CERTARA

Clinical Pharmacogenetic Dataset

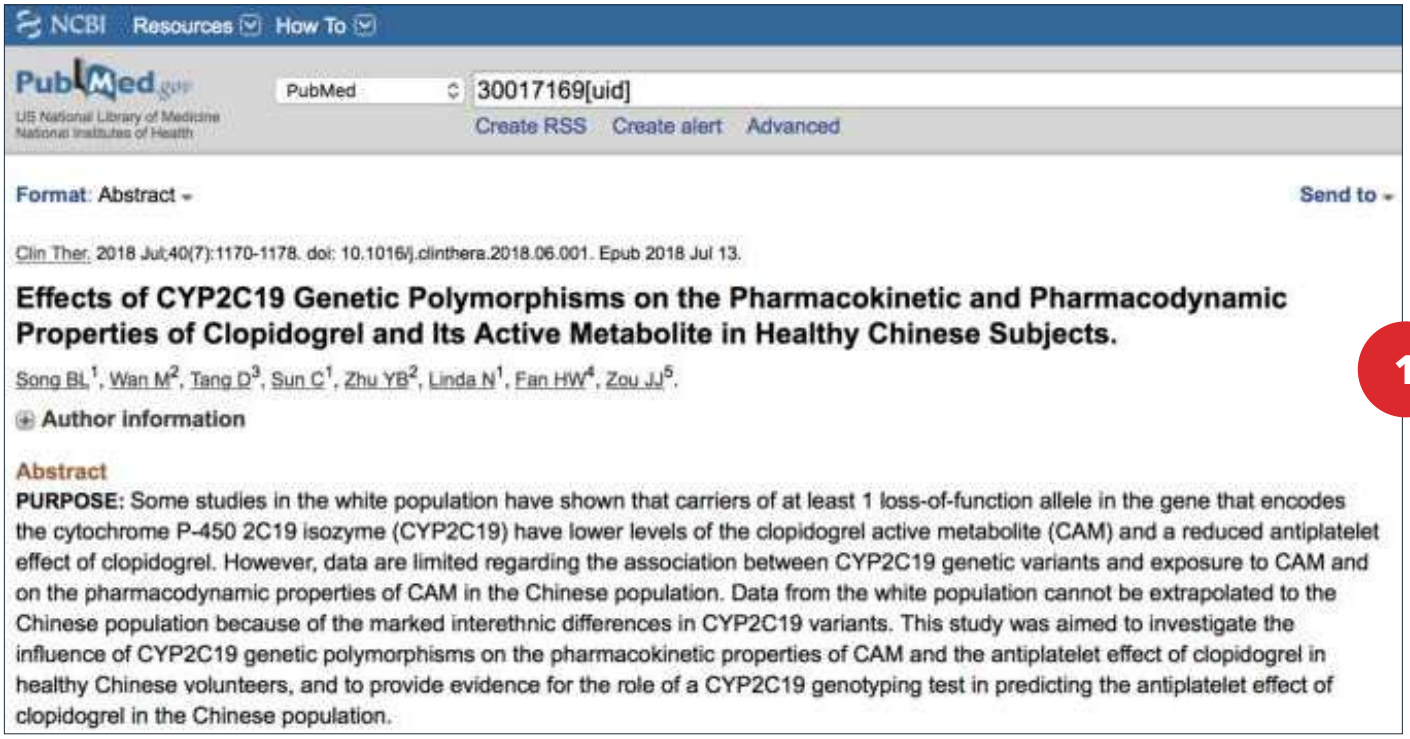
Transforming scientific data into clinical knowledge

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.

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.



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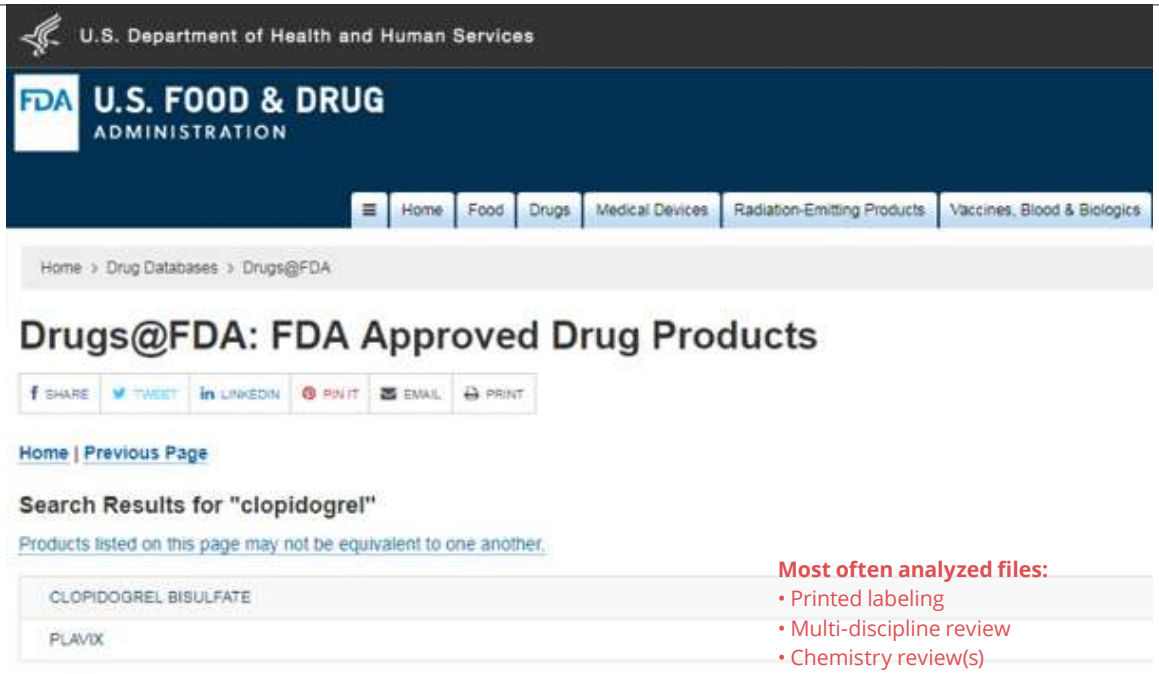

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Most often analyzed files:
- Printed labeling
- Multi-discipline review
- Chemistry review(s)
- Other review(s)

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.

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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 PharmGKB PharmVar	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

PK - Pharmacokinetics

clopidogrel Prodrug PubChem PharmGKB

Impact of Variant		No	No
AUC (ng/mL*h) Means ± SD	9.62 ± 3.26	9.97 ± 4.31	15.2 ± 0.88
Δ AUC%		3.6	58.0
C_{max} (ng/mL) Means ± SD	3.84 ± 1.94	4.9 ± 2.96	7 ± 1.98
Δ C_{max}%		27.6	82.3

clopidogrel thiol metabolite H4 active metabolite PubChem

Impact of Variant		Yes	Yes
AUC (ng/mL*h) Means ± SD	61.05 ± 21.63	37.67 ± 11.01	27.08 ± 2.72
Δ AUC%		-38.3*	-55.6*
C_{max} (ng/mL) Means ± SD	45.39 ± 12.57	29.15 ± 7.92	19.55 ± 2.19
Δ C_{max}%		-35.8*	-56.9*

*statistically significant

Impact of genetic variations on drug efficacy

PD - Pharmacodynamics

Measurements

- Coagulation and Hemostasis Parameters

Protocol

Blood samples for platelet aggregation testing were processed within 2 hours of collection. Maximum platelet aggregation (MPA) was measured by light-transmittance aggregometry in platelet-rich plasma after stimulation with 10 µmol/L adenosine diphosphate using a 4-channel LBY-NJ aggregometer. Platelet aggregation was expressed as the maximal percentage change of light transmission from baseline using platelet-poor plasma as a reference. Inhibition of platelet aggregation (IPA) was calculated as:

$IPA_t = (MPA_0 - MPA_t) / MPA_0 \times 100\%$

where IPA_t is the IPA at time t, and MPA_t and MPA_0 are MPA at times t and baseline, respectively. Platelet aggregation in this integrated analysis was assessed at 4 and 24 hours after the administration of a single 300-mg dose of clopidogrel.

clopidogrel Prodrug PubChem PharmGKB

Impact of Variant		Yes	Yes
Inhibition platelet aggregation (%) Means ± SD	56.5 ± 6	37.7 ± 12.01	24.2 ± 18.9
Δ Inhibition platelet aggregation%		-33.3*	-57.2*
maximum platelet aggregation (%) Means ± SD	32 ± 5.7	48.7 ± 7.7	61 ± 9.6

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

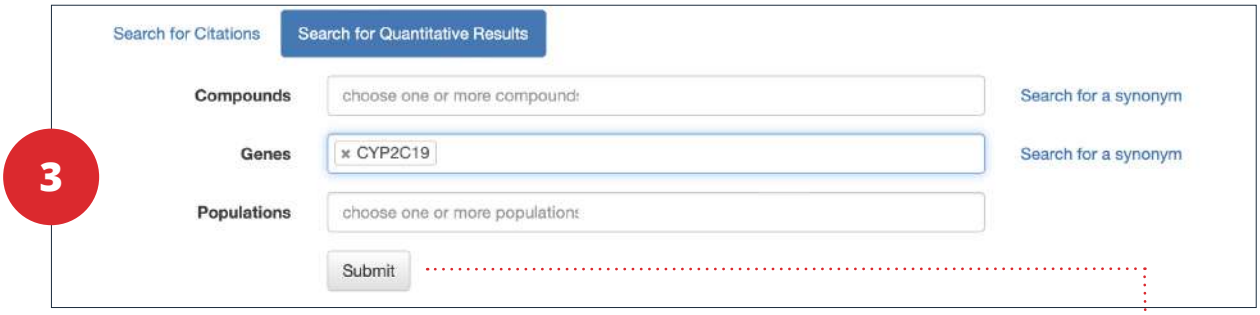

Table View of Query Results

Multiple formats for viewing and downloading

Filter

Showing 1 to 100 of 1,107 entries (filtered from 2,429 total entries)

Select columns | Copy | Excel | CSV | Print

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Genotype (reference)	Genotype	Phenotype (reference)	Phenotype	Overall Impact	Compound	Route of administration	Dose	AUC or AUC(0-infinity) % Δ	CL/F or CL % Δ
			× CYP2C19 Poor Metabolizers					-	-
CYP2C19*1/*1, CYP2C19*1/*2	CYP2C19*2/*2	CYP2C19 Intermediate Metabolizers, CYP2C19 Normal Metabolizers	CYP2C19 Poor Metabolizers		(R)-lansoprazole sulfone	oral	60 mg	22655.3	
CYP2C19*1/*1	CYP2C19*2/*2, CYP2C19*2/*3, CYP2C19*3/*3	CYP2C19 Normal Metabolizers	CYP2C19 Poor Metabolizers	Yes	(R)-mephobarbital	oral	200 mg	9100.0*	-98.9*
CYP2C19*1/*1	CYP2C19*2/*2, CYP2C19*2/*3	CYP2C19 Normal Metabolizers	CYP2C19 Poor Metabolizers		lansoprazole sulfone	oral	30 mg	8277.8*	
CYP2C19*1/*1	CYP2C19*2/*2, CYP2C19*2/*3	CYP2C19 Normal Metabolizers	CYP2C19 Poor Metabolizers		lansoprazole sulfone	oral	30 mg	7139.4*	-98.8*
CYP2C19*1/*1	CYP2C19*2/*2, CYP2C19*2/*3	CYP2C19 Normal Metabolizers	CYP2C19 Poor Metabolizers		omeprazole sulfone	IV	20 mg	5895.0*	

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

CLINICAL PGX DATASET IN NUMBERS

(as of Ocober 16, 2023)

3,248 *in vivo* PGx citations / **10,084** *in vivo* PGx entries

104 *in vivo* PGx NDAs/BLAs / **275** *in vivo* PGx entries

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

707 citations on PGx efficacy (PD) / **1,590** entries

714 citations on PGx safety (side effects) / **1,140** entries

307 case reports

725 drugs involved in *in vivo* PGx

APPLICATIONS OF THE CLINICAL PGx DATASET

PROVIDES CONTEXT for RESULTS OBTAINED with candidate compouds

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

CERTARA

To learn more, visit www.druginteractionsolutions.org

or email DIDBase@Certara.com

About Certara

Certara accelerates medicines using proprietary biosimulation software, technology and services to transform traditional drug discovery and development. Its clients include more than 2,000 biopharmaceutical companies, academic institutions, and regulatory agencies across 62 countries.

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