**PGxecute - carrying out the use of pharmacogenomics into patient care**

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**Pharmacogenomics/Pharmacogenetics/PGx**

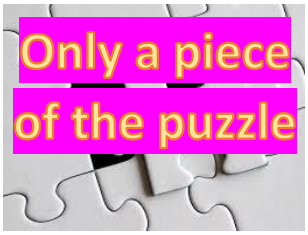
Do you have questions about PGx? What is pharmacogenomics/pharmacogenetics? How can it benefit my patients? How can I learn more? How can I use the information? Who actually uses this? Come to this roundtable to hear from someone who has been practicing PGx for 10 years and can help answer your questions.

**PGx** is the study of how heredity (DNA) and other factors affects your response to certain medications.

Drug safety/toxicity avoidance

– Aid in drug selection to avoid adverse drug reactions

– Aid in dose selection to avoid toxicity




Increased efficiency

– Aid in dose selection for maximum efficacy

– Identify patients who will be responsive to a particular drug

**Where is this relevant? Cardio, ID GI, Pain, Psych, Oncology, Transplant, etc**

| | |
|---|---|
| CYP3A5 | tacrolimus |
| CYP2B6 | efavirenz |
| CYP2C9 | aceclofenac, celecoxib, diclofenac, flurbiprofen, ibuprofen, indomethacin, lornoxicam, lumiracoxib, meloxicam, metamizole, nabumetone, naproxen, piroxicam, tenoxicam, fosphenytoin, phenytoin, warfarin |
| CYP2C19 | clopidogrel, dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, voriconazole, citalopram, escitalopram, sertraline |
| CYP2D6 | Atomoxetine, ondansetron, topisetron, tamoxifen, duloxetine, fluoxetine, fluvoxamine, paroxetine, venlafaxine, vortioxetine, codeine, hydrocodone, tramadol |
| CFTR | ivacaftor |
| DPYD | capecitabine, fluorouracil, tegafur |
| G6PD | Many examples |
| HLA | carbamazepine, oxcarbazepine, abacavir, allopurinol |
| MT-RNR1 | amikacin, dibekacin, gentamicin, kanamycin, neomycin, netilmicin, paromomycin, plazomicin, ribostamycin, streptomycin, tobramycin |
| CACNA1S, RYR1 | desflurane, enflurane, halothane, isoflurane, methoxyflurane, sevoflurane, succinylcholine |
| SCLO1B1, ABCG2 | statins |
| TPMT, NUDT15 | azathioprine, mercaptopurine, thioguanine |
| UGT1A1 | atazanavir |

**Who is implementing? https://cpicpgx.org/implementation/**

**Pharmacogenomics (PGx) Resources**

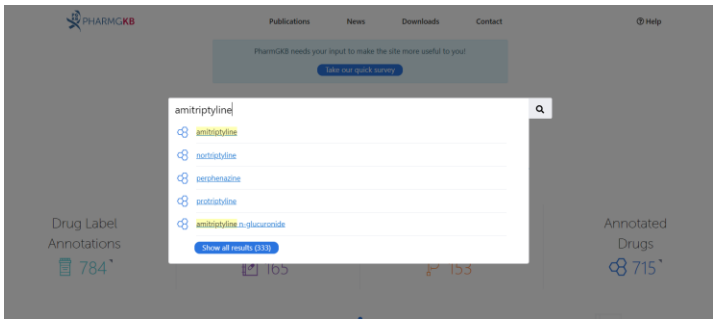
- The Pharmacogenetics Implementation Consortium (CPIC) guidelines https://cpicpgx.org/
- Dutch Pharmacogenetics Working Group (DPWG) guidelines
- FDA (United States Food and Drug Administration)
    - FDA Table of Pharmacogenomic Biomarkers in Drug Labeling: https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling
        - Contains genetic information contained on drug labeling
    - FDA Table of Pharmacogenetic Associations: https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations#about
        - Lists gene-drug interactions
        - FDA may or may not advocate for a pharmacogenetic test with the corresponding medication
        - Divided into 3 Sections on Pharmacogenetic Associations:

            1. Data Supports Therapeutic Management Recommendations

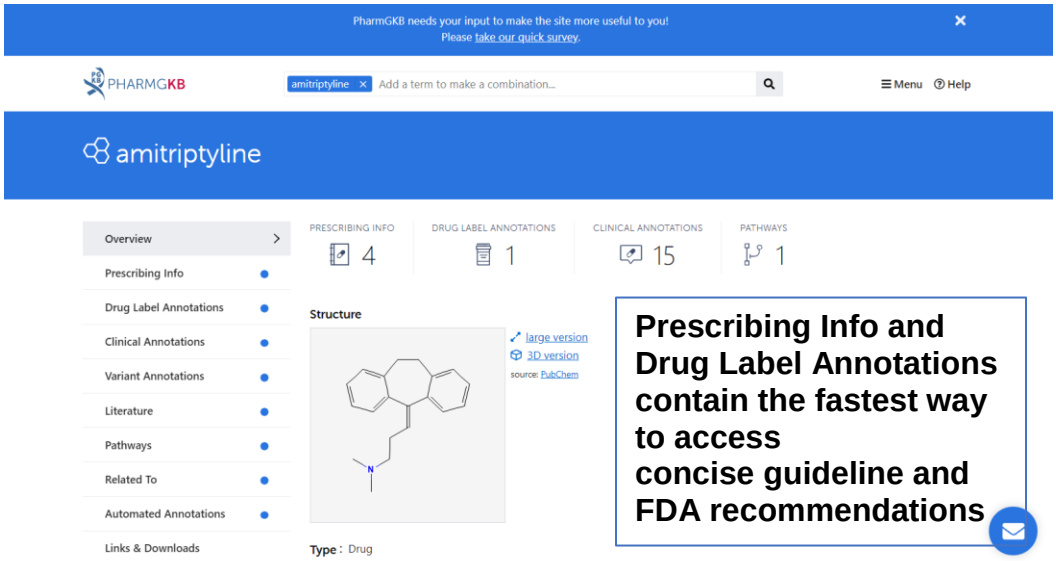
            2. Data Indicates a Potential Impact on Safety or Response

            3. Data Demonstrates a Potential Impact on Pharmacokinetic Properties Only

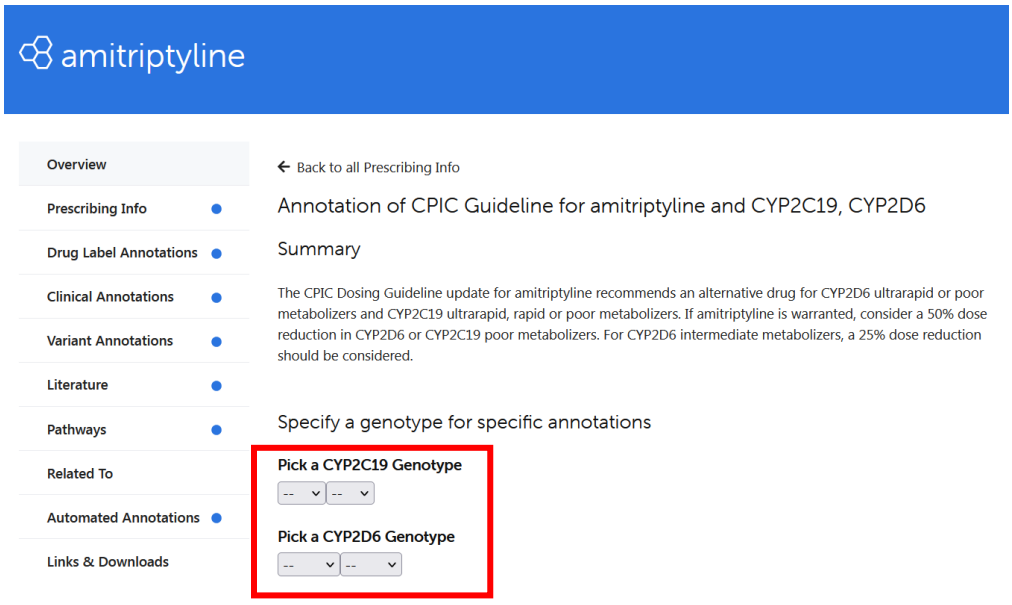
- **PharmGKB (The Pharmacogenomics Knowledge Base) https://www.pharmgkb.org**
    - Has information for CPIC, DPWF, FDA, primary lit all in 1 place!
        - Search drug name

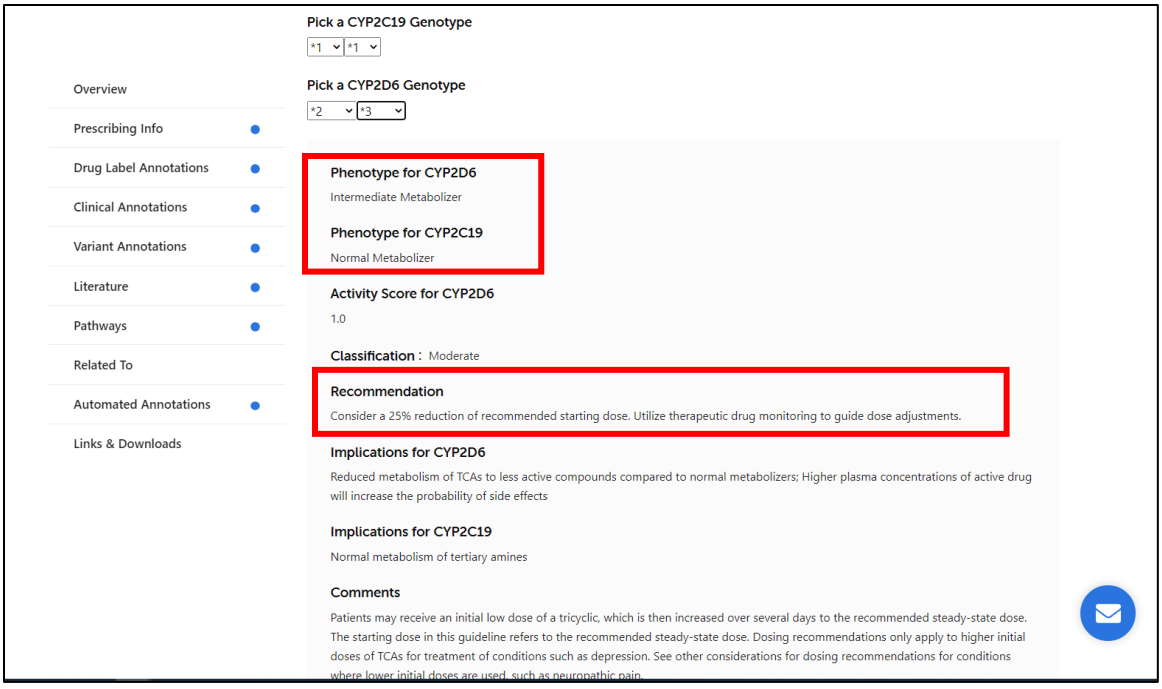


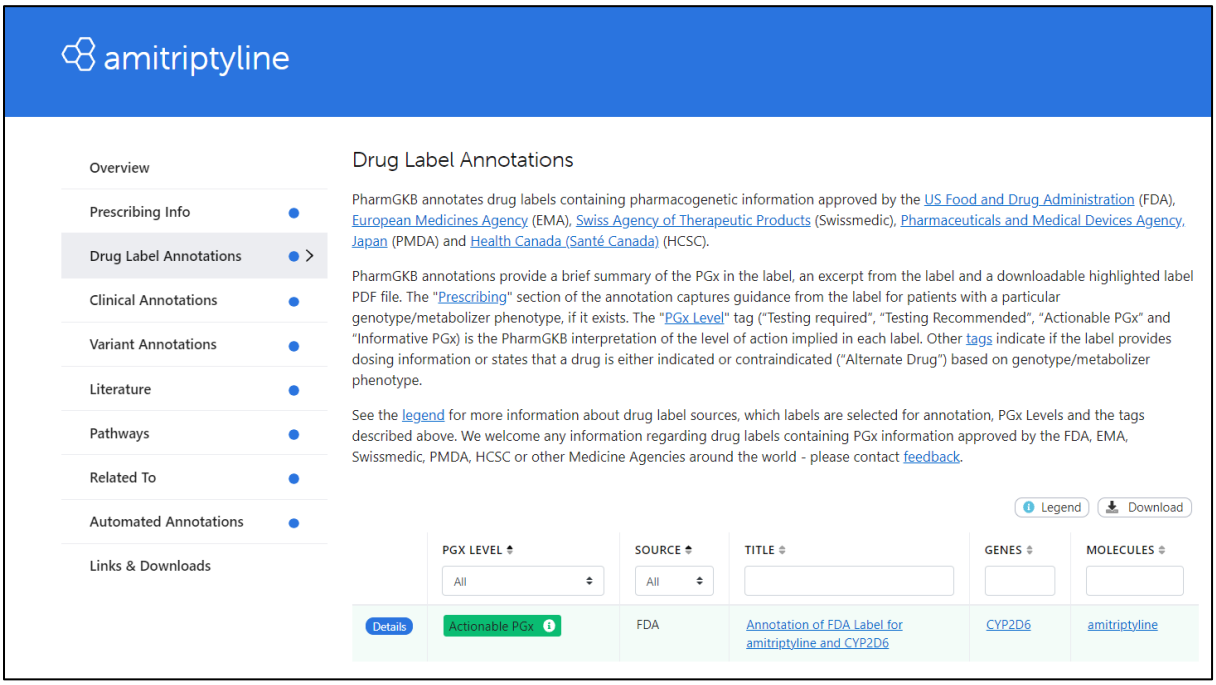

        - Prescribing Info = guidelines; Drug Label Annotations = drug labeling information

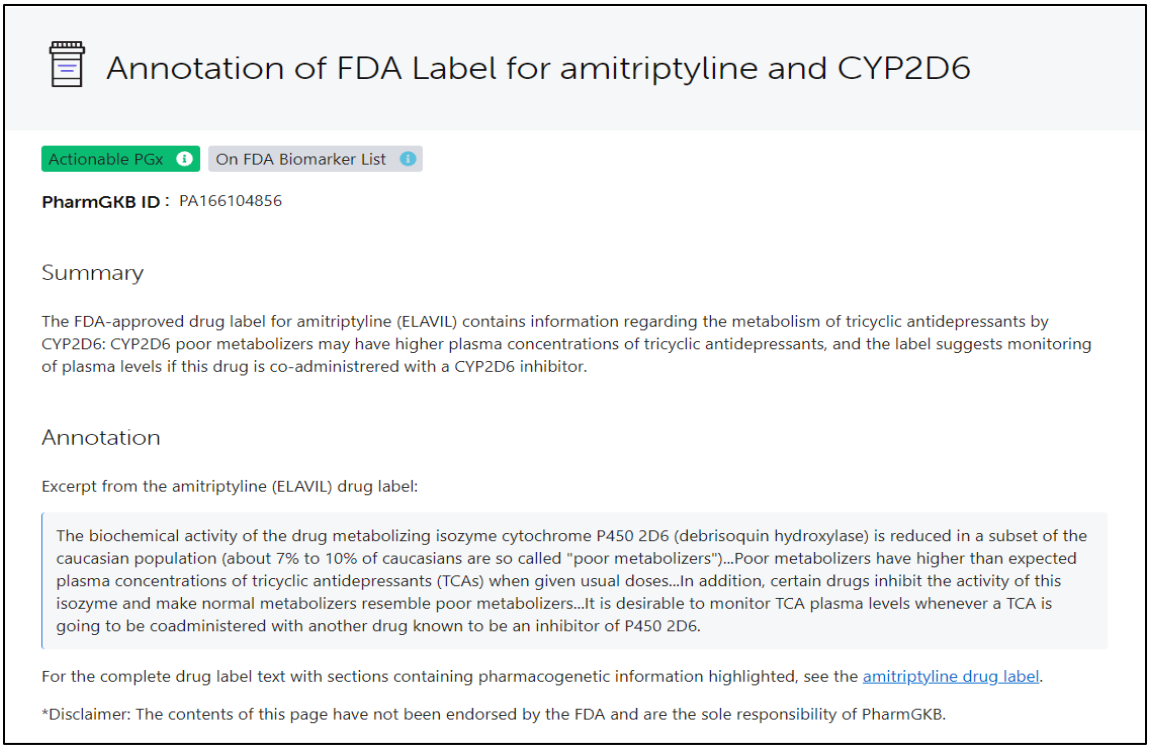



- Use drop down to enter genotype star alleles
- PharmGKB provides phenotype, activity score, CPIC recommendations, and implications for practice
- Scroll below for further commentary, link to guideline, and guideline excerpts




Pick a CYP2C19 Genotype
*1 *1
Pick a CYP2D6 Genotype
*2 *3
Overview
Prescribing Info
Drug Label Annotations
Clinical Annotations
Variant Annotations
Literature
Pathways
Related To
Automated Annotations
Links & Downloads
Phenotype for CYP2D6
Intermediate Metabolizer
Phenotype for CYP2C19
Normal Metabolizer
Activity Score for CYP2D6
1.0
Classification : Moderate
Recommendation
Consider a 25% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.
Implications for CYP2D6
Reduced metabolism of TCAs to less active compounds compared to normal metabolizers; Higher plasma concentrations of active drug will increase the probability of side effects
Implications for CYP2C19
Normal metabolism of tertiary amines
Comments
Patients may receive an initial low dose of a tricyclic, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose. Dosing recommendations only apply to higher initial doses of TCAs for treatment of conditions such as depression. See other considerations for dosing recommendations for conditions where lower initial doses are used, such as neuropathic pain.


amitriptyline
Overview
Prescribing Info
Drug Label Annotations
Clinical Annotations
Variant Annotations
Literature
Pathways
Related To
Automated Annotations
Links & Downloads
Drug Label Annotations
PharmGKB annotates drug labels containing pharmacogenetic information approved by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), Swiss Agency of Therapeutic Products (Swissmedic), Pharmaceuticals and Medical Devices Agency, Japan (PMDA) and Health Canada (Santé Canada) (HCSC).
PharmGKB annotations provide a brief summary of the PGx in the label, an excerpt from the label and a downloadable highlighted label PDF file. The "Prescribing" section of the annotation captures guidance from the label for patients with a particular genotype/metabolizer phenotype, if it exists. The "PGx Level" tag ("Testing required", "Testing Recommended", "Actionable PGx" and "Informative PGx) is the PharmGKB interpretation of the level of action implied in each label. Other tags indicate if the label provides dosing information or states that a drug is either indicated or contraindicated ("Alternate Drug") based on genotype/metabolizer phenotype.
See the legend for more information about drug label sources, which labels are selected for annotation, PGx Levels and the tags described above. We welcome any information regarding drug labels containing PGx information approved by the FDA, EMA, Swissmedic, PMDA, HCSC or other Medicine Agencies around the world - please contact feedback.
Legend
Download
PGX LEVEL
SOURCE
TITLE
GENES
MOLECULES
All
All
Details
Actionable PGx
FDA
Annotation of FDA Label for amitriptyline and CYP2D6
CYP2D6
amitriptyline



## Annotation of FDA Label for amitriptyline and CYP2D6

Actionable PGx | On FDA Biomarker List

**PharmGKB ID :** PA166104856

### Summary

The FDA-approved drug label for amitriptyline (ELAVIL) contains information regarding the metabolism of tricyclic antidepressants by CYP2D6: CYP2D6 poor metabolizers may have higher plasma concentrations of tricyclic antidepressants, and the label suggests monitoring of plasma levels if this drug is co-administrered with a CYP2D6 inhibitor.

### Annotation

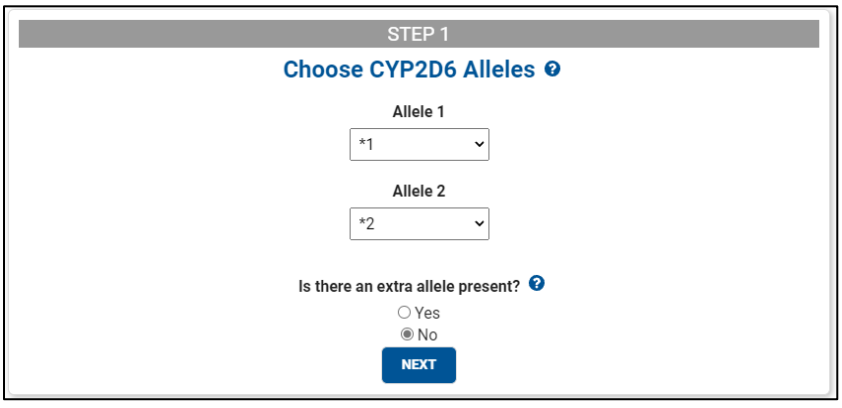
Excerpt from the amitriptyline (ELAVIL) drug label:

> The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7% to 10% of caucasians are so called "poor metabolizers")...Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses...In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers...It is desirable to monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of P450 2D6.

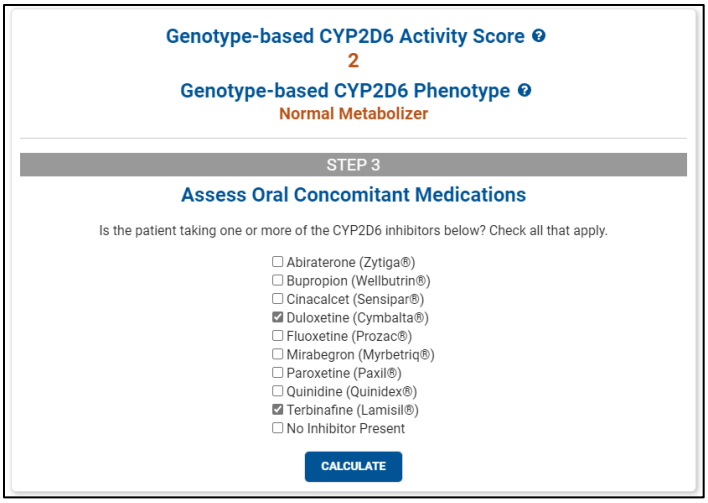
For the complete drug label text with sections containing pharmacogenetic information highlighted, see the amitriptyline drug label.

*Disclaimer: The contents of this page have not been endorsed by the FDA and are the sole responsibility of PharmGKB.

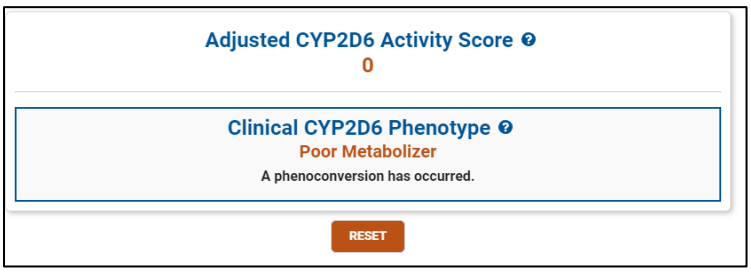
- Flockhart Table https://drug-interactions.medicine.iu.edu/MainTable.aspx
    - Contains the following sections: substrates, inhibitors, and inducers
- CYP2D6 Phenoconversion Calculator: https://precisionmedicine.ufhealth.org/phenoconversion-calculator/
    - standardized method of assessing CYP2D6 phenoconversion in practice when CYP2D6 genotype is available
    - Step 1 Choose CYP2D6 alleles




    - Step 2 CYP2D6 activity score and phenotype based on genotype alone provided. Select CYP2D6 inhibitors from list




- Step 3: CYP2D6 phenotype and adjusted activity score based on phenotype provided




# HOW CAN I LEARN MORE?

- ASHP Pharmacogenomics Certificate
  - https://www.ashp.org/professional-development/professional-certificates
- ACCP Pharmacogenomics Certificate
  - https://www.accp.com/store/product.aspx?pc=AC_PGX
- Test2Learn™ Pharmacogenomics Certificate Program
  - https://www.test2learn.org/pgxcertificateprogram/
- PGx ECHO (FREE!)
  - https://www.pharmacy.umn.edu/pgx-echo
  - meets the third Friday of every month at 12:00 PM CT
- Reach out!
  - Natasha.Petry@sanfordhealth.org
  - https://imagenetics.sanfordhealth.org/
  - 13th Annual ImaGENE Precision Medicine Summit – 9/6/2024
    - https://imagenetics.sanfordhealth.org/community/