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PGx ExploreEZ

A Web-Based User-Friendly Tool for Exploration of Pharmacogenomics Reference Resources

A Project submitted for the Master's degree in Bioinformatics

By

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Abstract

As it is clear that one size doesn't fit all, one medication with the same dosing regimen may not be effective or safe for all patients with the same disease due to various factors. One key factor is the genetic variations between individuals.

Pharmacogenomics (PGx), a rapidly evolving field within precision medicine, has the potential to revolutionize healthcare by tailoring treatments based on an individual's genetic makeup, which can optimize treatment outcomes and minimize the risks of adverse reactions.

However, several barriers hinder the successful implementation of pharmacogenomics in clinical practice. A major challenge is the lack of knowledge among healthcare providers, researchers, and other targeted communities.

To address this barrier, we present "**PGx ExploreEZ**", a web-based, user-friendly tool for exploring pharmacogenomics reference resources developed using the R shiny package. Supplied with manually collected and curated data about gene-drug associations, clinical recommendations, and other relevant data from pharmacogenomics reference resources, this tool serves as a gateway to explore these resources easily.

With its user-friendly and interactive interface, **'PGx ExploreEZ**' enables healthcare professionals, researchers, and interested users to easily access and explore essential information in pharmacogenomics.

"**PGx ExploreEZ**" aims to simplify the process of accessing valuable insights in the field of pharmacogenomics in order to bridge the knowledge gap and pave the way for the implementation of pharmacogenomics into clinical practice.

Keywords: pharmacogenomics, pharmacogenetics, personalized medicine, shiny package, R programming language, web-based tool.

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1.1 Preface:

Have you ever wondered why a medication that works well for one patient does not work as well for another? or why it occasionally causes adverse drug reactions (ADRs)? **(Figure 1)**

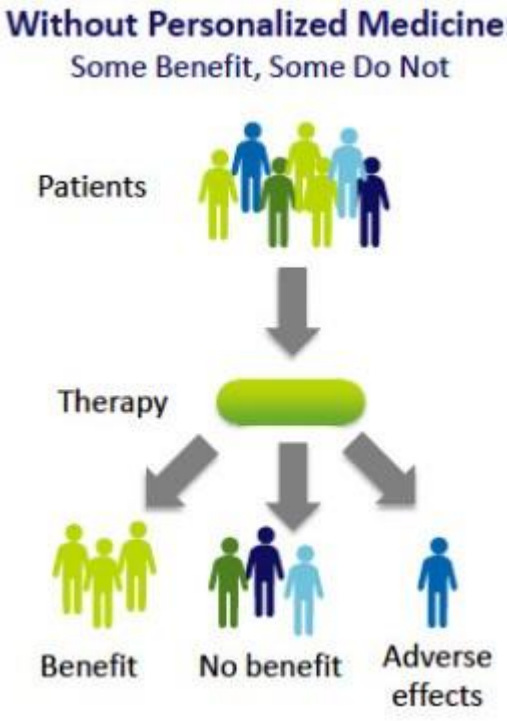

Figure 1: Conventional Medicine: same disease, same treatment (source: Bayer Healthcare)

Here is a hint for the answer… **(Figure 2)**

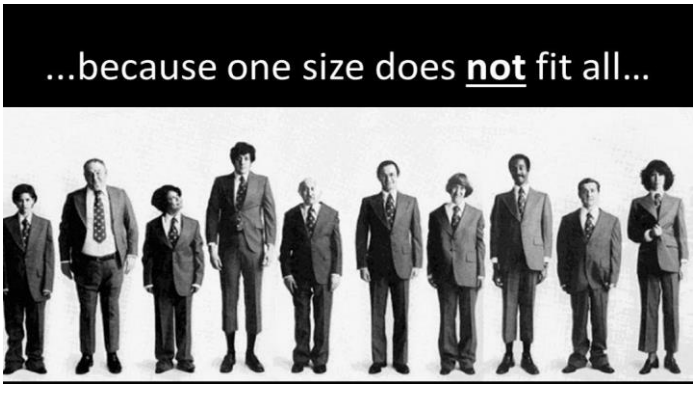

Figure 2: One Size Does Not Fit All

This commonly observed phenomenon, known as ***individual variability in drug response*** (***IVDR***), results in a wide range of therapeutic outcomes and even ***adverse***

drug reactions (***ADRs***) and consequently has a significant health and economic impact. (Zhao et al., 2023)

IVDR is a multifactorial phenomenon influenced by genetics, age, gender, lifestyle, disease state, drug-drug interactions, environmental factors, and gut microbiota. (Zhao et al., 2023) **(Figure 3)**

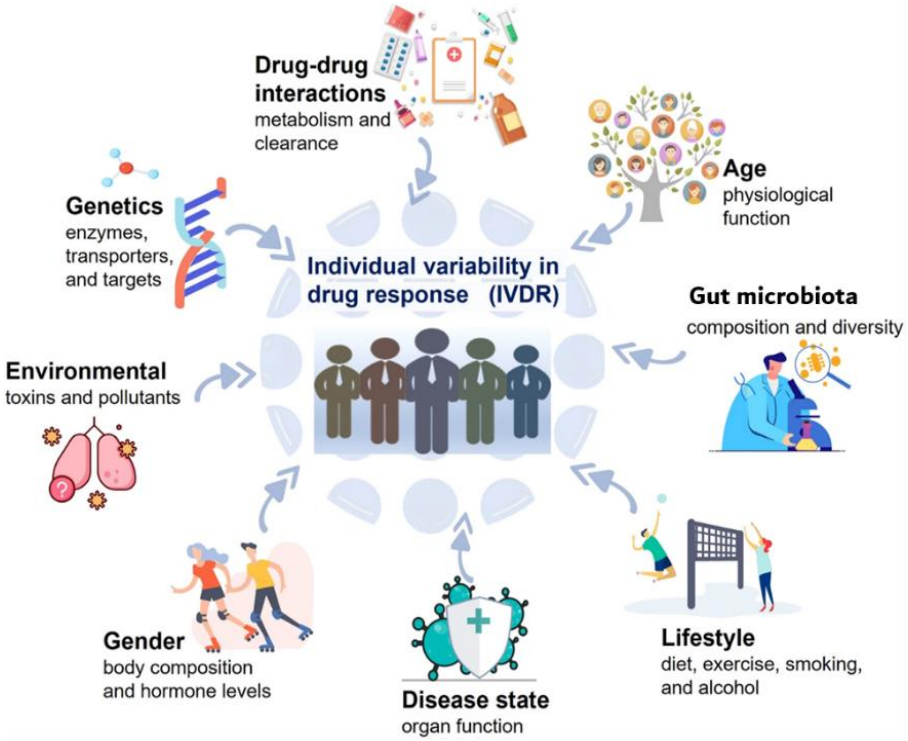

Figure 3: Causes of the individual variability in drug response (IVDR)

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Understanding these factors is crucial for optimizing drug therapy and minimizing ADR risk which resembles a major public health problem. (Zhao et al., 2023)

Precision medicine (also known as ***individualized*** or ***personalized*** medicine) aims to design tailored medical treatments based on a person's genetic, environmental, and lifestyle factors. (Zhao et al., 2023) **(Figure 4)**

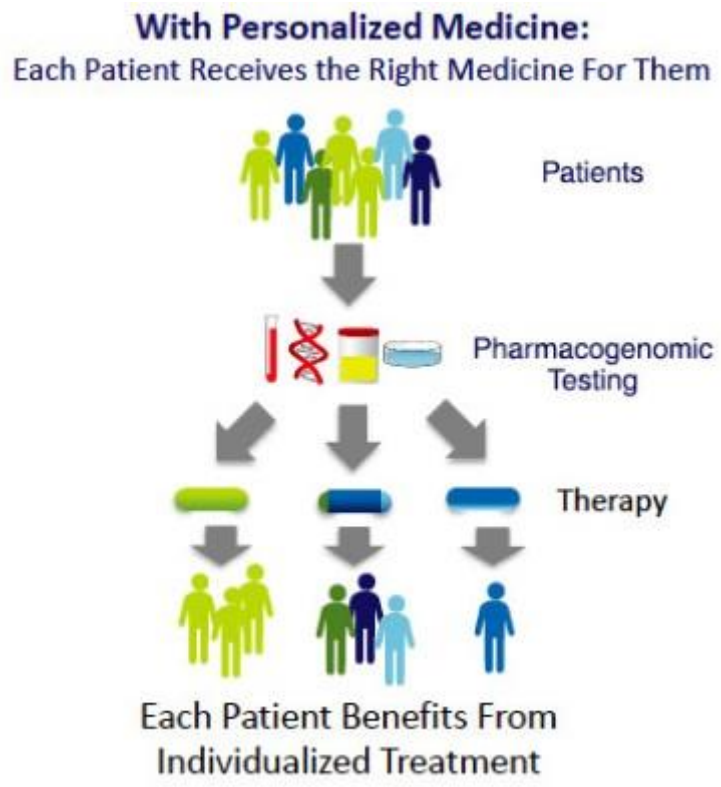

Figure 4: With precision Medicine, each patient gets the right drug in the right dose, maximizing the benefit and minimizing the adverse reactions. (source: Bayer Healthcare)

Interestingly, the roots of the emerging personalized and genome-based medicine can be traced back to the teachings of ***Hippocrates***, the Greek physician and so-called "***Father of Western Medicine***". The quote of Hippocrates: "***It's far more important to know what person the disease has than what disease the person has***" envisions precisely what precision medicine aims to achieve. (Lakiotaki et al., 2016)

Pharmacogenetics is the study of genetic factors that influence drug response. These genetic factors are variations in individual genes encoding drug-metabolizing enzymes, transporters, and targets, in other words, they influence drug ***pharmacokinetics* (*PK*)** (how the body affects the drug through ***ADME***: absorption, distribution, metabolism, and elimination), and ***pharmacodynamics* (*PD*)** (how the drug affects the body).

Pharmacogenomics studies how genome-wide analysis may be used to identify such genetic factors. We refer to both of them as ***PGx***. PGx has greatly advanced over the last decade. It revolutionized drug therapy during the latter half of the 20th century, and it continues to detect hundreds of associations between genes and drug response. (Lakiotaki et al., 2016)

Pharmacogenomics (***PGx***) is the most actionable field of knowledge that could motivate the integration of precision medicine into medical practice since pharmacogenomics plays a critical role in drug safety and efficacy; Studies show that the most commonly prescribed pharmaceuticals are effective in only ***25%*** to ***60%*** of patients. Furthermore, each year, hospitals in the United States report more than two million patients with ADRs, resulting in up to ***100,000*** mortalities and a total cost of up to ***$5.6 million*** per hospital. (John et al., 2021)

Even though the concept of pharmacogenomics has been around since the ***1950s***, it is only now that we witness its proper integration with clinical informatics for ***clinical decision support*** (***CDS***). (John et al., 2021)

Implementation of pharmacogenomics into clinical practice has been slow. Reasons include a perceived lack of clinical utility, inability to access genotyping tests, lack of clarity on cost-effectiveness, lack of knowledge on how to interpret pharmacogenomic tests and the actions to take when a patient has a variant allele, worries about disruption to the normal clinical pathway and concerns over confidentiality issues. (Pirmohamed, 2023)

1.2 Literature Review

1.2.1 A brief history of the emergence of team science in pharmacogenomics:

The concept of “pharmacogenetics” was first put forward by the famed American geneticist ***Arno Moltulsky*** at the University of Washington and ***Kalow*** at the University of Toronto over a half century ago. (Roden et al.,2019)

By the 1990's the field began to evolve to be the cornerstone for precision medicine. (Davis, B. H., & Limdi, N. A. ,2021)

The substantial progress in discovery, evidence synthesis, guideline development, and implementation efforts are achieved by national/ international efforts, supported and guided by the ***National Institutes of Health*** (***NIH***). (Davis, B. H., & Limdi, N. A. ,2021)

Much of the momentum was sparked by the creation of the ***Pharmacogenetic Research Network*** (***PGRN***) and ***Pharmacogenomics Knowledge Base*** (***PharmGKB***; ***2000***) and the technological advances brought to bear by the completion of the ***human genome project*** (***2003***). (**Figure 5**)

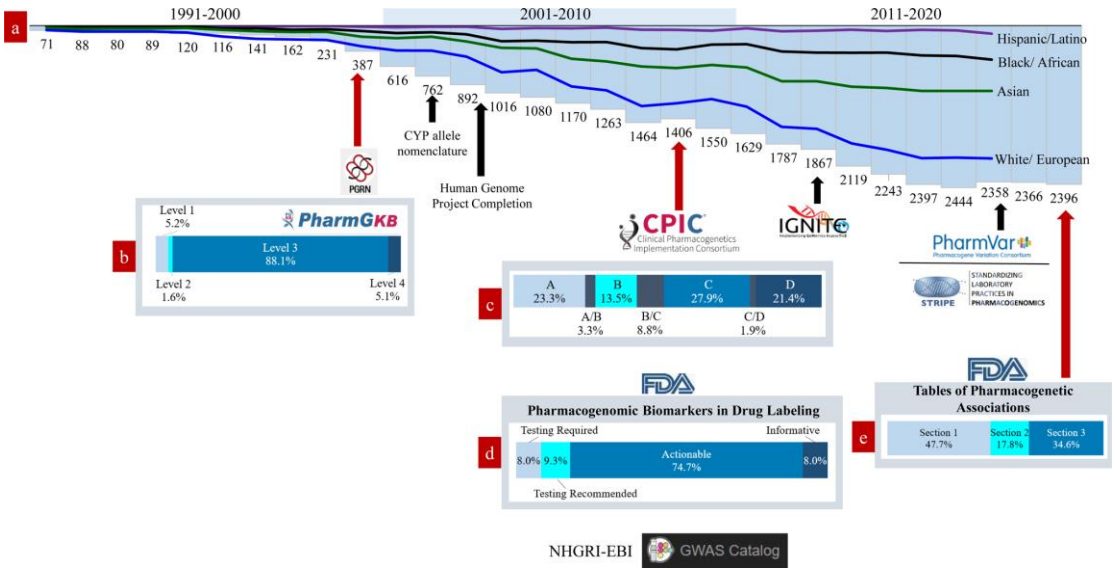

Figure 5: The timeline of pharmacogenomic discovery, the emergence of team science and the development of gene-drug clinical guidelines (Davis, B. H., & Limdi, N. A. ,2021)

Initial investigations interrogated variation in a small number of genes based on a priori knowledge of pharmacology (absorption, distribution, metabolism and excretion and drug receptors) through gene-centric approaches. (Davis, B. H., & Limdi, N. A. ,2021)

With advances in genome sciences and technology, evolution of ***pharmacogenetics*** to ***pharmacogenomics***, shifted focus from ***gene-centric studies*** to ***genome-wide association studies*** (***GWAS***) in large patient cohorts and assessed the entire spectrum of drug response to identify novel variants, inform new biology, and explain the genomic component of variable response. (Davis, B. H., & Limdi, N. A. ,2021)

The discovery efforts and translation of genomic variation influencing therapeutic effects and adverse drug reactions are catalogued by the ***PGRN*** (https://www.pgrn.org/), and genotype-phenotype relationships curated for dissemination by ***PharmGKB*** (https://www.pharmgkb.org).

PharmGKB also hosts genotype-guided drug selection and dosing guidelines published by the ***Clinical Pharmacogenetics Implementation Consortium*** (***CPIC***), the ***Dutch Pharmacogenetics Working Group (DPWG)***, the ***Canadian Pharmacogenomics Network for Drug Safety (CPNDS)*** and other professional societies.

The PharmGKB along with a comprehensive catalogue of allelic variation of genes influencing drug response provided by the ***Pharmacogene Variation Consortium*** (https://www.pharmvar.org/) CYP Allele Nomenclature until 2018, provides the foundation for expert review and development of gene/drug clinical guidelines by CPIC (https://cpicpgx.org/).

The Food and Drug Administration (FDA) catalogues package inserts updated with pharmacogenomic information (https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling), and in 2020, released guidance on gene/drug associations with evidence to suggest a genetic contribution to altered drug response (https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations). (Davis, B. H., & Limdi, N. A. ,2021)

1.2.2 Web Resources for Pharmacogenomics

Empowered by the advances in sequencing technology and genome-wide association studies, pharmacogenomic scientists are now capable of gathering larger and more precise amounts of genomic and clinical data. Thus, additional scientific literature, popular press articles, and useful web resources related to pharmacogenomic studies have been published in recent years.

- ***PharmGKB***

The Pharmacogenomics Knowledgebase (PharmGKB) is a database of genetic variations, annotations, drug pathways, and their relationship with drug response. It is a project managed by Stanford University and supported by the NIH/the National Institute of General Medical Sciences (NIGMS). PharmGKB aims to help researchers to understand how genetic variations in different individuals can affect drug reactions. Information in the PharmGKB database is mainly derived from the scientific literature, and is properly stored and displayed at different levels.

Additionally, PharmGKB also integrates information from the Clinical Pharmacogenetics Implementation Consortium (CPIC) to provide drug-dosing guidelines according to personal genotype.

PharmGKB is updated periodically in response to newly-published papers, and presents all its data such as variations, annotations, summary information, and guidelines on its website. PharmGKB is well known and is the preeminent resource for translational researchers and clinical doctors to implement pharmacogenomics information in their research or clinical practice. (Zhang, G., Zhang, Y., Ling, Y., & Jia, J., 2015)

- ***CPIC***

The Clinical Pharmacogenetics Implementation Consortium (CPIC) was formed in 2009 as a shared project of both the Pharmacogenomics Research Network (PGRN) and PharmGKB. The CPIC aims to provide detailed gene/drug clinical practice guidelines to promote the integration of pharmacogenetic research into clinical practice. The CPIC collects all levels of scientific evidence, from biological research to

clinical studies, and evaluates and incorporates this scientific evidence into the guidelines. Rather than defining the indications for testing, these CPIC guidelines will help the clinicians understand how a genetic test can be used to optimize drug therapy. A CPIC guideline is a comprehensive system of evidence linking genotypes with phenotypes including the rules of assigning phenotypes to genotypes, the rules of prescription according to genotypes or phenotypes, and the strength of the evidence. All CPIC guidelines are validated by peer review, updated periodically, and freely available via the CPIC website. (Zhang, G., Zhang, Y., Ling, Y., & Jia, J., 2015)

- ***DrugBank***

Unlike PharmGKB, which focuses on drug reactions according to human genomic variations or specific genotypes, the aim of DrugBank is to build a comprehensive resource on drugs including their pharmacological and biochemical information, mechanisms, and targets. The first version of DrugBank was released in 2006 and provided data only on selected FDA-approved drugs and their targets. With the development and upgrading of the database, more information is now available including, but not limited to, pharmacological, pharmacogenomic and molecular biological, drug-food and drug-drug interaction, metabolic enzymes, and quantitative structure activity relationships (QSAR) data as well as other drug-related data such as absorption, distribution, metabolism, and excretion (ADME) profiles. The basic drug information such as drug names, structures, salt-forms, targets and actions are still being expanded upon and updated.

In comparison to PharmGKB, DrugBank is a comprehensive database of drugs that can facilitate in silico drug design, drug target discovery, drug screening or docking, interaction prediction, metabolism prediction, and pharmaceutical education.

(Zhang, G., Zhang, Y., Ling, Y., & Jia, J., 2015)

- ***The U.S. Food and Drug Administration (FDA):***

With their famous, evidence-based pharmacogenetic tables:

- ✓ Table of Pharmacogenomic Biomarkers in Drug Labeling
- ✓ Table of Pharmacogenetic Associations

FDA is considered one of the most reliable resources of PGx Knowledge.

1.2.3 Web-Based Tools for Pharmacogenomics:

During the last few years, a number of pharmacogenomics web-based tools has been developed to translate the state-of-the-art PGx knowledge into practical guidelines and recommendations that could be integrated in daily clinical practice.

- ***electronic Pharmacogenomics Assistant (ePGA):***

http://www.epga.gr/ (accessed in December 2023)

ePGA is designed to efficiently couple individual data with state-of-the-art pharmacogenomics (PGx) knowledge. Its primary purpose is to provide personalized genotype-to-phenotype translation linked to clinical guidelines. This allows clinicians and researchers to make greater use of public genotype-phenotype databases, identify population differences in drug response, and customize translation based on subsets of variants of clinical interest. (Lakiotaki et al., 2016)

Basically, it provides two services; Explore and Translate:

- ✓ The explore service contains a collection of state-of-the-art gene-drug interactions. The dataset contains also metabolizing status and related haplotype information with links to original content. The interactions might be either dosing guidelines (high confidence clinical guidelines) or clinical annotation (minor or unvalidated guidelines). The dataset can be browsed and the recommendations are appeared as an expandable tree.
- ✓ The translation service offers the ability to upload an individual's genotype profile in VCF format. This profile is matched with a collection with known variants that are associated with ADME reactions. The results is a set of drugs that according to the database, their efficacy, dosage or action might be different from the reference. These results are indicative and by no means substitute a doctor's, clinician's or other expert's medical opinion.

ePGA is built using the Django framework and utilizes R Studio's Shiny web-application framework for its web-based interface.

Note: when accessing the ePGA website, it didn't seem to be properly working.

- ***Pharmacogenomics Clinical Annotation Tool (PharmCAT):***

https://pharmcat.org/ (accessed December 2023)

PharmCAT is a tool designed to help with the implementation of pharmacogenomics (PGx) by extracting genomic variants, inferring haplotypes, and generating a report containing genotype/diplotype-based annotations and guideline recommendations. (Sangkuhl et al., 2020)

PharmCAT requires several types of ***input***, including a user-provided VCF file and multiple files packaged with the tool. The user-provided normalized VCF file is the key input for PharmCAT. The VCF file must be aligned to the GRCh38 and verified that the variant representation format matches that in the allele definition files.

The ***output*** of PharmCAT is an HTML-formatted report. The report is divided into four sections: Genotype Summary, CPIC Recommendation, Allele Call Details, and Disclaimers. The report contains diplotypes and recommendations based on the genetic data provided. The report is human-readable and provides extensive formatting and layout. PharmCAT can also be configured to output the supporting data model as a JSON document.

Some of its features:

- Extracts genomic variants from a genetic data set.
- Infers haplotypes and generates a report containing genotype/diplotype-based annotations and guideline recommendations.
- Highly concordant with the Genetic Testing Reference Materials Coordination Program (GeT-RM) sample characterization.
- Available for evaluation, testing, and reporting back to the community on GitHub.
- Adheres to the FAIR (findable, accessible, interoperable, and reusable) guiding principles.

Some of its limitations:

- Assumes the sample VCF file has already undergone extensive quality control
- Produces an output report containing diplotypes and recommendations based on the genetic data provided. If the genetic data that are entered into PharmCAT are of low quality, inaccurate diplotypes may result, potentially leading to inaccurate recommendations.
- Uses allele definitions based on GRCh38 requiring users to provide samples in the same build
- Only considers variants contained in the allele definition files; novel variants and variants not in existing allele definitions are not considered
- The initial release of PharmCAT contains genes and variants found in CPIC guidelines and provides CPIC recommendations in the output.

- ***PharmaKU:***

http://ppgr.dasmaninstitute.org/login/?next=/ (accessed in December 2023)

PharmaKU is a web-based tool designed to facilitate the translation of an individual's whole genome variant data into clinical recommendations. The tool aims to improve the outreach and clinical utility of pharmacogenomics by providing healthcare professionals with a comprehensive pharmacogenomic report that includes prescribing recommendations for a list of drugs affected by nine well-annotated pharmacogenes. (John et al., 2021)

PharmaKU takes individual whole genome sequencing (WGS) variant call format (VCF) files as ***inputs*** through its web portal. These files should meet minimum quality requirements and have a coverage of at least 30X. The VCF files should be in hg19 or GRCh38 reference format.

The ***outputs*** of PharmaKU include a personalized pharmacogenomics report, which is generated in PDF format and provides comprehensive information on the individual's pharmacogenomic profile, including prescribing recommendations for a list of drugs affected by the nine pharmacogenes included in the tool.

Some of its features:

- PharmaKU accepts individual WGS VCF files as inputs through its web portal.
- The user-friendly web interface allows for choosing hg19 or hg38 as the reference genome version.
- PharmaKU extracts genetic variants from nine well-annotated pharmacogenes and assigns diplotypes using Stargazer software.
- The tool applies prescribing recommendations from pharmacogenomic resources, including PharmGKB and the Clinical Pharmacogenetics Implementation Consortium (CPIC).
- The personalized pharmacogenomics report generated by PharmaKU is downloadable in PDF format.

Some of its limitations:

- The cost of WGS remains prohibitively expensive for widespread clinical use.
- The number of drugs for which prescription information is available is limited by the information provided by the CPIC guidelines.
- The diplotypes called and the authenticity of the final report largely depend on the credibility of the input file.

- ***Pharmacogenomic Variant Analysis and Interpretation Platform (PharmVIP):*** https://pharmvip.nbt.or.th/ (accessed in December 2023)

The purpose of PharmVIP is to provide a comprehensive web-based tool for pharmacogenomic variant analysis and interpretation, aiming to assist in personalized medicine and improve patient outcomes. PharmVIP offers three main analysis/interpretation modules: Pharmacogenes, HLA, and Guideline. The Pharmacogenes module provides variant effect prediction results, the HLA module performs HLA allele prediction and reports associated adverse drug reactions (ADRs) and relevant Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines, and the Guideline module offers drug dosing guidelines. (Piriyapongsa et al., 2021)

Input Files: PharmVIP accepts input variants in a standard VCF format (*.vcf), which can be produced by various workflows such as GATK, SpeedSeq, and DeepVariant. For HLA typing and CYP2D6 allele prediction, PharmVIP requires a BAM file (*.bam), containing aligned NGS short reads to a human genome reference sequence (GRCh38).

Outputs:

1. **Analysis Reports**: PharmVIP provides detailed, customizable reports as exportable files and as an interactive web version. These reports include information from the three main interpretation modules: Guideline, HLA, and Pharmacogenes. The reports cover CPIC drug dosing recommendations, HLA genotypes, potential adverse drug reactions, relevant drug guidelines, and variant effect predictions.
2. **Summary Report**: PharmVIP also generates summary reports for all modules, which can be utilized for further applications such as clinical practice.

Some of its features:

- Input file support for VCF and BAM formats.
- Single variant-based analysis function.
- Haplotype analysis function.
- CPIC drug dosing guidelines.
- HLA allele prediction/HLA-ADR association/HLA-related CPIC guidelines.
- Variant effect prediction.
- Web-based user interface.
- Exportable report files.
- Post-analysis output filtering.
- Group (multiple samples) analysis.
- Choice of hg19 or hg38 as reference genome.

Some of its limitations:

- PharmVIP is currently in beta version and is provided for research and informational purposes, not as a substitute for medical advice from a physician.

- As with any computational tool, the accuracy and reliability of the results depend on the quality of input data and the underlying algorithms.
- Users may encounter challenges related to data interpretation and the need for continuous updates and improvements based on user feedback.

- ***Sequence2Script:***

https://sequence2script.com/#/ (accessed in December 2023)

Sequence2Script is a web-based tool designed to assist in the efficient translation of pharmacogenetic (PGx) testing results into evidence-based prescribing recommendations. The tool was developed to address the absence of regulatory standards for PGx testing and to ensure that prescribing recommendations align with current peer-reviewed PGx-based prescribing guidelines developed by expert groups or approved product labels. (Bousman et ai., 2021)

The ***inputs*** for Sequence2Script are pharmacogenetic (PGx) testing results, which include information on the patient's genotype for specific genes and variants associated with drug metabolism and response. The user enters this information into the tool using a combination of drop-down menus and radio buttons.

The ***outputs*** of Sequence2Script are evidence-based prescribing recommendations based on the patient's PGx testing results. The tool generates a clinical report summarizing the patient's genotype, inferred phenotype, phenoconverted phenotype (if applicable), and corresponding prescribing recommendations. The report also includes hyperlinks to the original information, which is housed within the PharmGKB website. The tool is customizable to align with local laboratory reporting standards and practices.

Some of its features:

- Supports 97 gene-drug pairs.
- Allows users to adjust recommendations for concomitant inhibitors and inducers.

- Generates a clinical report summarizing the patient's genotype, inferred phenotype, phenoconverted phenotype (if applicable), and corresponding prescribing recommendations.
- Provides hyperlinks to the original information, which is housed within the PharmGKB website.
- Customizable features to align with local laboratory reporting standards and practices.
- Free, efficient, and evidence-based solution.

Some of its limitations:

- Not all gene-drug pairs with evidence-based prescribing recommendations are supported by the tool.
- The methods used to perform phenoconversion adjustments of inferred phenotypes are blunt and will need to be further refined as the evidence evolves.
- The tool does not currently support batched PGx data.
- The tool does not save data supplied or reports produced by the user.
- The tool is not designed for direct integration into electronic health records.
- Utilization of the tool is at the user's own risk, and the information produced by the tool is intended to be interpreted by a licensed physician or other licensed healthcare professional.

1.3 The Unmet Need:

NGS and related technologies are increasing knowledge in the research sphere, yet rates of genomic literacy remain low, resulting in a widening gap in knowledge translation to the patient. Multidisciplinary teams (including physicians, nurses, genetic counselors, and pharmacists) will need to combine their expertise to deliver optimal pharmacogenomics-informed care. (Hippman & Nislow, 2019)

Major challenges of implementation lie at the point of delivery into healthcare systems, including the modification of current clinical pathways coupled with a

massive knowledge gap in pharmacogenomics in the healthcare workforce. (Pirmohamed, 2023) **(Figure 6)**

Figure 6: Aaron Bacall's "Here's my DNA sequence" cartoon published in 2000. Licensed for publication in JAPhA by www.CartoonStock.com.

As mentioned before, ***the lack of knowledge*** in pharmacogenomics among healthcare providers is one of the main challenges to implementing PGx guidelines into clinical practice. With very few, if none, simple, and user-friendly tools that deliver basic PGx knowledge to non-PGx specialists in a straightforward way, developing such tools is a high-priority need.

1.4 Project Objectives:

As a pharmacist and a pharmacogenomics enthusiast with good skills in R programming language and building web-based applications with R Shiny package, I

aim to develop a web-based tool "***PGx ExploreEZ***" to be a gateway to reference knowledge resources in pharmacogenomics.

With its user-friendly and interactive interface, "***PGx ExploreEZ***" enables healthcare professionals, researchers, and interested users to easily access and explore essential information in pharmacogenomics to bridge the knowledge gap and pave the way for the implementation of pharmacogenomics into clinical practice which will have a great impact on patient's health and medication costs.

2 Materials and Methods:

The project of "***PGx ExploreEZ"*** as a web-based tool for easy exploration of pharmacogenomics' resources has been implemented through two phases:

- ✓ ***Phase one***: collecting the data from the well-known pharmacogenomic databases and resources and manually curating it in Excel sheets in order to build the app's database that will be explored interactively on the user interface.
- ✓ ***Phase two***: designing and developing the web-based application using ***R*** programming language and the ***Shiny*** package in ***RStudio*** environment then deploying it on the ***shinyapps.io*** server to be freely accessible through the link: *https://rasha-hamama.shinyapps.io/PGx_ExploreEZ/*

2.1 Collecting and Curating the Data:

2.1.1 FDA Table of Pharmacogenetic Associations:

The FDA (U.S. Food and Drug Administration) has evaluated a list of pharmacogenetic associations and believes there is sufficient scientific evidence to suggest that certain subgroups of patients with certain genetic variants may have altered drug metabolism and differential therapeutic effects.

As a result, the FDA has posted a table of pharmacogenetic associations on its website. However, this table is limited to pharmacogenetic associations that are related to drug-metabolizing enzyme gene variants, drug transporter gene variants, and gene variants that have been related to a predisposition for certain adverse events.

The FDA recognizes that various other pharmacogenetic associations exist that are not listed in the table which will be updated periodically with additional pharmacogenetic associations supported by sufficient scientific evidence.

The pharmacogenetic associations and relevant data from the *FDA Table of Pharmacogenetic Associations* (accessed December 2023) have been manually collected and curated in an Excel sheet as a table consisting of the following fields:

- ✓ **Drug**: includes ***114 drugs*** (124 entries in total since some drugs are associated with more than one gene like warfarin and carbamazepine).
- ✓ **Gene:** includes ***20 genes*** (BCHE, CYP2B6, CYP2C19, CYP2C19 and/or UGT2B17, CYP2C9, CYP2D6, CYP3A5, CYP4F2, DPYD, HLA-A, HLA-B, HLA-DQA1, HLA-DRB1, NAT2, Nonspecific (NAT), SLCO1B1, TPMT and/or NUDT15, UGT1A1, VKORC1).
- ✓ **Affected Subgroups:** includes subgroups of patients with certain genetic variants, or genetic variant-inferred phenotypes that are likely to have altered drug metabolism, and in certain cases, differential therapeutic effects, including differences in risks of adverse events.
- ✓ **Gene-drug interaction and Recommendations:** describes the gene-drug interaction and mentions specific information regarding therapeutic management
- ✓ **FDA Table Section:** since the FDA table of pharmacogenetic associations is divided into three parts based on the strength of scientific evidence; this field clarifies to which section of the FDA table the association belongs. The three sections of the FDA table are:
  - **Section 1:** the data support therapeutic management recommendations.

- **Section 2:** the data indicate a potential impact on safety or response.
- **Section 3:** the data demonstrate a potential impact on pharmacokinetic properties only.

2.1.2 CPIC Guidelines:

The Clinical Pharmacogenetics Implementation Consortium (CPIC) is an international consortium of individual volunteers and a small dedicated staff who are interested in facilitating the use of pharmacogenetic tests for patient care.

CPIC is creating, curating, and posting freely available, peer-reviewed, evidence-based, updatable, and detailed gene/drug clinical practice guidelines that follow standardized formats, include systematic grading of evidence and clinical recommendations, use standardized terminology, are peer-reviewed, and are published in a leading journal (in partnership with Clinical Pharmacology and Therapeutics) with simultaneous posting to cpicpgx.org, where they are regularly updated.

We have reviewed the latest *CPIC guidelines publications* (accessed December 2023) for a list of ***43 drugs*** that have special therapeutic recommendations and dosing adjustments due to evidence-based implications of the different diplotype/genotype inferred phenotype, associated with ***12 genes*** (HLA-B, HLA-A, CYP2D6, CYP2C19, CYP2C9, CYP2B6, CYP3A5, UGT1A1, SLCO1B1, TPMT, NUDT15, ABCG2) encoding drug-metabolizing enzymes, drug transporters, or related to a predisposition for certain adverse events.

Then we collected the data from the ***Diplotype/Genotype-Phenotype*** tables and integrated it with the data extracted from the tables of ***therapy recommendations based on phenotype*** in an Excel sheet as a table consisting of the following fields:

- ✓ **Drug:** includes the drug name.

- ✓ **Gene:** includes the name of the gene whose variations impact the efficacy or safety of the associated drug.
- ✓ **Diplotype / Genotype:** the combination of two alleles, written in the star nomenclature system, that are assigned to a specific functionality group.
- ✓ **Phenotype:** the predicted impact of the diplotype/genotype on the functionality of the enzyme or the transporter.
- ✓ **Implications:** the concomitant effects of the phenotype on the efficacy and/or safety of the drug.
- ✓ **Therapeutic recommendation:** the clinical therapeutic recommendations and dosage adjustments suggested by the CPIC to get the optimal treatment outcomes while minimizing the adverse effects.
- ✓ **Classification of recommendation:** includes terms evaluating the evidence supporting dosage recommendations. CPIC's dosing recommendations are based on weighing the evidence from a combination of preclinical functional and clinical data as well as on some existing disease-specific consensus guidelines. The used terms are:
    - **Strong:** The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.
    - **Moderate:** There is a close or uncertain balance as to whether the evidence is high quality and the desirable effects clearly outweigh the undesirable effects.
    - **Optional:** The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.

2.1.3 CYP450 – Drug Interactions (Flockhart Table):

The Drug Interaction Flockhart Table™ is designed as a teaching and reference tool for healthcare providers and researchers interested in drug interactions that are mediated by cytochrome P450 enzymes.

The effective, intelligent management of many problems related to drug interactions in clinical prescribing can be helped by an understanding of how drugs are metabolized. Specifically, if a prescriber is aware of the dominant cytochrome P450 isoform involved in a drug's metabolism, it is possible to anticipate, from the inhibitor and inducer lists for that enzyme, which drugs might cause significant interactions. The Flockhart Table™ is focused on clinically relevant interactions and is updated at least twice yearly.

The table contains eight columns, one for each of the P450 isoform groups. In each column you will find:

- Substrates: drugs that are metabolized as substrates by the enzyme
- Inhibitors: drugs that prevent the enzyme from metabolizing the substrates
- Inducers: drugs that increase the enzyme's ability to metabolize the substrates

A drug appears in a column if there is published evidence that it is metabolized, at least in part, via that isoform. It does not necessarily follow that the isoform is the principal metabolic pathway in vivo, or that alterations in the rate of the metabolic reaction catalyzed by that isoform will have large effects on the pharmacokinetics of the drug.

The Flockhart Table™ only catalogs drug-drug interactions that are mediated by CYPs. Drug-drug interactions caused via other enzymes (e.g., UGTs) are not included in this table. In addition, some of the drugs listed could be substrates of uptake and efflux drug transporters. However, drug-drug interactions caused by inhibition or induction of drug transporters are not included in the table.
The data has been collected from the *CYP450 Drug Interactions Table (The Flockhart Table™)* (accessed December 2023) and curated in an Excel sheet table containing the following fields:

- ✓ **CYP450 Enzyme**: includes eight of the CYP450 enzymes which are (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5).

- ✓ **Substrates**: includes the substrates of each enzyme.
- ✓ **Inhibitors**: includes the inhibitors of each enzyme.
- ✓ **Inducers**: includes the inducers of each enzyme.

2.1.4 The PGx Glossary:

We have searched highly trusted and reliable knowledge resources like *PharmGKB*, the *National Human Genome Research Institute*, and other reference books and websites for pharmacogenomics-related terms and their clear, simple, and comprehensive definitions. Then we arranged these definitions in an Excel sheet that contains ***more than 150 terms***.

2.1.5 PGx Web Resources:

We have created a list of the most trusted and reliable knowledge resources of pharmacogenomics with links to their websites to be a guiding reference for deeper pharmacogenomics knowledge search and exploration:

- ✓ ***The Pharmacogenomic Knowledge Base (PharmGKB):***

  An NIH-funded resource that provides information about how human genetic variation affects response to medications. PharmGKB collects, curates, and disseminates knowledge about clinically actionable gene-drug associations and genotype-phenotype relationships.
- ✓ ***The Clinical Pharmacogenetics Implementation Consortium (CPIC):***

  An international consortium of individual volunteers and a small dedicated staff who are interested in facilitating the use of pharmacogenetic tests for patient care. CPIC is creating, curating, and posting freely available, peer-reviewed, evidence-based, updatable, and detailed gene/drug clinical practice guidelines. CPIC guidelines follow standardized formats, include systematic grading of evidence and clinical recommendations, use standardized terminology, are peer-reviewed, and are published in a leading

journal (in partnership with Clinical Pharmacology and Therapeutics) with simultaneous posting to cpicpgx.org, where they are regularly updated.

- ✓ ***Pharmacogenomics Global Research Network (PGRN):***

  The mission of the Pharmacogenomics Global Research Network (PGRN) is to catalyze and lead research in precision medicine for the discovery and translation of genomic variation influencing therapeutic and adverse drug effects.

- ✓ ***U.S. Food and Drug Administration (FDA):***

  It is responsible for protecting public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices. FDA is responsible for advancing public health by helping to speed innovations that make medical products more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medical products and foods to maintain and improve their health.

- ✓ ***DRUGBANK ONLINE:***

  A comprehensive, free-to-access, online database containing information on drugs and drug targets. DrugBank Online is widely used by the drug industry, medicinal chemists, pharmacists, physicians, students, and the general public. Because of its broad scope, comprehensive referencing, and detailed data descriptions, DrugBank is enabling major advancements across the data-driven medicine industry.

- ✓ ***The Pharmacogene Variation Consortium (PharmVar):***

  A central repository for pharmacogene variation that focuses on haplotype structure and allelic variation. The information in this resource facilitates basic and clinical research as well as the interpretation of pharmacogenetic test results to guide precision medicine. The major focus of PharmVar is to catalog allelic variation of genes impacting drug metabolism, disposition, and response and provide a unifying designation system (nomenclature) for the global pharmacogenetic/genomic community.

- ✓ ***SNPedia:***

A wiki investigating human genetics. It shares information about the effects of variations in DNA, citing peer-reviewed scientific publications. It is used by Promethease to create a personal report linking your DNA variations to the information published about them.

- ✓ ***NIH dbSNP:***

  It contains human single nucleotide variations, microsatellites, and small-scale insertions and deletions along with publication, population frequency, molecular consequence, and genomic and RefSeq mapping information for both common variations and clinical mutations.

- ✓ ***NIH ClinVar:***

  It aggregates information about genomic variation and its relationship to human health.

- ✓ ***The Pharmacogenomics Clinical Annotation Tool (PharmCAT):***

  is a software that generates a report containing clinically relevant genotype-based information, including CPIC drug prescribing recommendations, from genotype or sequencing data provided as input. The tool extracts genetic variants from a VCF file and predicts haplotypes and diplotypes for the majority of genes with CPIC guidelines. PharmCAT then uses CPIC diplotype to phenotype mapping to produce metabolizer phenotypes and provide corresponding CPIC drug prescribing recommendations.

- ✓ ***Drug Interactions Flockhart Table:***

  This table is designed as a teaching and reference tool for healthcare providers and researchers interested in drug interactions that are mediated by cytochrome P450 enzymes.

- ✓ ***CDC: Genetic Testing Reference Materials Coordination Program (GeT-RM):***

  Coordinates a self-sustaining community process to improve the availability of appropriate and characterized reference materials such as The Reference Materials for Pharmacogenetics.

2.2 PGx ExploreEZ Application Design & Development:

"PGx ExploreEZ" is a web-based application written in **R** programming language (***version 4.3.2***), using the **Shiny** package (***version 1.8.0***) in the **RStudio** environment. **(Figure 7)** The application is deployed on the shinyapps.io server and is freely accessible to all users through the link: *https://rasha-hamama.shinyapps.io/PGx_ExploreEZ/*

Basically, our application reads the data supplied to it as Excel sheets then its programming code (the **server** section in the shiny app) manipulates that data according to the inputs from the user interface (the **ui** section in the shiny app) and display the results in the user interface mainly as interactive data tables, texts and external links.

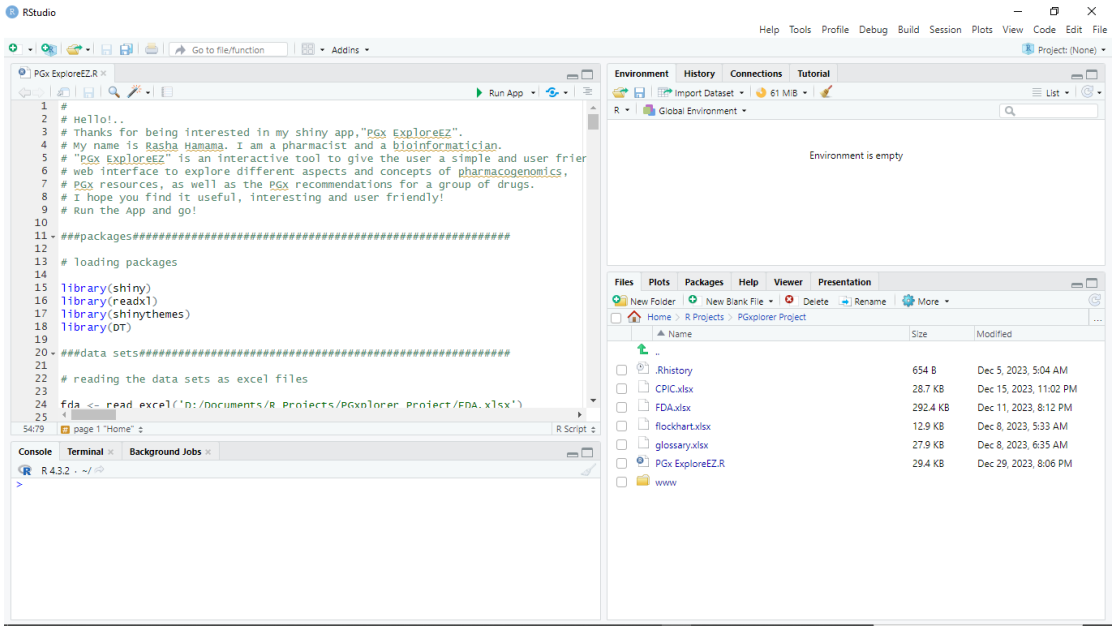

Figure 7: The RSudio environment with the code of "PGx ExploreEZ" application

3 Results & Discussion:

PGx ExploreEZ is a user-friendly, simple, and interactive web-based tool for easy search, reach, and exploration of pharmacogenomics core knowledge and data from their multiple original sources in one place. To achieve that, the website contains a navigation bar with ***7 tabs*** as shown below:

3.1 The homepage:

The first tab, "***Home***", is a welcoming page that introduces some ***general information*** about the application and its ***main purposes***, and helps the users figure out how they could benefit from this website. **(Figure 8)**

Additionally, it presents a ***warning note*** about the safe usage of the application and its provided information. It strictly clarifies that the application is for educational and research purposes only, and that the information on this website is not intended for direct diagnostic use or medical decision-making without review by a health care professional.

Since pharmacogenomics is a rapidly evolving field of knowledge, the date of the ***last update*** of the website is clearly displayed on the homepage, and the user may need to check the original resource to be certain that the information is up-to-date.
All pharmacogenomics knowledge resources are being updated periodically. similarly, "***PGx ExploreEZ***" will be reviewed and updated periodically as needed (once or twice a year).

The need for a regular update of our database could be considered as one of the main ***limitations*** of this tool, but it is not exclusive to it since all pharmacogenomic databases and depending tools need to be updated periodically.

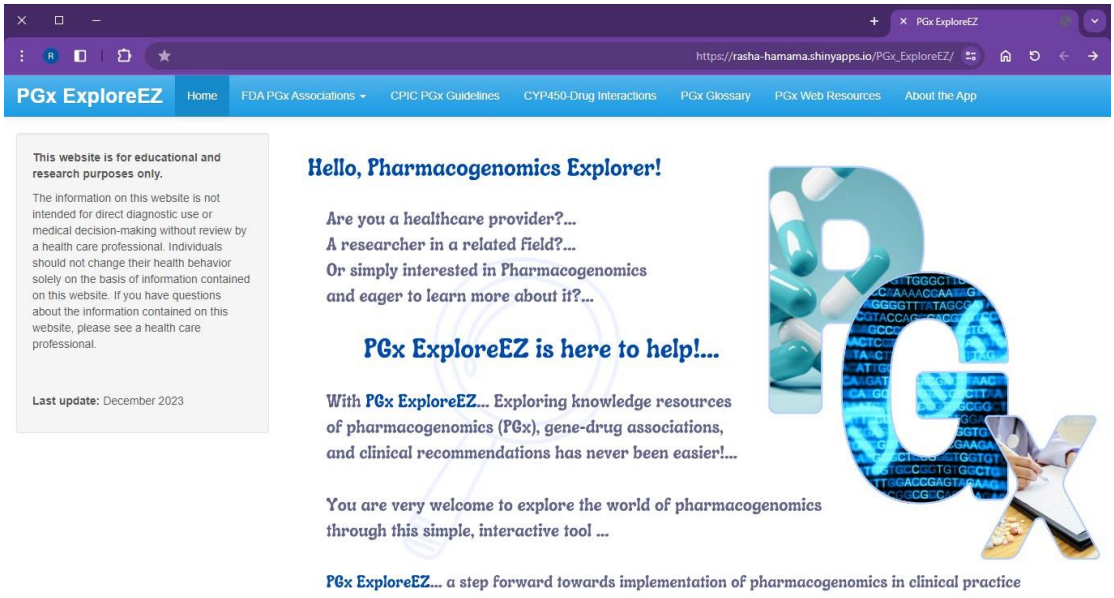

Figure 8: The PGx ExploreEZ homepage

3.2 The FDA PGx Associations tab:

This tab is an interactive window to explore the ***FDA table of pharmacogenetic associations***. It has *two subtabs*:

3.2.1 Search by Drug:

It enables the user to search through the table by selecting the drug name from the drop-down menu that shows a list of choices which includes:

- ✓ A "***Show All***" option that displays the complete table as an interactive data table of 124 entries corresponding to the list of 124 gene-drug associations in the three sections of the FDA table. **(Figure 9)**
- ✓ Other options are the ***names of all drugs*** mentioned in the FDA table, alphabetically ordered. By selecting a drug name, only the entries of this drug will be displayed to provide the related information about its genetic associations, clinical recommendations, besides naming the section of the FDA table it belongs to depending on the strength of evidence according to the FDA. **(Figure 10)**

It also offers an external link to the original page on the FDA website as a reference.

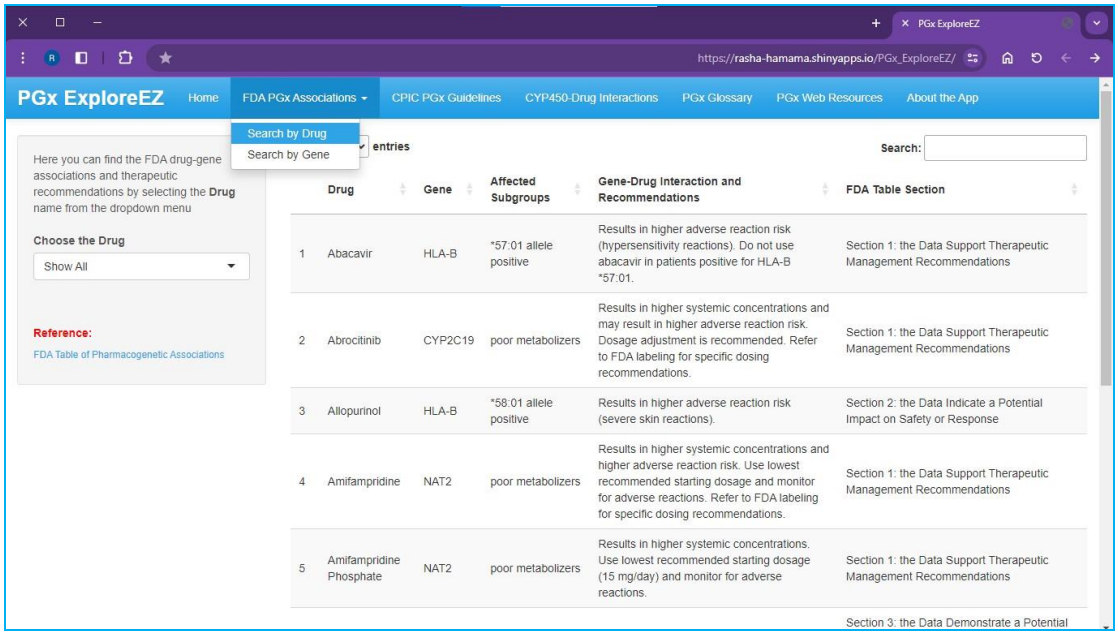

Figure 9: The FDA PGx Associations tab, the Search by Drug subtab, Show All option

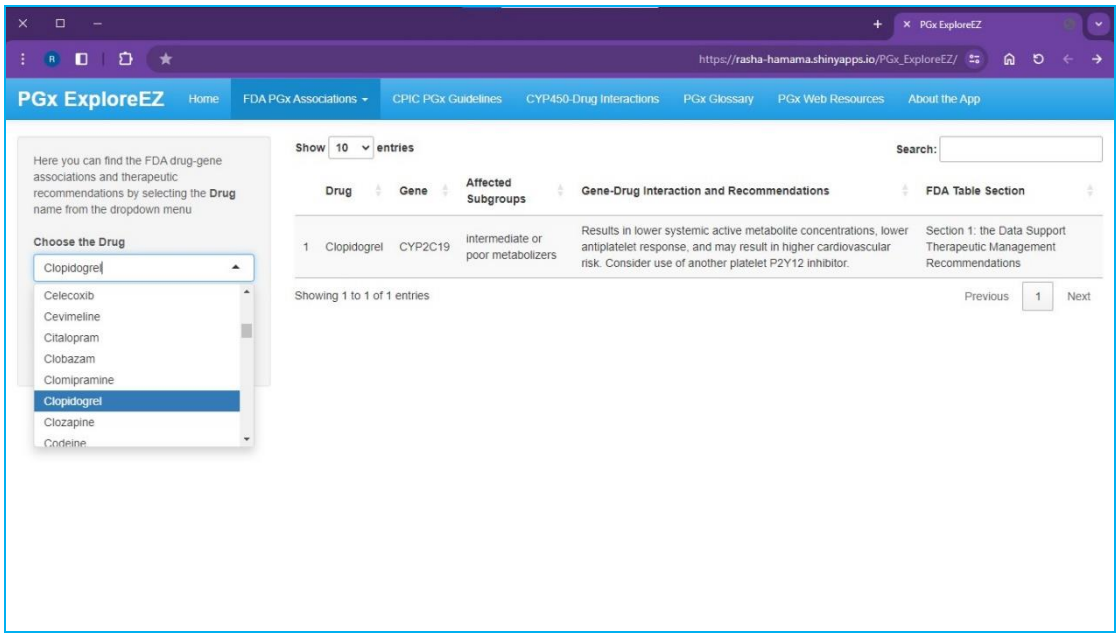

Figure 10:The FDA PGx Associations tab, the Search by Drug subtab, choosing a drug name from the drop-down menu displays all corresponding entries.

3.2.2 Search by Gene:

It enables the user to search through the table by selecting the gene name from the drop-down menu that shows a list of choices which includes:

- ✓ A "***Show All***" option that displays the complete table as an interactive data table of 124 entries corresponding to the list of 124 gene-drug associations in the three sections of the FDA table. **(Figure 11)**

- ✓ Other options are the ***names of all genes*** mentioned in the FDA table.

By selecting a gene name, only the entries of this gene will be displayed to provide the related information about its drug associations, clinical recommendations, besides naming the section of the FDA table it belongs to depending on the strength of evidence according to the FDA. **(Figure 12)**

It also offers an ***external link*** to the original page on the FDA website as a ***reference***.

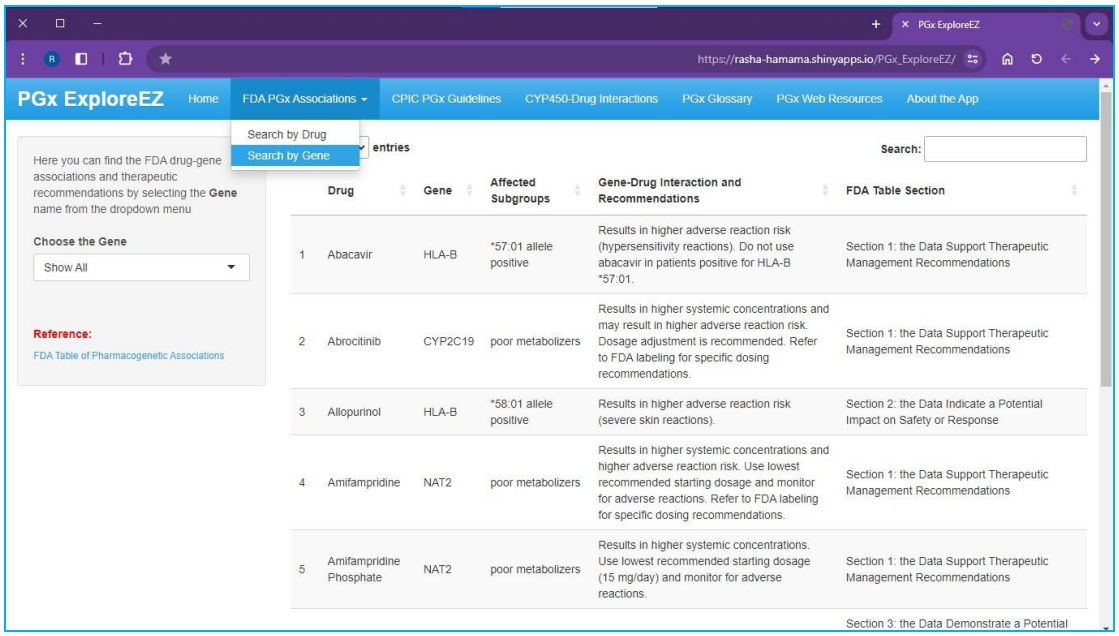

Figure 11: The FDA PGx Associations page, the Search by Gene subtab, Show All option

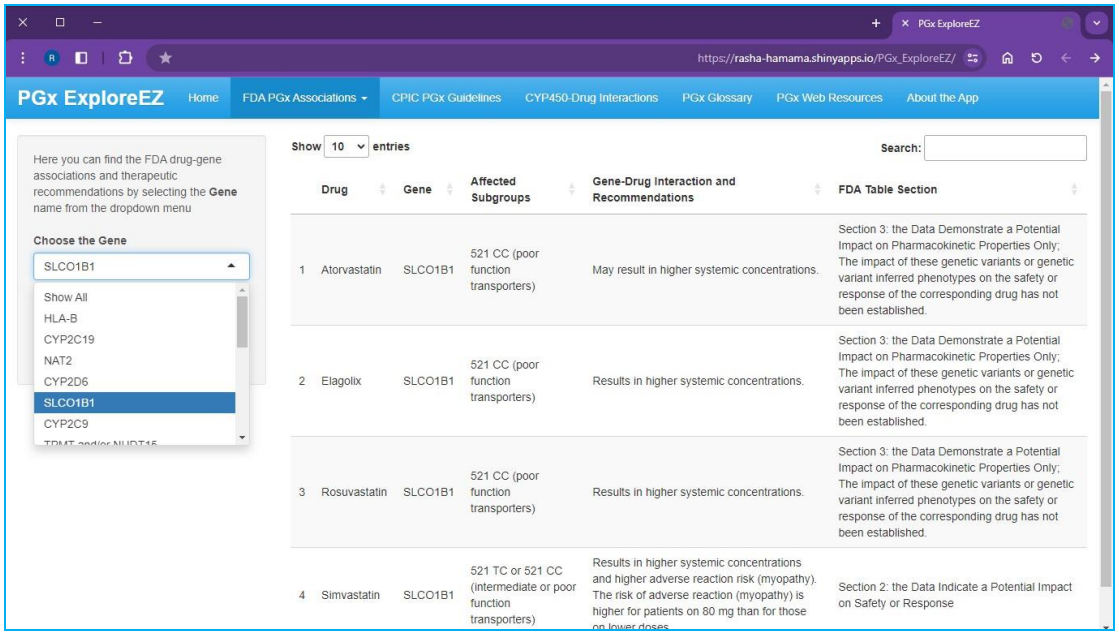

Figure 12: The FDA PGx Associations page, the Search by Gene subtab, choosing a gene name from the drop-down menu displays all corresponding entries.

3.3 CPIC PGx Guidelines tab:

This tab displays an interactive data table of the latest ***CPIC guidelines*** for a list of ***43 drugs*** that have special therapeutic recommendations and dosing adjustments due to evidence-based implications of the different diplotype/genotype inferred phenotype, associated with ***12 genes*** (HLA-B, HLA-A, CYP2D6, CYP2C19, CYP2C9, CYP2B6, CYP3A5, UGT1A1, SLCO1B1, TPMT, NUDT15, ABCG2) encoding drug-metabolizing enzymes, drug transporters, or related to a predisposition for certain adverse events.

The "***Show All"*** option displays the complete table of CPIC guidelines (***220 entries***) **(Figure 13)**, while ***choosing a drug name*** from the drop-down menu will display only the entries of that drug with related information like the associated genes with their different diplotypes / genotypes and predicted phenotypes, and the implications and clinical recommendations with the strength of the recommendations. **(Figure 14).**

It also provides ***external links*** to the original publications of CPIC Guidelines included in the table as ***references***.

CPIC Guidelines also recommend that pharmacogenetic ***warfarin*** dosing be accomplished through the use of one of the ***pharmacogenetic dosing algorithms***. So, we offered a link to download the ***IWPC Warfarin Dose Calculator.***

As a ***limitation*** of our application, we have to mention here that our CPIC guidelines table do not include all the drugs that CPIC has published guidelines for because some genes have a special genotyping nomenclature like ***G6PD*** and should be presented in its own table.

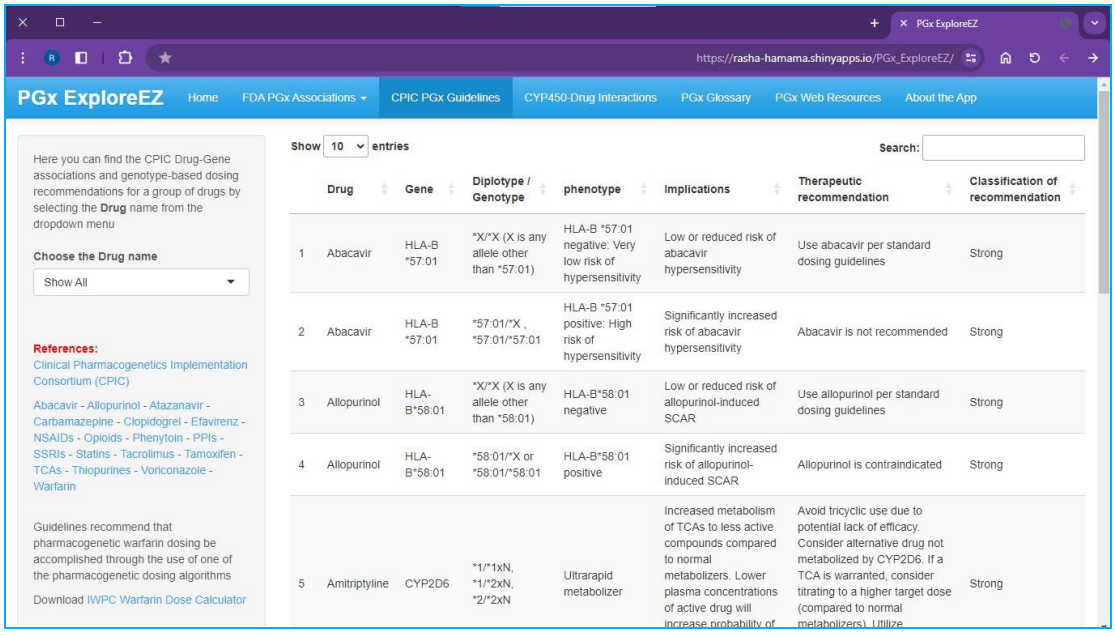

Figure 13: the CPIC PGx Guidelines tab, Show All option displays the complete table

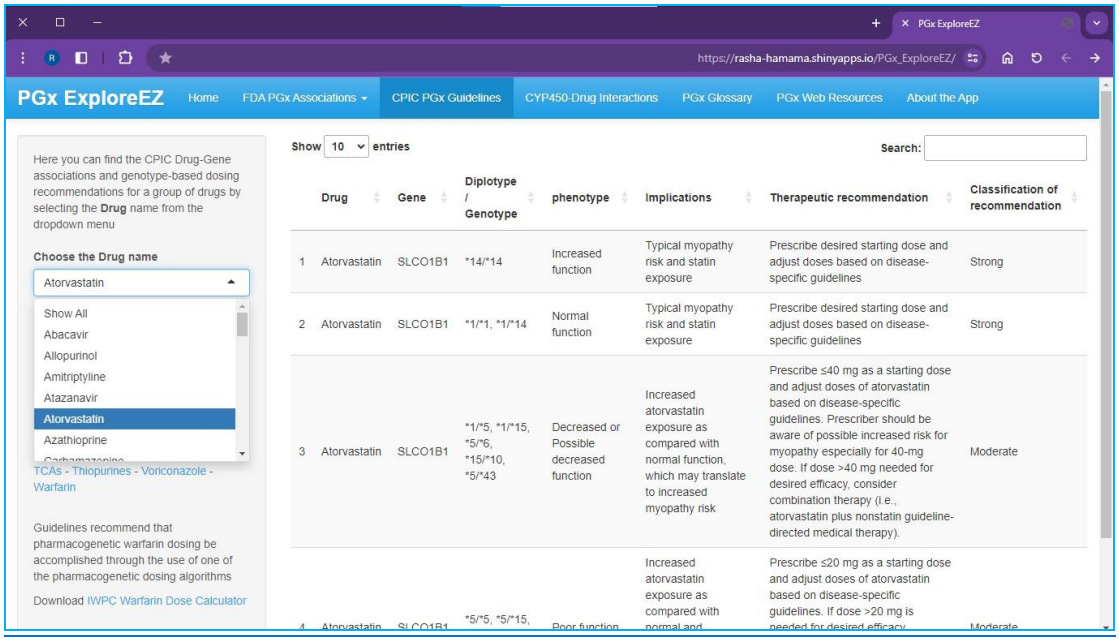

Figure 14: the CPIC PGx Guidelines tab, choosing a drug name from the drop-down menu will display the corresponding entries

3.4 The CYP450 Drug Interactions tab:

This tab displays an interactive data table of eight of the CYP450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5) which mediate a lot of drug-drug interactions since some drugs acts as inhibitors or as inducers of these enzymes.

The "***Show All***" option displays the complete table (***8 entries***) **(Figure 15)**, while choosing a ***CYP450 enzyme name*** from the drop-down menu displays the corresponding entry for that enzyme which shows the enzyme's substrates, inhibitors, and inducers. **(Figure 16)**

It also provides an ***external link*** to the original page of Flockhart Table as a ***reference***.

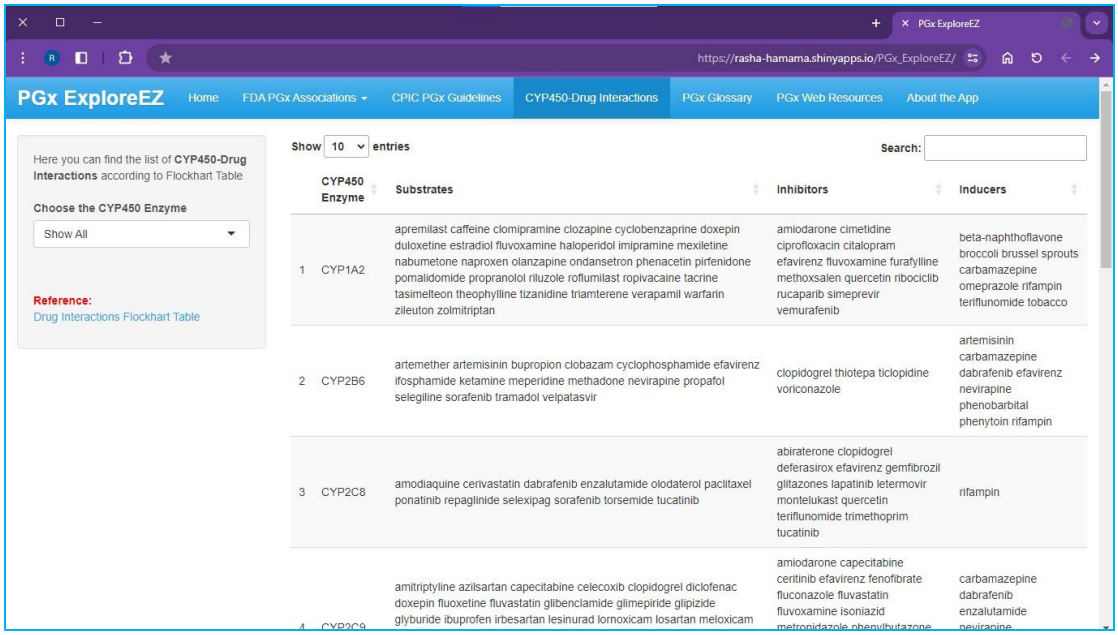

Figure 15: The CYP450 Drug Interactions tab, the "Show All" option displays the complete table

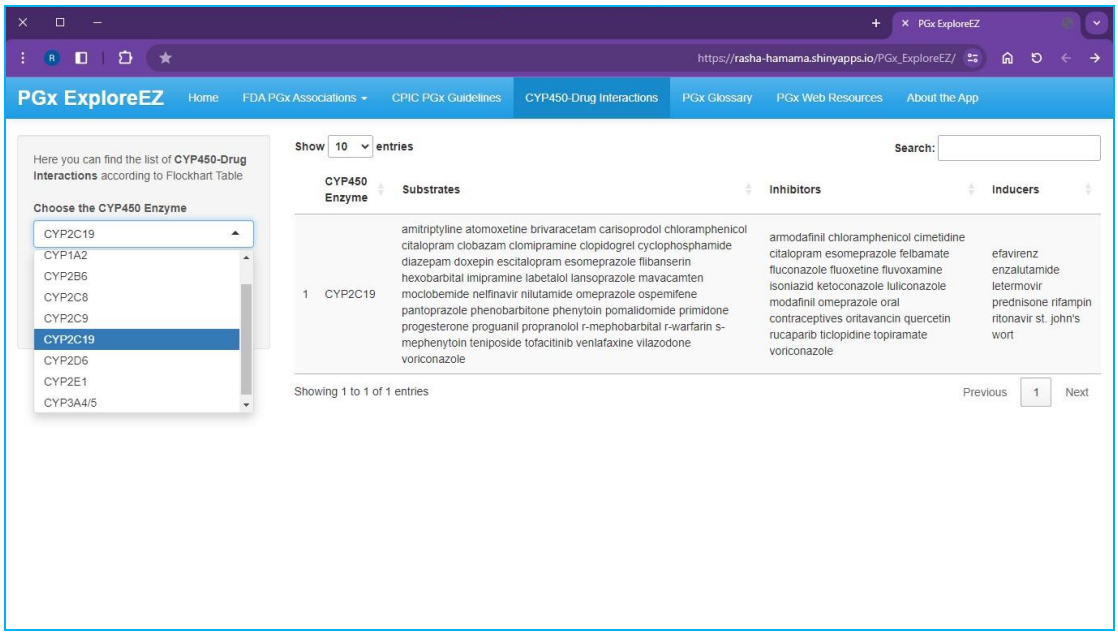

Figure 16: The CYP450 Drug Interactions tab; choosing a CYP450 enzyme from the drop-down menu displays the corresponding entry.

3.5 The PGx Glossary tab:

This tab displays an interactive table of more than ***150 pharmacogenomics-related terms*** and their clear, simple, and comprehensive ***definitions***.

The "***Show All***" option displays the complete table of terms alphabetically ordered. **(Figure 17)**

The user can search for a specific term in the drop-down menu. By selecting the term from the drop-down menu; its definition will be displayed on the interface.

(Figure 18)

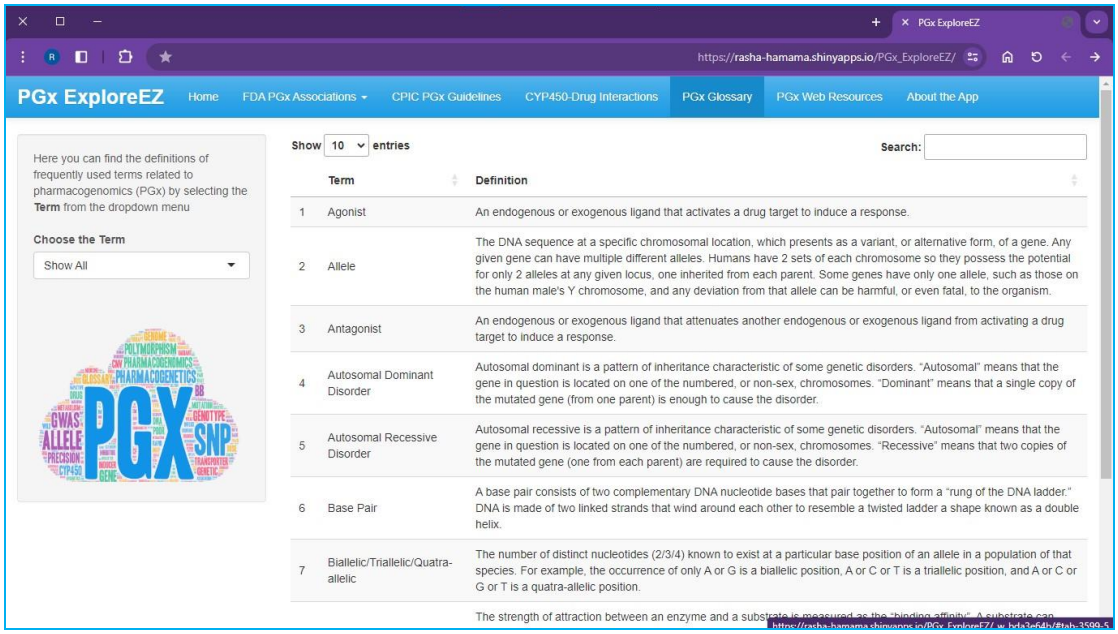

Figure 17: The PGx Glossary tab, the "Show All" option displays the complete table of terms

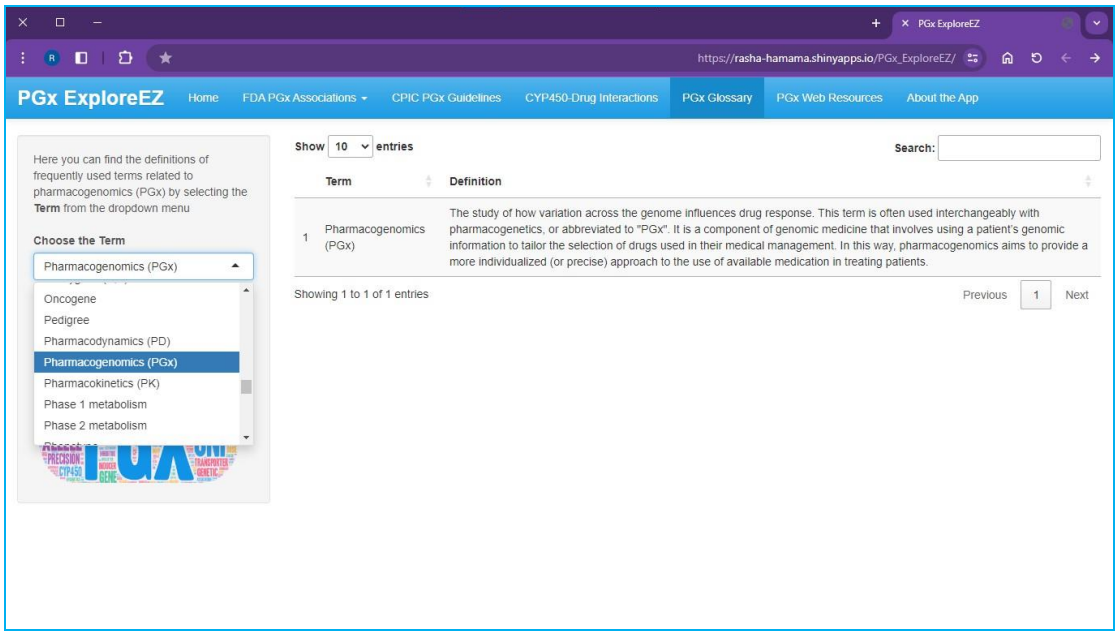

Figure 18: The PGx Glossary tab; selecting a term from the drop-down menu displays its definition

3.6 The PGx Web Resources tab:

This tab supplies the user with a list of the most trusted and reliable ***knowledge resources*** of pharmacogenomics with ***links*** to their websites to be a guiding reference for deeper pharmacogenomics knowledge search and exploration **(Figure 19)**

The list of web resources has been discussed thoroughly in the (Materials and Methods).

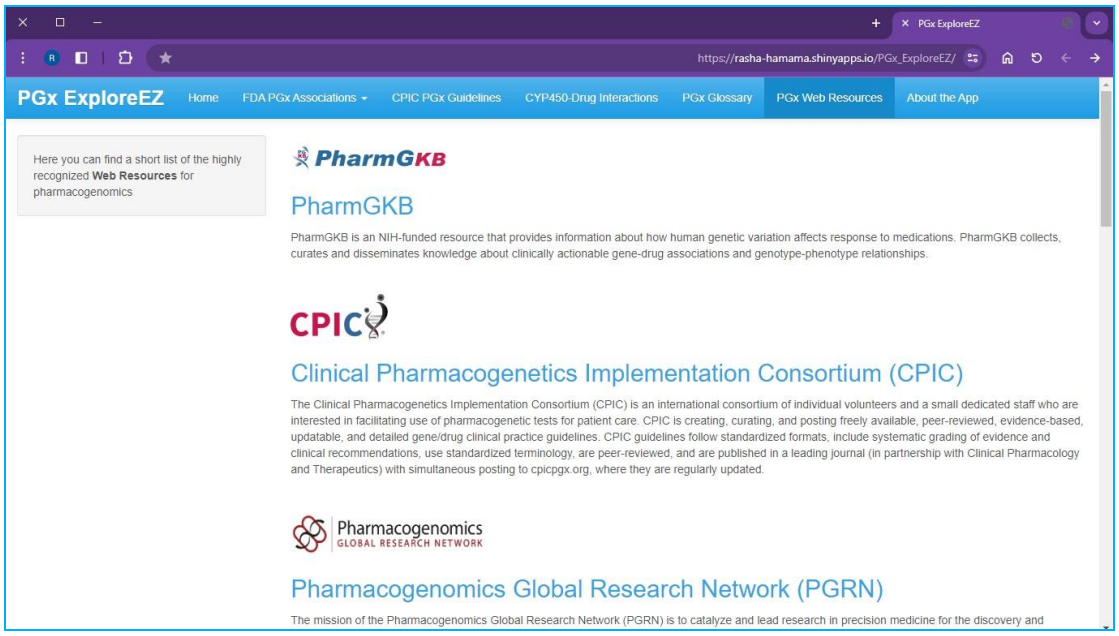

Figure 19: The PGx Web Resources tab

3.7 The About the App tab:

This tab provides the user with some more ***in-detail information*** about the app; how it has been developed and why, the developer behind, and ***contacting information*** to enable the user from giving his feedback or suggestions. **(Figure 20)**

It clearly assigns the role of the ***Syrian Virtual University***, specifically the ***Master in Bioinformatics*** program in developing this app, since that accomplishing this project

would not be possible without the knowledge and experience acquired from their qualified teachers, and effective teaching system.

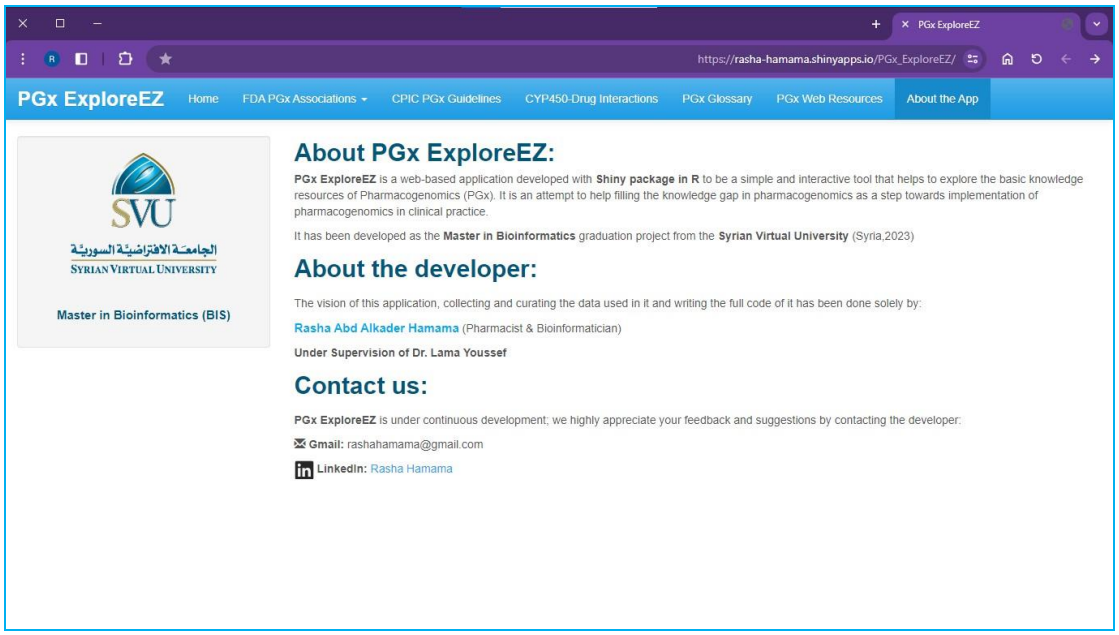

Figure 20: The About the App tab; developing and contacting information

However, **PGx ExploreEZ** have some ***limitations*** as we mentioned before, some we could acknowledge:

- For educational and research purposes only.
- Need regular updates.
- Do not include all the drugs that CPIC has published guidelines for.
- Need more enhancements in content and design.

4 Conclusion

"**PGx ExploreEZ**" is a web-based, user-friendly tool for exploration of reference resources of pharmacogenomics.

The application collects and curates the data from the diverse reference resources to display it in one place, making it easier for users to access and explore.

The application's various tabs, such as the FDA PGx Associations, CPIC PGx Guidelines, CYP450 Drug Interactions, PGx Glossary, and PGx Web Resources, provide users with basic and up-to-date information in a convenient manner.
By offering search options based on drugs and genes, users can quickly find the information they need, including gene-drug associations, clinical recommendations, and definitions of pharmacogenomics-related terms.

All tabs have external links to the original data resources to help the user check it out for updates and more detailed information.

Furthermore, the "**PGx ExploreEZ**" application acknowledges the importance of regular updates to ensure the accuracy of the database. While this may pose a limitation, it is a common challenge faced by all pharmacogenomic databases and related tools. As a result, "**PGx ExploreEZ**" will be in continuous development.

With the ability to provide feedback and suggestions, users are encouraged to contribute to the ongoing improvement of the application.

Overall, the "**PGx ExploreEZ**" application enhances the accessibility and exploration of pharmacogenomics knowledge, empowering healthcare providers to make informed decisions in the field, and contributes to the advancement of pharmacogenomics research and its practical applications in healthcare.

5 *Supplementary Materials:*

All the data used in our application ***PGx ExploreEZ*** can be accessed through this link:
PGx ExploreEZ Supplementary Materials

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