DRUG
INTERACTION
SOLUTIONS

Clinical Pharmacogenetic

DATASET

Transforming **scientific data** into **clinical knowledge**

SCHOOL OF PHARMACY
UNIVERSITY of WASHINGTON

Clinical Pharmacogenetic

DATASET

The Clinical Pharmacogenetic (PGx) Dataset provides in-depth analysis of the impact of genetic variants of enzymes and transporters on the PK, PD, and safety of drugs in various populations. Available information comes from publications and NDA reviews describing gene-drug interactions (GDI), ethnicity-drug interactions, and case reports.

- **Detailed study information** regarding design, drug dosing, genetic polymorphisms, population characteristics, PK, PD, and safety results are structured and presented according to the latest PGx scientific consensus. Common metrics for active compounds (percent changes in AUC, plasma concentrations, oral clearance, dose requirements) and metabolites (AUC ratio of metabolite/parent, and formation clearance) are used across all studies to allow metadata analysis of quantitative results.
- **Study results** are categorized according to the overall impact of genetic variants on drug exposure, PD, and safety/efficacy compared to a reference group (non-carriers of variant).
- **Comprehensive PK parameters** for parent drugs and their metabolites are available.
- **Pre-formulated queries** allow users to retrieve an *in vivo* PGx dataset by drug name, gene name, and/or ethnicity.
- **Results** can be viewed, customized, and downloaded, allowing users to compile and organize the large body of information available.

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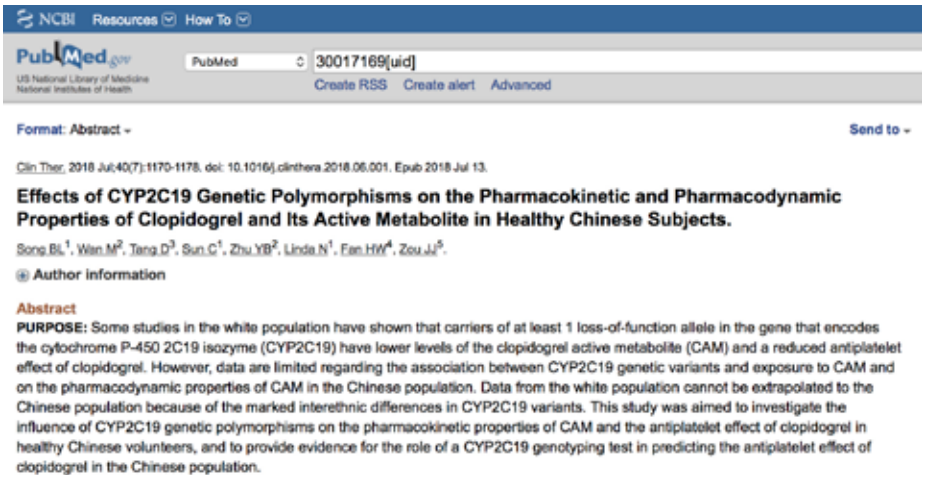
FROM A **CITATION** OR **NDA/BLA REVIEW**

The latest, most relevant, peer-reviewed publications and regulatory documents are identified and fully analyzed. Study protocol and results are manually curated to update the knowledgebase on a daily basis.

1



1

Most often analyzed files:

- Printed labeling
- Multi-discipline review
- Chemistry review(s)
- Other review(s)

TO A FULLY **CURATED DATASET**

Prior to integration, all data are carefully and critically evaluated. The richness of each citation, including relevant insights, is exploited, generating a highly detailed dataset.

2

Dosing

Design and Drug Administration	Genotyping Method	Alleles Tested
clopidogrel 300 mg oral single dose Design: Single Dosing, Open-label	iPLEX Sequenom MassArray	CYP2C19 636A CYP2C19 636G CYP2C19 681A CYP2C19 681G CYP2C19*2 CYP2C19*3

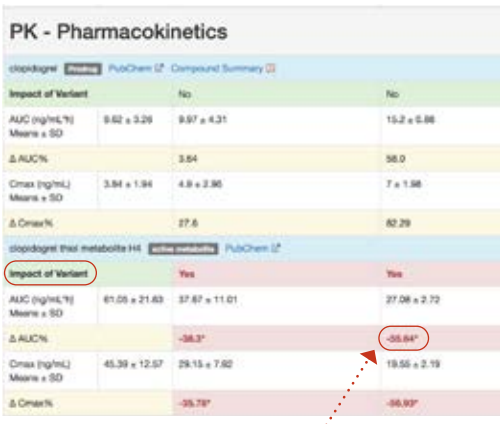
Genotyping
Phenotyping

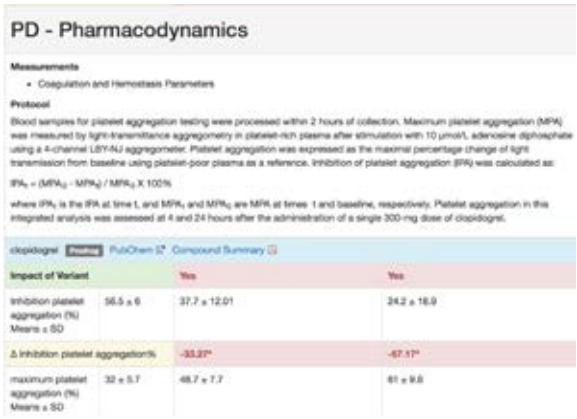
CYP2C19 NCBI Gene Gene Summary	8 Healthy volunteer(s) (reference) CYP2C19*1/*1 CYP2C19 Normal Metabolizers Asian Chinese Male(s) non-smokers	10 Healthy volunteer(s) CYP2C19*1/*2 CYP2C19*1/*3 CYP2C19 Intermediate Metabolizers Asian Chinese Male(s) non-smokers	2 Healthy volunteer(s) CYP2C19*2/*2 CYP2C19*2/*3 CYP2C19*3/*3 CYP2C19 Poor Metabolizers Asian Chinese Male(s) non-smokers

Populations with different genotypes

Impact of genetic variations on drug disposition

Impact of genetic variations on drug efficacy





*statistically significant

Clopidogrel exposure is significantly impacted in CYP2C19 poor metabolizers.

What other drugs have an AUC change of at least 2-fold in carriers of CYP2C19 loss-of-function alleles?

POWERFUL TOOL FOR **DATA INTEGRATION**: FROM ONE CITATION TO METADATA ANALYSIS

The data are formatted for immediate use and can be filtered and re-arranged to allow meta-analysis of multiple results.

Query all drugs exhibiting exposure increases of at least 2-fold in CYP2C19 poor metabolizers

3

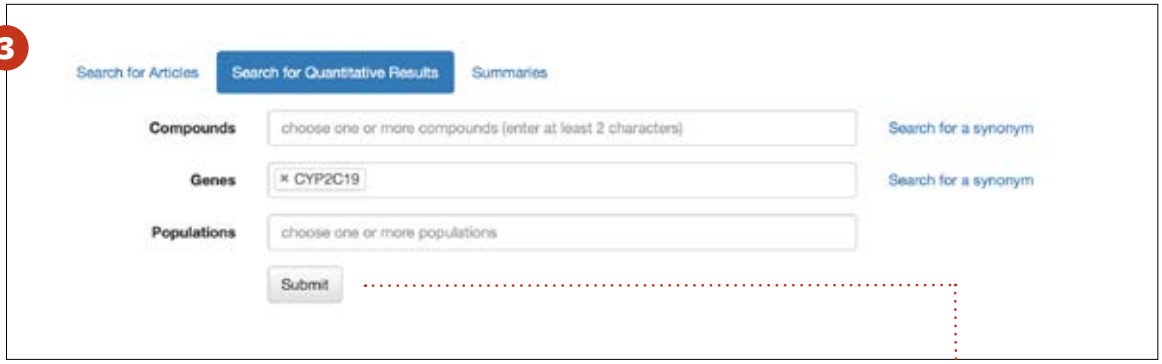
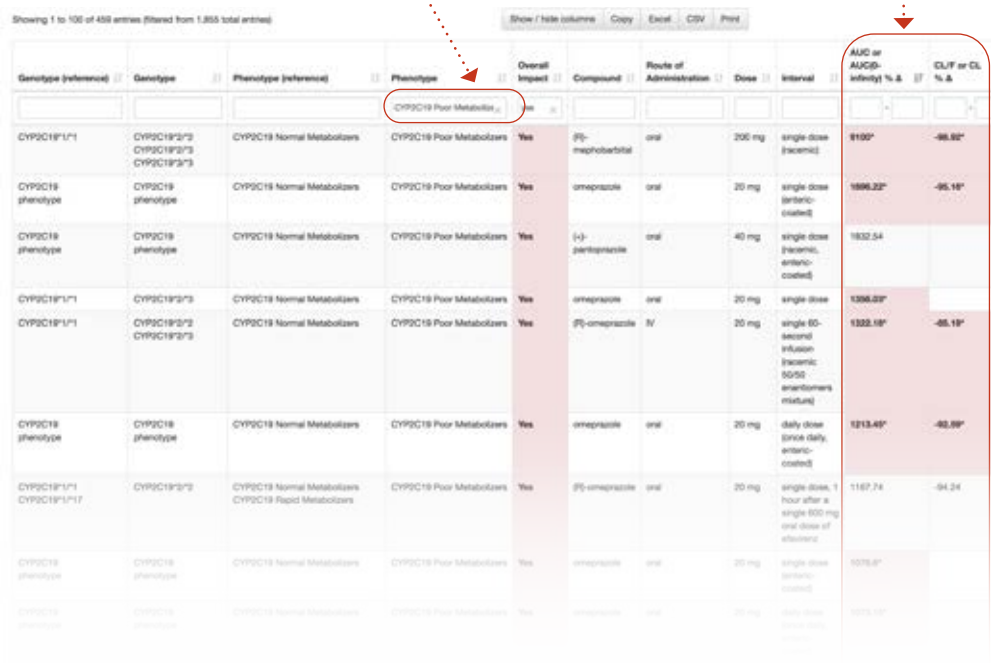


Table View of Query Results

4

Filter

Multiple formats for viewing and downloading



Obtain a complete list of drugs that may need dosing adjustment in CYP2C19 poor metabolizers

CLINICAL PGx DATASET IN NUMBERS

(as of April 16, 2020)

2,667 *in vivo* PGx citations / **7,875** *in vivo* PGx entries

60 *in vivo* PGx NDAs/BLAs / **159** *in vivo* PGx entries

Dedicated *in vivo* PGx queries with **10** possible searches

603 citations / **1,331** entries on PGx efficacy (PD)

583 citations / **909** entries on PGx safety (side effects)

292 case reports

1,485 drugs involved in *in vivo* PGx

APPLICATIONS OF THE CLINICAL PGx DATASET

PROVIDES CONTEXT for RESULTS OBTAINED with candidate compounds

HELPS DEVELOP OVERALL REGULATORY STRATEGY and optimize clinical PGx trials:

- Refines inclusion/exclusion criteria
- Helps select dose, duration, and timing of drug administration in the context of PGx
- Provides PK variability data for power calculations
- Quickly identifies known substrates of enzymes/transporters among marketed drugs to understand GDI risk

SUPPORTS STATIC PREDICTIONS and PBPK MODELING with input parameters

ACCESSES REGULATORY GDI STUDIES for recently marketed drugs

PROVIDES REFERENCE RESOURCE for ASSESSMENT of DRUG INTERACTION SAFETY

HELPS IMPLEMENT PERSONALIZED MEDICINE in the context of GDI and gene-DDI

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