# Guide to TreatGx$^{plus}$


To ensure that we are providing up-to-date information, there are many links within this document. We therefore recommend that you refer to the online version of this document rather than printing it.

# Table of Contents

# 1. TreatGx$^{plus}$ Pharmacogenetic Test

## 1.1. Kit contents

The test kit currently includes:

- Sample collection kit
- TreatGx$^{plus}$ requisition form
- Pre-paid mailer

## 1.2.Sample collection

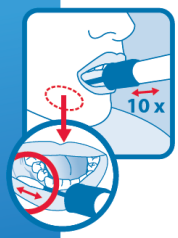
See a video demonstration of sample collection technique.

**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.

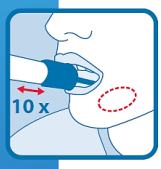
* NOTE: The collection kit expires 3 months from the date of purchase.

**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 register for a TreatGx account when they purchase their test. They will receive an email once the laboratory analysis of their sample is complete and their results are available on TreatGx. Patients can access TreatGx from their home or a health care practitioner's office using a computer, tablet or mobile device. Patients can invite a health care provider, a clinic, or a pharmacy to access their TreatGx$^{plus}$ report and use the software.

### 1.4.Health care provider account creation

There are two ways to register for a health care provider account:

1. Single provider account
2. Corporate account (for pharmacies and clinics)
   - See 3.6 for details

If the healthcare provider enters their TreatGx account ID number when registering for an account, they will be able to see the patient's results in their account.

### 1.5.Lab technology

Agena MassArray, an industry standard platform for high-quality multiplex SNP testing is the primary analytical platform. MassArray analyses are highly reproducible and precise (higher than 99% reproducibility on calls; published literature suggests 99.7% reproducibility).

Sanger sequencing and/or long-range sequencing are used as a gold standard for HLA typing, and quantitative LightCycler PCR is used to confirm the CNV calls for CYP2A6 and CYP2D6.

There are established criteria for sample acceptance/rejection, DNA concentration, and DNA quality cut-offs. The lab performs double checks on tube racks and specimen lists to ensure correct patient samples have been pulled before assay set-up.

### 1.6.Processing time

TreatGx$^{plus}$ pharmacogenetic test results are uploaded to the patient's TreatGx account within 10 business days of the lab receiving the sample.

## 2. TreatGx$^{plus}$ Pharmacogenetic Report

### 2.1.Report Overview

The Report Overview is on the second page of the TreatGx$^{plus}$ 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, sorted by treatment category, 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 ℹ. Online, the report is interactive and all the medication names are hyperlinks to more detailed medication information contained in the Medication Report.

**Analgesia**

- Acetylsalicylic acid
- Alfentanil
- ℹ Celecoxib
- Codeine
- ℹ Diclofenac
- Fentanyl
- ℹ Flurbiprofen
- Morphine
- ℹ Oxycodone
- ℹ Piroxicam
- ℹ Tramadol

**Autoimmune**

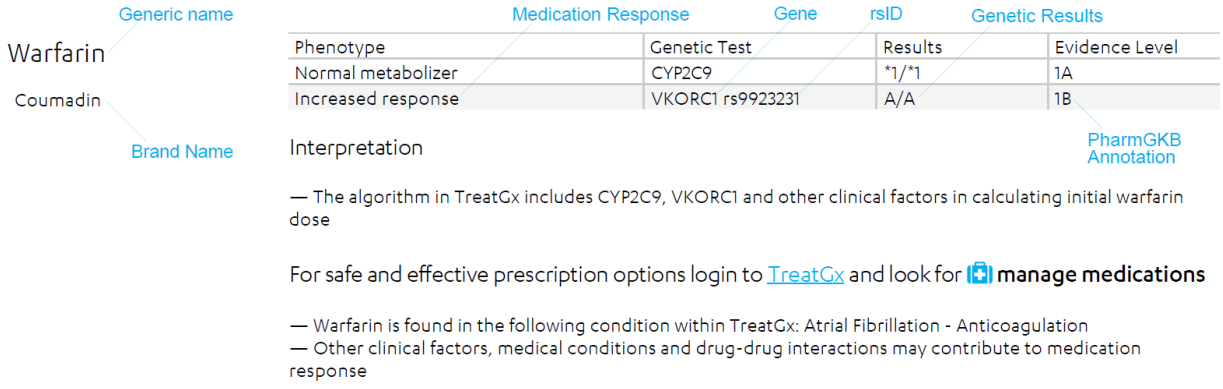
- ℹ Adalimumab
- ℹ Captopril
- ℹ Cilazapril
- ℹ Clopidogrel
- ℹ Enalapril
- ℹ Flecainide
- ℹ Fosinopril
- ℹ Hydrochlorothiazide
- ℹ Lisinopril
- ℹ Metoprolol
- ℹ Perindopril
- ℹ Propafenone
- ℹ Quinapril
- ℹ Ramipril
- Rosuvastatin
- ℹ Simvastatin
- Gentamicin
- ℹ PEG-interferon alpha
- Streptomycin
- Tobramycin
- ℹ Voriconazole

**Mental Health**

- ℹ Alprazolam
- ℹ Amitriptyline
- ℹ Aripiprazole
- ℹ Asenapine
- Atomoxetine
- ℹ Bromazepam
- Bupropion
- Carbamazepine
- ℹ Haloperidol
- ℹ Imipramine
- Lamotrigine
- ℹ Lorazepam
- ℹ Loxapine
- ℹ Lurasidone
- ℹ Methotrimeprazine
- ℹ Nitrazepam
- ℹ Nortriptyline
- ℹ Olanzapine
- ℹ Oxazepam
- ℹ Paliperidone
- Paroxetine
- ℹ Perphenazine
- Pimozide

## 2.3.Medication Report

The Medication Report provides information on how a patient's pharmacogenetic results affect each medication. Patients and healthcare providers are encouraged to use the TreatGx decision support software to discover personalized medication options.



## 2.4. Levels of Evidence

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

Strongest Evidence

**PharmGKB evidence levels for genetic variants influencing drug response:**[1]

| | | | |
|---|---|---|---|
| ▪ ▪ ▪ ▪ ▪ ▪ | 1A | - | Pharmacogenetic guideline available |
| ▪ ▪ ▪ ▪ ▪ | 1B | - | Cohort studies with statistical significance and strong effect size |
| ▪ ▪ ▪ ▪ | 2A | - | Established drug response variants likely to have functional significance |
| ▪ ▪ ▪ | 2B | - | Association studies, some studies do not show statistical significance and/or have small effect size |
| ▪ ▪ | 3 | - | Single study or multiple studies with no clear association |
| ▪ | 4 | - | Preliminary level of evidence from a case study, non-significant study, molecular or functional assay |

Least Evidence

In some cases, Health Canada and FDA drug label warnings are included if they are deemed to be clinically relevant. For pharmacogenetic recommendations that are based on a clinical study, a reference to the original paper is given since no PharmGKB level of evidence is available.

## 2.5. Guidelines Table

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 TreatGx$^{plus}$ 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.

## 2.7.Limitations & Liability

The TreatGx$^{plus}$ report includes the following limitations and liability disclaimer for genetic translation and interpretation:

### Limitations

The annotations and interpretations provided in this report are based on scientific literature and do not take into account drug-drug interactions, medical conditions or other clinical factors that may affect medication response. Gene-drug interactions are ranked according to guidelines, level of evidence and clinical utility. Predicted phenotype and interpretation may change depending upon the emergence of new literature, industry standards and guidelines. Genetic test results and interpretation may be inaccurate for individuals who have undergone or are receiving non-autologous blood transfusion, tissue, or organ transplant therapies.

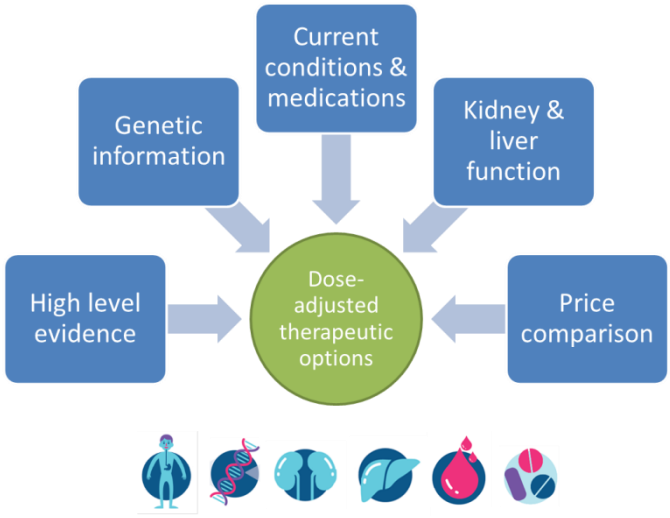
The report includes alleles of proteins involved in the metabolism of many medications. In rare cases, a variant that is not covered may be typed as *1 or other variants. In the case of pseudogenes and mutations in the untranslated regions of genes, incorrect allele typing may occur despite proper SNP detection. Preferential amplification of one allele over another present in the sample may also lead to incorrect genotyping. Copy number variations are detected as 0, 1, 2, 3, or >=4 copies.

### Liability Disclaimer

The report is not a diagnostic test, and TreatGx is not a prescribing system. You should discuss your pharmacogenetic information with a physician or other health care provider before you act upon the pharmacogenetic information resulting from this report. The medication brand names are not an exhaustive list and do not include combination therapies. Not all medications in this report are included in the TreatGx application.

# 3. TreatGx Clinical Decision Support Software

The TreatGx clinical decision support software 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 many different patient-specific factors, including current symptoms, concurrent medications & conditions, renal & hepatic function, and medication history. See sections 3.4-3.7 below for more information.




## 3.1. Conditions

Conditions covered by TreatGx.

Most conditions in TreatGx are primary care oriented. As new evidence becomes available the algorithms that drive the medication decision support are updated. The team strives to add new conditions as frequently as possible with each algorithm taking more than 400 hours to build.

***As of July 6th, 2020, 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.

*Endocrine*: Diabetes Mellitus (Type 2).

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

*Genitourinary Renal*: Urinary Tract Infection.

*Mental Health*: Attention-Deficit Hyperactivity Disorder (ADHD), Anxiety Disorders (Generalized Anxiety Disorder, Social Anxiety Disorder), Bipolar 1 Disorder, Depression, Schizophrenia.

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

*Neurology*: Alzheimer's (coming soon), Epilepsy, Migraine (Acute, Prophylaxis).

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

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

*Other*: Insomnia, Smoking Cessation.

## 3.3.Patient factors

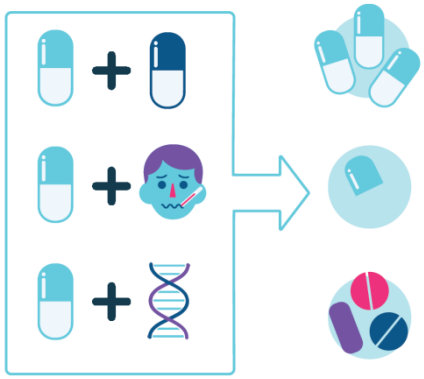
Patient factors are used to personalize medication options for each condition, including:

- 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

## 3.4.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).

## 3.5.Drug-drug, drug-disease, drug-gene interactions



Three main types of drug interactions are taken into account by the TreatGx software when generating personalized medication options:

- Drug-Drug (for example, when taking an NSAID with an SSRI, PPIs will be offered as gastroprotection due to the significantly increased risk of gastrointestinal bleeding)
- Drug-Disease (for example, NSAIDs should be avoided in those patients with severe renal impairment)
- Drug-Gene (for example, those who test positive for HLA-B*58:01 should avoid allopurinol due to a higher risk of Stevens Johnson syndrome and toxic epidermal necrolysis, febuxostat would be a safer choice)

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.

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, weight, height, and laboratory test results.

Other companies, e.g. myDNA, provide only a genetic report and only report drug-gene interactions.

## 3.6.Limitations

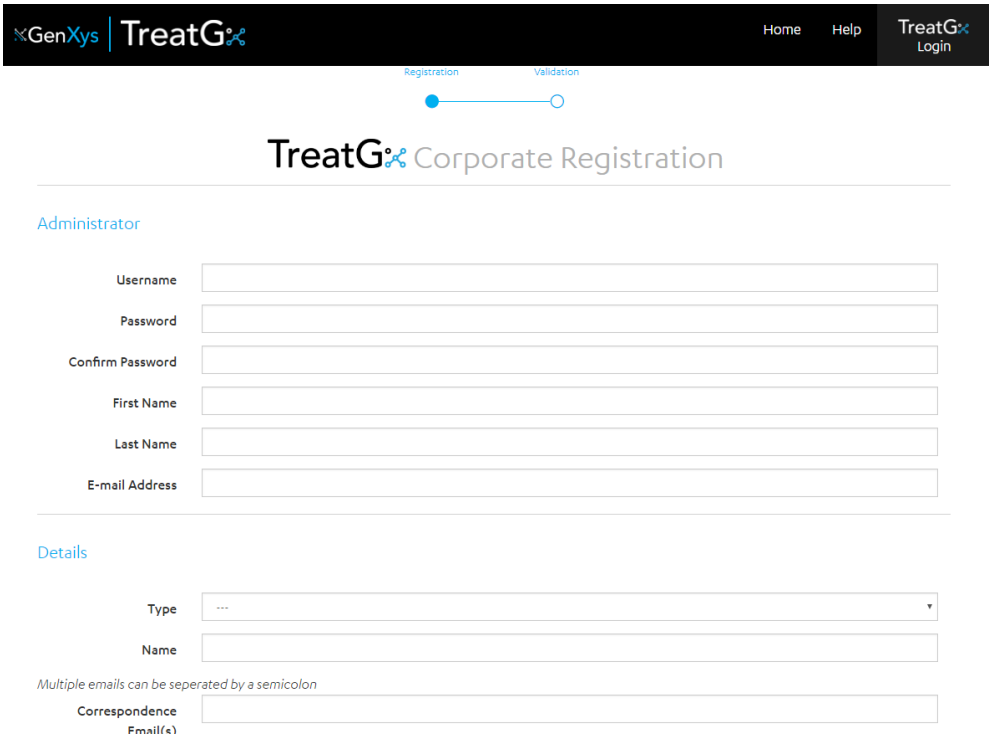
The TreatGx software is not intended for use in children and adolescents, or those who are pregnant or breastfeeding, unless otherwise specified. Certain algorithms have been developed with special populations in mind:

- GERD: includes options for pregnancy
- ADHD and pediatric asthma: include dosing for children and adolescents

The TreatGx$^{plus}$ pharmacogenetic results included in the report can be used by a health care provider to inform treatment decisions in these special populations where appropriate.

## 3.7.Creating a corporate account (for pharmacies or clinics)

To register for a corporate, go to registration page.
For additional account creation information, see corporate accounts.




Account administrators can add and manage provider accounts as well as accept invitations from patients. However, administrator accounts do not have access to patient information. To access patient profiles and pharmacogenetic results, each health care professional needs to have their own account.

Complete the following on the registration page:

*Administrator*

• Username: This user only has access to the administration dashboard and ***does not have access to patient profiles***.
• Password
• First Name, Last Name
• Email: this email will be associated with the administration account. For correspondence emails, see 'Details' below.

*Details*

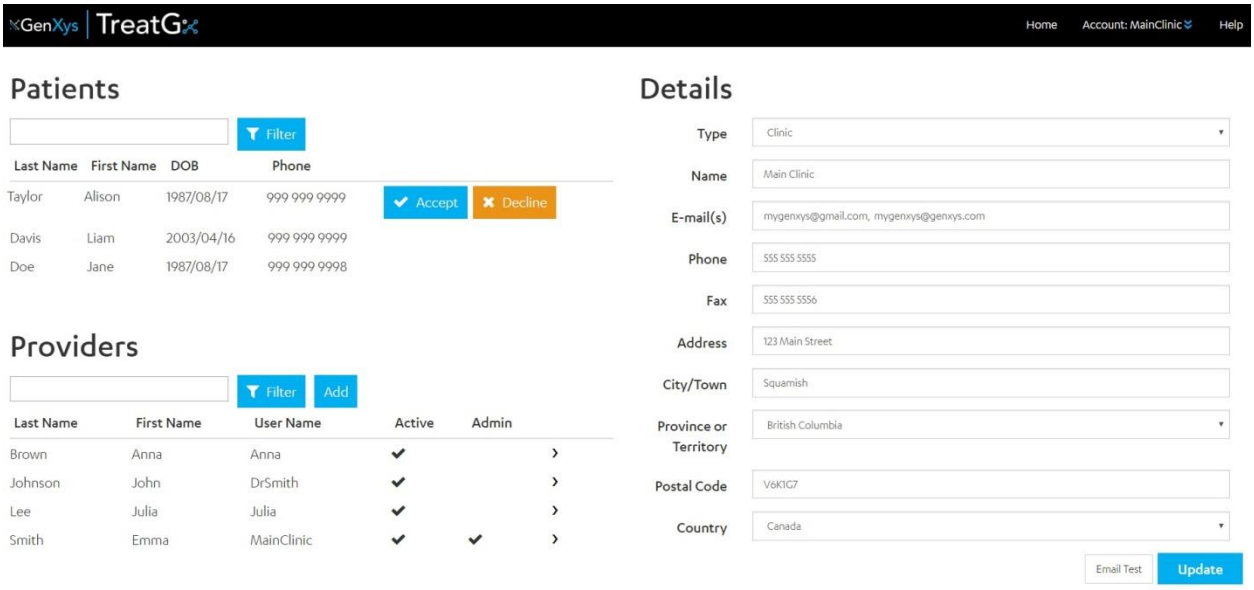
(Note: name, type, and address are visible to patients. Phone, fax and emails are not visible to patients.)
• Type: Select the type of corporate account from the drop-down menu (this includes clinics, pharmacies, and other)
• Name: Name of clinic, pharmacy, etc
• Correspondence Email(s): Multiple emails can be separated by a semicolon. This (these) email(s) will be used to send notifications (for example, patient invitations) and updates. As an account administrator, you can update the correspondence emails at any time from your account dashboard.
• Address
• Phone, Fax

• Time zone
• Agree to Terms of Service and Communications

Once the corporate account has been approved, a notification email will be sent and online log in will be available with the administrator user name and password.

*Logging in to TreatGx*
Log in using the administrator username and password to manage provider accounts and see a list of clinic patients. It is helpful to bookmark the login page.

The corporate account dashboard displays the patient cases the team has access to (Patients), the list of provider accounts (Providers) and the corporate account details (Details):




From the dashboard, new providers can be added to the corporate account and existing provider accounts can be searched. Search and filter the healthcare providers in your account using the "Filter" button.

To add a new provider, select 'Add' in the 'Provider' section of the dashboard. From there a new healthcare provider account will be created. The healthcare provider should be present to enter a secure password and agree to the terms of service.

Please note: Title, First Name, and Last Name are visible to patients and will help them when searching for the clinic.

Healthcare providers need to take note of their user name and password as they will need them to log in. Healthcare providers log in using their own username and password to access patient reports and use the medication decision support. Passwords can be updated after login. It is helpful to bookmark the login page.

For more information regarding corporate accounts, see corporate accounts.

## 3.8.Accepting patient invitations

Access additional information on accepting patient invitations.

Patient invitations can be accepted or declined from the patient list in the dashboard. After an invitation is accepted, all the health care 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 patients and their date of birth. All providers can access these patients' records and see patient invitations in the queue.

Account administrators do not have access to patients' records.

*Please note*: Invitations cannot be accepted from individual health care provider accounts and must be accepted from the corporate administrator's dashboard. To access a patient case, providers need to log in using their provider account credentials (i.e. username and password).

Declined invitations are removed from the account.

## 4. Comparison of TreatGx$^{plus}$ with other PGx testing services

TreatGx$^{plus}$ offers more than a test; the service also includes an interactive pharmacogenetic report and access to the TreatGx medication decision system. Unlike any other medication decision support system, TreatGx$^{plus}$ incorporates pharmacogenetics, the clinical stage of the disease, the biophysical profile and concurrent medications to provide personalized medication options.

## 5. Resources

The GenXys website contains information regarding what is included with the service, details about the test, FAQs, and further resources.

Client-care specialists are available for support: info@genxys.com

Patient and healthcare professional resources

Education

Frequently asked questions

The TreatGx software is not intended as a prescribing tool and patients should always consult with their health care providers before making any changes to their medication therapy. No personalized medication advice or evaluation will be given to individual patients by the TreatGx$^{plus}$ support team, except to help clarify information provided in the TreatGx$^{plus}$ medication report or in the TreatGx software. Patients are encouraged to talk to their pharmacist (and undergo a medication review, if applicable) or other health care providers to discuss their current medication therapy.

For patients already taking medications affected by genetic variants in the TreatGx$^{plus}$ report, this should not be cause for discontinuation of the medication if it is effective and well tolerated.

The TreatGx$^{plus}$ pharmacogenetic test results are most useful when selecting and dosing new medications.