{plus} pharmacogenetic service

The TreatGx\textsuperscript{plus} pharmacogenetic panel includes single nucleotide polymorphisms (SNPs), copy number variants (CNVs), and human-leukocyte antigen (HLA) variants. The test was designed to only include genetic variants which have a high level of scientific evidence to ensure the test provides maximum effectiveness and specificity. The resulting panel covers an extensive range of medications commonly prescribed. As pharmacogenetics can be hard to interpret and apply, TreatGx\textsuperscript{plus} makes the results available through an on-line software tool. This tool considers not only the genetics of the patient, but other clinical information that is relevant for the patient’s treatment plan. The following pages discuss this in greater detail.

1.1 Kit contents

KIT COMPONENTS

- 1 instruction leaflet
- 3 identical labels with a unique Patient Identifier Number (PIN)
- 1 buccal swab tube to collect the sample
- 1 specimen bag with absorbent strip inside
- 1 return mailing envelope & prepaid return shipping label
- 1 requisition form

NOTE: The requisition MUST be filled out and signed by a healthcare provider in order for the sample to be processed by the laboratory.

LifeLabs can facilitate this process by coordinating with an external physician. For more information please contact us at 1-844-363-4357 (1-84-GENE-HELP).
1.2 Sample collection

Sample collection is easy and is performed by the patient at their convenience.

1 Prepare*

Rinse your mouth with water and do not eat, drink, smoke, chew gum or brush your teeth for 30 minutes before collecting your sample.

2 Take Sample

Open package and remove collector without touching sponge tip. Place sponge as far back in the mouth as comfortable and rub along the lower gums (see close up image) in a back and forth motion. Gently rub the gums 10 times, if possible, avoid rubbing the teeth.

3

Gently repeat rubbing motion on the opposite side of the mouth along the lower gums for an additional 10 times.

4

Hold the tube upright to prevent the liquid inside the tube from spilling. Unscrew the blue cap from the collection tube without touching the sponge.

5

Turn the cap upside down, insert the sponge into the tube and close cap tightly.

Invert the capped tube and shake vigorously 10 times.

1.3 Patient account creation

Patients will receive an email once the laboratory analysis of their sample is complete and their results are available on TreatGx. The email contains a link to open a TreatGx account and create a personalized profile. The patient will create their account by using the PIN number that is included in the kit and is required to confirm their identity. If the patient loses their PIN number, they can contact LifeLabs Genetics at Ask.Genetics@LifeLabs.com. Patients can access TreatGx from their home or their healthcare professional’s office using a computer, tablet or mobile device.

LifeLabs strongly recommends that the patient reviews their results with their healthcare provider (HCP). Patients can invite their HCP during account creation, by either, selecting a provider from the drop-down list, or by inputting the provider email.
1.4  Healthcare provider account creation

Healthcare providers will receive a summary report via fax. An account must be created in order to use the tool. There are two ways to open a healthcare provider account:

1. Single Provider account
2. Clinic/Corporate account
   a) Administration account
   b) HCP account (multiple providers are able to access a single patient account within a medical clinic or pharmacy)

For more information about setting up an account please visit the link below:
https://www.lifelabsgenetics.com/product/treatgxplus-service/

Browse the product resources section of the website as per the screen shot below.

1.5  Accepting patient invitations for corporate accounts

Patient invitations can be accepted or declined from the patient list in the dashboard. After an invitation is accepted, all the healthcare providers in the corporate account will have access to the case, including the pharmacogenetic results.

The ‘Patient’ panel in the dashboard shows the list of patient cases (including the date of birth) which the team has access to, including the patient’s invitation which is in the queue.

Account administrators do not have access to patient cases.

HCP and Administrator accounts are different

<table>
<thead>
<tr>
<th>HCP Account</th>
<th>Admin Account</th>
</tr>
</thead>
<tbody>
<tr>
<td>View genetic report</td>
<td>Accept patient invites</td>
</tr>
<tr>
<td>Generate med options</td>
<td>Add HCPs</td>
</tr>
<tr>
<td>View test case</td>
<td></td>
</tr>
</tbody>
</table>

If the administrator is also an HCP, they must add a provider account for themselves to access the features of the HCP account.
1.6 Lab technology

The TreatGx pharmacogenetic test has 99% specificity and 100% sensitivity, and has been validated across multiple platforms. The panel combines single nucleotide polymorphisms (SNPs), copy number variants (CNVs), and human leukocyte antigen (HLAs) in a highly multiplexed, cost-effective assay. Variants are detected on the MassArray® (Agena Bioscience), a non-fluorescent detection platform that uses mass spectrometry and time-of-flight chemistries (MALDI-TOF) to accurately distinguish variant alleles.

TreatGxplus was previously developed and validated at GenXys for the QuantStudio 12K Flex Real-Time OpenArray PCR System (Thermo Fisher Scientific).

Based on this evaluation and validations across platforms, all assays included in the test panel have an accuracy of 99.4%, repeatability of 99.7%, and reproducibility of 99.7%.

1.7 Processing time

TreatGxplus pharmacogenetic test results are uploaded to the patient’s TreatGxplus account within 7-10 business days of the lab receiving the sample.

1.8 Conditions Covered by TreatGx

*As of March 1, 2019, the conditions covered by TreatGx include:*

**Cardiovascular:**
Atrial Fibrillation (Anticoagulation, Rate Control), Heart Failure (Chronic, Fluid Retention), Hyperlipidemia, Hypertension, Peripheral Arterial Disease (Symptomatic), Post-Myocardial Infarction.

**Musculoskeletal:**
Gout (Acute, Chronic), Osteoarthritis, Osteoporosis, Rheumatoid Arthritis.

**Chronic Pain:**
Fibromyalgia, Low Back Pain, Neuropathic Pain, Trigeminal Neuralgia.

**Mental Health:**
Anxiety (Generalized Anxiety Disorder, Social Anxiety Disorder), Bipolar 1 Disorder, Depression, Schizophrenia, ADHD

**Neurological:**
Epilepsy, Migraine (Treatment, Prophylaxis).

**Respiratory:**
Asthma, Chronic Obstructive Pulmonary Disease (Acute Exacerbation, Stable).

**Endocrine:**
Diabetes Mellitus Type 2.

**Gastrointestinal:**
Dyspepsia/Peptic Ulcer Disease, Gastroesophageal Reflux Disease, H. Pylori Eradication, and Prevention of NSAID-Induced Ulcers.

**Genitourinary:**
Urinary Tract Infection.

**Other:**
Smoking Cessation.

For an up-to-date list of conditions please visit [https://www.lifelabsgenetics.com/product/treatgxplus-service/](https://www.lifelabsgenetics.com/product/treatgxplus-service/)
2. TreatGx\textsuperscript{plus} pharmacogenetic report

A full report is available on the TreatGx portal, a summary report is faxed to the HCP specified on the requisition.

### 2.1 Full report overview

The report overview is on the second page of the TreatGx\textsuperscript{plus} report, and outlines the three main sections of the report:

1. Medication summary
2. Medication report
3. Laboratory report

### 2.2 Medication summary

The medication summary is a list of medications with evidence for the use of pharmacogenetic information. Medications that may have an altered response based on a patient’s pharmacogenetic results are highlighted with this symbol as seen in Figure 1. Online, the report is interactive and all the medication names are hyperlinked to more detailed medication information contained in the medication report.

**Figure 1. Sample medication summary**

<table>
<thead>
<tr>
<th>Acetylsalicylic acid</th>
<th>Codeine</th>
<th>Lansoprazole</th>
<th>Propafenone</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Adalimumab" /></td>
<td><img src="image" alt="Cold medication" /></td>
<td><img src="image" alt="Desipramine" /></td>
<td><img src="image" alt="Lisinopril" /></td>
</tr>
<tr>
<td><img src="image" alt="Alfentanil" /></td>
<td><img src="image" alt="Diazepam" /></td>
<td><img src="image" alt="Lorazepam" /></td>
<td><img src="image" alt="Quetiapine" /></td>
</tr>
<tr>
<td><img src="image" alt="Allopurinol" /></td>
<td><img src="image" alt="Quinapril" /></td>
<td><img src="image" alt="Ramipril" /></td>
<td></td>
</tr>
</tbody>
</table>

### 2.3 Medication report

The medication report provides information on how a patient’s pharmacogenetic results affect each medication as can be seen in figure 2. Patients and providers are encouraged to use the TreatGx decision support software to discover personalized medication options.

**Figure 2. Sample of medication-specific results**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Medication Response</th>
<th>Gene</th>
<th>rsID</th>
<th>Genetic Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Phenotype: Normal metabolizer</td>
<td>CYP2C9</td>
<td>*1/*1</td>
<td>1A</td>
</tr>
<tr>
<td>Coumadin</td>
<td>Increased response</td>
<td>VKORC1 rs9923231</td>
<td>A/A</td>
<td>1B</td>
</tr>
</tbody>
</table>

**Interpretation**

- The algorithm in TreatGx includes CYP2C9, VK0RC1 and other clinical factors in calculating initial warfarin dose

For safe and effective prescription options, login to TreatGx and look for manage medications

- Warfarin is found in the following conditions with TreatGx: Atrial Fibrillation - Anticoagulation
- Other clinical factors, medical conditions and drug-drug interactions may contribute to medication response
2.4 Levels of evidence

PharmGKB evidence levels are included for each genetic variant that influences medication response:

<table>
<thead>
<tr>
<th>Strongest Evidence</th>
<th>PharmGKB evidence levels for genetic variants influencing drug response:¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>•••••</td>
<td>1A - Pharmacogenetic guideline available</td>
</tr>
<tr>
<td>••••</td>
<td>1B - Cohort studies with statistical significance and strong effect size</td>
</tr>
<tr>
<td>•••</td>
<td>2A - Established drug response variants likely to have functional significance</td>
</tr>
<tr>
<td>••</td>
<td>2B - Association studies, some studies do not show statistical significance and/or have small effect size</td>
</tr>
<tr>
<td>•</td>
<td>3 - Single study or multiple studies with no clear association</td>
</tr>
<tr>
<td></td>
<td>4 - Preliminary level of evidence from a case study, non-significant study, molecular or functional assay</td>
</tr>
</tbody>
</table>

The level of evidence for each genetic variant tested is indicated to provide the clinician with more information as to the strength of the recommendations.

2.5 Guidelines

Since pharmacogenetic guidelines sometimes categorize phenotypes differently for certain genes and drugs, the guidelines table at the end of the medication report summarizes which guidelines are used for each drug. The guidelines used in the TreatGxPlus report include those from DPWG, CPIC, and CPNDS, along with Health Canada and FDA labelling.

2.6 Laboratory report

The laboratory report provides detailed information on the genetic markers in a technical table.

---

*Laboratory Report*

The Laboratory Report contains your genetic results.

<table>
<thead>
<tr>
<th>Gene</th>
<th>rsID</th>
<th>HGVS</th>
<th>HGVS Reference</th>
<th>Alleles</th>
</tr>
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<tr>
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<td>T/T</td>
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<td>G/G</td>
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<td>CYP2C9</td>
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<td>g.47394A&gt;C</td>
<td>NG_000335.1</td>
<td>A/A</td>
</tr>
</tbody>
</table>
3. TreatGx clinical decision support software

The TreatGx online medication decision support tool incorporates each patient’s pharmacogenetic test results into condition-specific treatment algorithms to generate personalized medication options. The medication options are selected and dose-adjusted based on different patient-specific factors. See sections below for more information.

3.1 Conditions

TreatGx covers common chronic conditions, and medications that are affected by genetics, and drug-to-drug interactions. Most conditions in TreatGx are primary care oriented. Condition treatment algorithms are regularly updated as new guidelines or relevant studies are published. New conditions are regularly added. For an up-to-date list of conditions please visit https://www.lifelabsgenetics.com/product/treatgxplus-service/

We are committed to evolving the software and the panel as new evidence emerges. The team will continue to use the highest level of evidence available to advance the online medication decision support tool and the pharmacogenetic test.

3.2 Patient factors

Patient factors should be added to the patient’s TreatGx account as they are used to personalize medication options for each condition. These include:

- Current symptoms or severity of condition
- Drug history
- Medical history
- Current medications
- Age
- Sex
- Weight
- Height
- Ethnicity
- Genetics
- Renal function (eGFR)
- Hepatic impairment (Child-Pugh scale)
- Other Lab Values
  - Potassium level
  - INR
  - Cholesterol panel (TC, non-HDL, LDL, triglycerides)
- Culture & sensitivity results
- Cardiovascular disease risk
3.3 Medication options

The condition-specific medication options generated by the TreatGx clinical decision support software are selected and dose-adjusted based on multiple patient-specific factors, including the TreatGx plus pharmacogenetic test results, which are automatically uploaded into the software.

3.4 Drug-drug, drug-condition, drug-gene interactions

Three main types of drug interactions are taken into account by the TreatGx software when generating personalized medication options: drug-drug, drug-condition, and drug-gene.

In addition to these three main drug interaction types, TreatGx also takes into account drug-biophysical interactions, which includes weight-based dosing calculations and other adjustments based on age, height, and laboratory test results.

Drug - Gene: Do you have a genetic variation that may prevent you from experiencing pain relief from codeine?

Drug - Drug: Are you at risk of side effects while taking your new antibiotic medication with your cholesterol medication?

Drug - Condition: Might the calcium channel blocker you have been prescribed for hypertension cause your ankles to swell?

Drug - Biophysical: How does your weight affect your starting dose of insulin for diabetes?

If there are multiple interactions affecting a medication and there is no guidance as to how to combine several adjustment factors (such as renal impairment requiring lower dose in combination with a genetic variant requiring a higher dose), the medication is not included in the personalized medication options since its safety and effectiveness cannot be accurately predicted.

3.5 Limitations

To use or access the services independently you must be at least 13 years of age or older. A parent or guardian may access the website and services on behalf of his/her child.
4. Comparison of TreatGx\textsuperscript{plus} with other PGx testing services

1. TreatGx\textsuperscript{plus} offers more than a test; the service also includes an interactive pharmacogenetic report and access to the TreatGx medication decision software tool.

2. TreatGx proactively considers the pharmacogenetic test results along with all other relevant patient factors needed to create a list of condition-specific medication options. TreatGx includes all essential variables for prescribing and generates safe and effective medication options, including calculations for insulin and warfarin dosing.

3. TreatGx\textsuperscript{plus} covers common chronic conditions, and includes more genetic markers and medications compared to most competitors.

4. The genetic markers in TreatGx\textsuperscript{plus} include custom assays called copy number variants (CNVs) and human-leukocyte antigen (HLA) variants. The HLA variants in TreatGx\textsuperscript{plus} are associated with drug hypersensitivity reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

5. TreatGx provides the healthcare professional with a list of personalized, safe and effective medication options, eliminating the need for alerts and enabling accuracy and efficiency.

6. Other companies offering a medication decision support tool and pharmacogenetic testing only consider pharmacogenetics and drug-drug interactions and are not able to detect other interactions (e.g. drug-disease, drug-biophysical) or individualize medication/dose. Pharmacogenetic companies offering only a report, detect drug-genetic and drug-drug interactions, missing other patient healthcare considerations which fail to facilitate adoption into clinical practice.

<table>
<thead>
<tr>
<th>TreatGx\textsuperscript{plus features}</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Detects drug - genetic interactions</td>
<td>✓</td>
</tr>
<tr>
<td>Precision prescribing software informed by genetics, drugs, conditions, biophysical data and highest levels of evidence</td>
<td>✓</td>
</tr>
<tr>
<td>Detects drug - condition, drug - biophysical data, drug - genetic interactions</td>
<td>✓</td>
</tr>
<tr>
<td>Drug-drug interactions covered</td>
<td>&gt;200k</td>
</tr>
<tr>
<td>Calculates warfarin, insulin, antibiotic doses</td>
<td>✓</td>
</tr>
<tr>
<td>Condition based MDSS</td>
<td>✓</td>
</tr>
<tr>
<td>Fits into a professional’s workflow</td>
<td>✓</td>
</tr>
<tr>
<td>Patient and HCP interface</td>
<td>✓</td>
</tr>
<tr>
<td>Drug price comparison</td>
<td>✓</td>
</tr>
<tr>
<td>EMR and EHR integration</td>
<td>coming soon</td>
</tr>
<tr>
<td>Robust PGx test (HLAs, CNVs)</td>
<td>✓</td>
</tr>
</tbody>
</table>
5. Support

5.1 Resources

LifeLabs Genetics has an established centralized customer care centre to support patients and healthcare providers ordering genetic testing through LifeLabs Genetics.

**Main contact methods:**

- Ask.Genetics@LifeLabs.com
- 1-844-GENE-HELP (1-844-363-4357)
- www.LifeLabsGenetics.com

Our genetics customer care team provides both patient and HCP assistance from 8am-6pm EST. We support inquiries in both English and French.

Our website offers an extensive amount of information to assist patients and healthcare providers in understanding and ordering this test, including a medication search tool, that allows for a quick and easy search of genetic markers that impact drug metabolism.

The product resource section of our website offers specific information about: patient login, patient and corporate account creation, how-to guide for sample collection, patient case studies, and much more, as per the screen shot of the website below.
6. Patient communication & education

There are four main elements of pharmacogenetic testing that can be discussed with patients prior to them purchasing the TreatGx\textsuperscript{plus} service:

1. The purpose of testing and role of genes in drug response
   i. The purpose of pharmacogenetic testing is to determine the risk of side effects and/or the likelihood of effectiveness of a given medication.

2. The test risks, benefits, limitations, and alternatives
   i. Identification of a genetic change or metabolic activity does not necessarily indicate an absolute diagnosis of non-response or that a side effect will or will not occur upon use of a given drug.
   ii. A "normal" PGx test result doesn't necessarily mean the patient is not at risk for adverse events or non-response because current tests only include known variants in known genes.

3. That testing involves analysis of DNA
   i. The patient needs to be reassured that that the DNA sample will only be analyzed for the specific genes included on the TreatGx\textsuperscript{plus} panel.
   ii. DNA from samples sent to the TreatGx\textsuperscript{plus} service may be used for future research and/or test development unless the patient checks the box on the requisition that they do not consent

4. Future benefits of pharmacogenetic testing
   i. Commonly prescribed drugs are impacted by a handful of genes; it is very likely that the results will be useful for future treatments.

Patients can learn more about pharmacogenetic testing and TreatGx\textsuperscript{plus} on the LifeLabs genetics website www.LifeLabsGenetics.com

Table 2 on the following page, outlines some examples of how to discuss pharmacogenetic test results with patients. The example used is that of SLC01B1 for simvastatin, a SNP that is included in TreatGx\textsuperscript{plus}. Statin-induced myalgia has been associated with a variant in SLC01B1, a hepatic transporter gene, particularly in patients prescribed simvastatin.\textsuperscript{30}
Table 2. Examples of post-test communication with patients

<table>
<thead>
<tr>
<th>PGx test results and possible clinical implications</th>
<th>Use effective risk communication strategies in discussing PGx results</th>
<th>Inform patients what, if any, changes will be made to the prescribed drug</th>
<th>Emphasize importance of relevance of test results for future treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype TT: this genotype is associated with normal activity and a decreased risk for simvastatin-associated myopathy</td>
<td>“The pharmacogenetic test did not identify any changes in a gene that affects how simvastatin is broken down.”</td>
<td>“Based on these test results, you should continue to take simvastatin at your current dose.”</td>
<td>“At this time, simvastatin is the only medicine related to the gene we tested. However, it is very likely that more medicines will be developed or more discoveries will be made about this gene. Therefore it is important for you to remember this result and share it with other healthcare providers.”</td>
</tr>
<tr>
<td>Genotype TC: this genotype is associated with intermediate activity and an increased risk for simvastatin-associated myopathy. A decreased dose or alternate drug may be warranted</td>
<td>“The pharmacogenetic test found that you have a change in a gene that affects how simvastatin is broken down.”</td>
<td>“Based on these results, we can consult with your physician and consider decreasing your dose and continuing to monitor your cholesterol, or consider switching to a different cholesterol medication.” “Based on these results, we will closely monitor you; it is important that you report any muscle pain or weakness while you continue to take simvastatin.”</td>
<td>“At this time, simvastatin is the only medicine related to the gene we tested. However, it is very likely that more medicines will be developed or more discoveries will be made about this gene. Therefore, it is important for you to remember this result and share it with other healthcare providers.”</td>
</tr>
<tr>
<td>Genotype CC: this genotype is associated with low activity and a highly increased risk for simvastatin-associated myopathy. A decreased dose or alternate drug may be warranted</td>
<td>“The pharmacogenetic test found that you have a change in a gene that affects how simvastatin is broken down.”</td>
<td>“Based on these results, we can consult with your physician and consider decreasing your dose and continuing to monitor your cholesterol, or consider switching to a different cholesterol medication.” “Based on these results, we will closely monitor you; it is important that you report any muscle pain or weakness while you continue to take simvastatin.”</td>
<td>“At this time, simvastatin is the only medicine related to the gene we tested. However, it is very likely that more medicines will be developed or more discoveries will be made about this gene. Therefore, it is important for you to remember this result and share it with other healthcare providers.”</td>
</tr>
</tbody>
</table>
Frequently Asked Questions

1. Can TreatGx\textsuperscript{plus} tell me who is going to have an adverse drug reaction (ADR) to a specific medication or who is going to need a dosing adjustment for a specific medication?

The TreatGx decision support tool uses condition-specific prescribing algorithms informed by the highest levels of evidence and the patient information that is entered. In cases where there is a high level of clinical evidence, TreatGx\textsuperscript{plus} can identify patients at an increased risk of adverse drug reactions (ADRs) to a medication due to specific genetic variants.

The genetic markers on the TreatGx\textsuperscript{plus} pharmacogenetic test have strong associations with response to specific medications. Other genetic and clinical factors may also influence a patient’s metabolism of specific medications and risk of adverse effects.

TreatGx\textsuperscript{plus} includes multiple genetic markers for ADRs, for example:

- With antipsychotics, certain genetic variants on the HTR2C gene indicate increased risk of metabolic syndrome and variants in the ANKK1 gene indicate an increased risk of weight gain and hyperprolactinemia.
- In Chronic Heart Failure, Hypertension, and Post-Myocardial Infarction, certain genetic variants on the KCNIP4 gene indicate increased risk of ACE inhibitor-induced cough.
- Several genetic variants on HLA genes predict risk of severe ADRs, including severe cutaneous adverse reactions (SCAR). SCAR includes Stevens-Johnson syndrome and toxic epidermal necrolysis, and results in mortality rates of up to 25%. In those who test positive for HLA-B*58:01, the odds ratio for developing SJS has been reported to be as high as 580, and a recent meta-analysis suggested an odds ratio for allopurinol-induced SCAR in HLA-B*58:01 carriers as 165 compared to allopurinol-tolerant controls. Due to the low incidence of this reaction in general, the positive predictive value for HLA-B*58:01 is ~1.5%, but the negative predictive value is 100% (based on data from the Han-Chinese and Thai populations: Clinical Pharmacogenetics Implementation Consortium Guidelines for Human Leukocyte Antigen-B Genotype and Allopurinol Dosing 2013).

TreatGx\textsuperscript{plus} also provides dosing optimized for a patient’s unique genetic makeup and health information which can help prevent adverse side effects or ineffective course of treatment, for example:

- In depression, patients that are poor metabolizers for CYP2C19 should consider a reduction of the recommended dose of SSRIs, such as citalopram and sertraline. Patients that are poor metabolizers for CYP2D6 should consider a reduction of the recommended dose of fluvoxamine.
2. What are positive predictive values (PPV) and negative predictive values (NPV) of the test?

Pharmacogenetic testing is much more complicated than Mendelian genetics (where a single gene mutation can cause the occurrence of a disease). Response to medications is multifactorial and can be affected by multiple genetic variants (some of which may not be discovered yet), so the PPV and NPV for single genetic variants are not as straightforward as with other types of genetic tests.

The TreatGx\textsuperscript{plus} pharmacogenetic test reports on outcome risks with use of certain medications, and is not intended as a diagnostic tool. The pharmacogenetic results should be used in combination with other non-genetic patient factors within TreatGx to help select the safest and most effective medications for individual patients. The potential benefit of pharmacogenetic tests is often concluded from the strength of the association between the genetic variant and an outcome (i.e. adverse event or treatment success), and measures of clinical validity such as positive predictive value (PPV) or negative predictive value (NPV) are generally not reported.

3. Why is the medication included in the report but not adjusted by genetics in the TreatGx decision support tool?

Overall, TreatGx\textsuperscript{plus} includes more than 100 medications with genetic markers. Some medications are included in the report but are not included in the decision support tool.

The medications that are not adjusted for genetics in the decision support tool:

- may not have a condition in the tool yet,
- may not be commonly used as a first or second line therapy option or
- may not have clear evidence for treatment adjustment based on genetics.

The decision support tool is updated regularly as new evidence becomes available, and as new medications are included.

4. If a patient doesn’t have any of the conditions covered, should they buy the test?

The service is targeted for people with the conditions covered so they can use the software. If their condition is not covered, patients might still get useful information in the interactive TreatGx\textsuperscript{plus} PDF report which is medication based.

5. Can you advise whether the test expense would qualify under the Canadian Revenue Agency medical expense rules (and therefore qualify for health spending account reimbursement)?

With certain insurance companies TreatGx\textsuperscript{plus} can be reimbursed through your Health Spending Account (HSA) with a prescription from your doctor. The test includes a requisition form in the kit so you can take it to your provider and ask them to complete and sign it. According to the CRA website, you will be able to claim the cost of the test under your HSA with a signed requisition form.
6. What are you referring to by “cold medication” in the TreatGx plus report?

The statement included in the report ("increased risk or severe and sometimes fatal cold medication induced cutaneous adverse reaction with ocular complications") is referring to Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), both of which are severe skin reactions. Both are very rare and affect approximately 1 in 1 million people per year. Often these skin reactions are thought to be triggered by a particular medication, but because they are so rare, it can be difficult to study. If SJS or TEN occurs with ocular complications, this is a more specific type of reaction often associated with the use of cold medications, and can cause ongoing issues such as dry eye and ingrowth of eyelashes.

7. I am trying to confirm that a prescribed medication is appropriate for my patient, but it is not coming up as an option in the TreatGx software. Why not?

TreatGx is intended to be used as a decision support tool when modifying medication therapy. The software assumes the current therapy is ineffective or not tolerated and offers the next line of medication options. If you would like to use TreatGx to check the dosing for a medication or its appropriateness for a patient, remove the medication from the "Current Medication" list.

You can change any of the patient attributes, except genetics, to see if the medication has been contraindicated due to one of these factors.

8. I am not getting the result I was expecting in TreatGx. Please help!

1. Please ensure that all the patient information has been entered correctly, particularly the "Drug History," "Medication History" and "Current Medications" sections.

2. TreatGx is an evidence-based software designed to help identify safe and effective medications. While we do take into consideration popular prescribing practices within the system, we have excluded some medications or have moved them to second- or third-line options in accordance with the most up-to-date, highest levels of evidence. The best available evidence should always be used when determining the medication options for each patient.

3. "Seek Specialist Advice" may appear alongside drug options. This is often due to numerous contraindications, drug interactions, complexity of drug regimen, or severity of the disease. It may also be due to monitoring requirements for the drug, or there may be non-drug therapy that specialists can provide.

9. Will pharmacogenetic testing be useful for a patient’s current medications?

If a medication is working and is well tolerated, pharmacogenetic test results should not be used to change therapy for the following reasons:

• If a patient is already taking a medication, we know how they react to it
• Pharmacogenetic testing is most relevant to new medications (i.e. for selecting one that is more likely to be effective and less likely to cause side effects, or for dose adjustment) but may be used to help support a decision to change a current medication due to lack of effect or side effects
References


