

**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.

## 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

NCBI Resources How To

PubMed.gov  
US National Library of Medicine  
National Institutes of Health

PubMed 30017169[uid]  
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Format: Abstract - Send to -

Clin Ther. 2018 Jul;40(7):1170-1178. doi: 10.1016/j.clinthera.2018.06.001. Epub 2018 Jul 13.

**Effects of CYP2C19 Genetic Polymorphisms on the Pharmacokinetic and Pharmacodynamic Properties of Clopidogrel and Its Active Metabolite in Healthy Chinese Subjects.**

Song BL<sup>1</sup>, Wen M<sup>2</sup>, Teng D<sup>3</sup>, Sun C<sup>1</sup>, Zhu YB<sup>2</sup>, Linda N<sup>1</sup>, Fan HW<sup>4</sup>, Zou JJ<sup>5</sup>.

Author information

**Abstract**  
**PURPOSE:** Some studies in the white population have shown that carriers of at least 1 loss-of-function allele in the gene that encodes the cytochrome P-450 2C19 isozyme (CYP2C19) have lower levels of the clopidogrel active metabolite (CAM) and a reduced antiplatelet effect of clopidogrel. However, data are limited regarding the association between CYP2C19 genetic variants and exposure to CAM and on the pharmacodynamic properties of CAM in the Chinese population. Data from the white population cannot be extrapolated to the Chinese population because of the marked interethnic differences in CYP2C19 variants. This study was aimed to investigate the influence of CYP2C19 genetic polymorphisms on the pharmacokinetic properties of CAM and the antiplatelet effect of clopidogrel in healthy Chinese volunteers, and to provide evidence for the role of a CYP2C19 genotyping test in predicting the antiplatelet effect of clopidogrel in the Chinese population.

1

U.S. Department of Health and Human Services

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**Drugs@FDA: FDA Approved Drug Products**

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**Search Results for "clopidogrel"**

Products listed on this page may not be equivalent to one another

CLOPIDOGREL BISULFATE
PLAVIX

### 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**  
clopidogrel 300 mg oral single dose  
Design: Single Dosing, Open-label

**Genotyping Method**  
iPLEX Sequenom MassArray

**Alleles Tested**

CYP2C19 636A  
CYP2C19 636G  
CYP2C19 681A  
CYP2C19 681G  
CYP2C19\*2  
CYP2C19\*3

Genotyping  
Phenotyping

CYP2C19 NCBI Gene ID 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
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Populations with different genotypes

## Impact of genetic variations on drug disposition

**PK - Pharmacokinetics**

clopidogrel [PubMed](#) [PubChem ID](#) [Compound Summary](#)

Impact of Variant	No	Yes
AUC (ng/mL <sup>h</sup> ) Means ± SD	9.62 ± 3.29	9.97 ± 4.31
Δ AUC%		3.64
C <sub>max</sub> (ng/mL) Means ± SD	3.94 ± 1.94	4.8 ± 2.95
Δ C <sub>max</sub> %		27.6

clopidogrel final metabolite H4 [PubMed](#) [PubChem ID](#)

Impact of Variant	Yes	Yes
AUC (ng/mL <sup>h</sup> ) Means ± SD	61.08 ± 21.63	37.67 ± 11.01
Δ AUC%		-38.3*
C <sub>max</sub> (ng/mL) Means ± SD	45.39 ± 12.57	29.15 ± 7.62
Δ C <sub>max</sub> %		-35.93*

\*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-ANJ 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<sub>t</sub> = (MPA<sub>0</sub> - MPA<sub>t</sub>) / MPA<sub>0</sub> × 100% where IPA<sub>t</sub> is the IPA at time t, and MPA<sub>0</sub> and MPA<sub>t</sub> are MPA at times 1 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 [PubMed](#) [PubChem ID](#) [Compound Summary](#)

Impact of Variant	Yes	Yes
Inhibition platelet aggregation (%) Means ± SD	56.5 ± 6	37.7 ± 12.01
Δ Inhibition platelet aggregation%		-33.2*
maximum platelet aggregation (%) Means ± SD	32 ± 5.7	49.7 ± 7.7
Δ maximum platelet aggregation (%)		57.5*

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

Search for Articles   **Search for Quantitative Results**   Summaries

**Compounds**  [Search for a synonym](#)

**Genes**  [Search for a synonym](#)

**Populations**

## Table View of Query Results

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Showing 1 to 106 of 458 entries (filtered from 1,855 total entries)

Show / Hide columns   Copy   Excel   CSV   Print

Genotype (reference)	Genotype	Phenotype (reference)	Phenotype	Overall Impact	Compound	Route of Administration	Dose	Interval	AUC or AUC(0-infinity) % Δ	CL/F or CL % Δ
CYP2C19*1/*1	CYP2C19*2/*2 CYP2C19*2/*3 CYP2C19*3/*3	CYP2C19 Normal Metabolizers	CYP2C19 Poor Metabolizers	Yes	PS-meprobamate	oral	200 mg	single dose (fasted)	8190*	-86.82*
CYP2C19 phenotype	CYP2C19 phenotype	CYP2C19 Normal Metabolizers	CYP2C19 Poor Metabolizers	Yes	omeprazole	oral	20 mg	single dose (fasted, enteric-coated)	1896.22*	-95.18*
CYP2C19 phenotype	CYP2C19 phenotype	CYP2C19 Normal Metabolizers	CYP2C19 Poor Metabolizers	Yes	(-)-perphenazine	oral	40 mg	single dose (fasted, enteric-coated)	1832.54	
CYP2C19*1/*1	CYP2C19*2/*3	CYP2C19 Normal Metabolizers	CYP2C19 Poor Metabolizers	Yes	omeprazole	oral	20 mg	single dose	1386.83*	
CYP2C19*1/*1	CYP2C19*2/*2 CYP2C19*2/*3	CYP2C19 Normal Metabolizers	CYP2C19 Poor Metabolizers	Yes	(S)-omeprazole	IV	20 mg	single 60-second infusion (fasted, 10/50 enantiomers mixture)	1332.18*	-85.18*
CYP2C19 phenotype	CYP2C19 phenotype	CYP2C19 Normal Metabolizers	CYP2C19 Poor Metabolizers	Yes	omeprazole	oral	20 mg	daily dose (POA (fast), enteric-coated)	1213.49*	-83.89*
CYP2C19*1/*1 CYP2C19*1/*17	CYP2C19*2/*2	CYP2C19 Normal Metabolizers CYP2C19 Rapid Metabolizers	CYP2C19 Poor Metabolizers	Yes	(S)-omeprazole	oral	20 mg	single dose, 1 hour after a single 500 mg oral dose of omeprazole	1167.74	-84.34
CYP2C19 phenotype	CYP2C19 phenotype	CYP2C19 Normal Metabolizers	CYP2C19 Poor Metabolizers	Yes	omeprazole	oral	20 mg	single dose (fasted, enteric-coated)	5076.8*	
CYP2C19 phenotype	CYP2C19 phenotype	CYP2C19 Normal Metabolizers	CYP2C19 Poor Metabolizers	Yes	omeprazole	oral	20 mg	daily dose (fasted, enteric-coated)	5073.18*	

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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