# Pharmacogénétique

-

## Implémentation de la PGx à partir des WGS/WES

RÉSEAU FRANCOPHONE DE PHARMACOGÉNÉTIQUE

*Dr Louis Lebreton (CHU Bordeaux)*

*01/04/2025 – Séminaire BioinfoDiag*

Pythagore (-580 à -495)

« Pythagore interdisait les fèves car elles contiennent des âmes, ou provoquent des troubles corporels. »

- *Jamblique, Vie de Pythagore*, §94-95

« Aristote rapporte que Pythagore défendait de manger des fèves, de passer sur une traverse de bois, de toucher un coq blanc [...] »

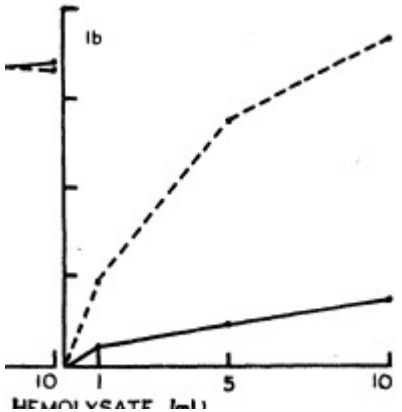
— *Diogène Laërce*, Livre VIII, §34

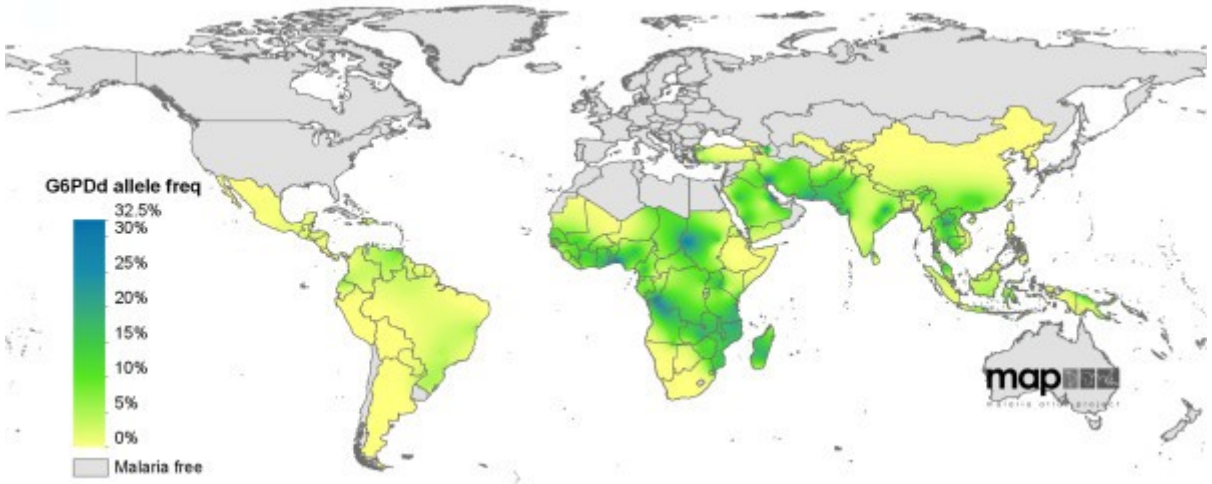
Science. 1956 Sep 14;124(3220):484-5. doi: 10.1126/science.124.3220.484-a.

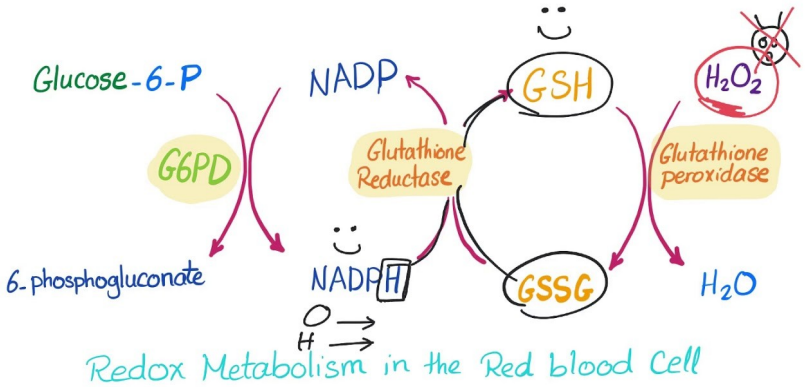
## Enzymatic deficiency in primaquine-sensitive erythrocytes

A S ALVING, P E CARSON, C L FLANAGAN, C E ICKES

PMID: 13360274 DOI: 10.1126/science.124.3220.484-a




G6PD (4057)

NM_001360016.2:c.563C>T MD canonical MANE Select

r.(?)

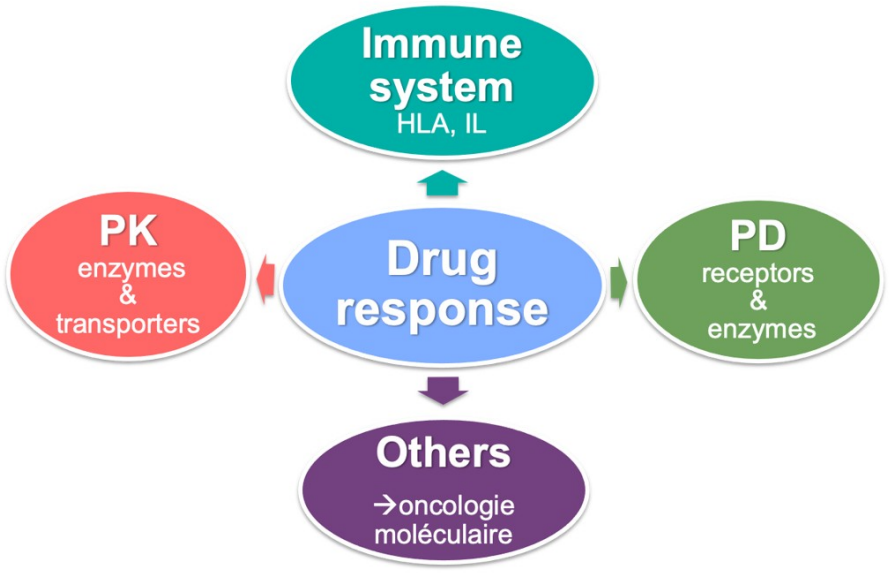
NP_001346945.1:p.(Ser188Phe)

Variant « Med »

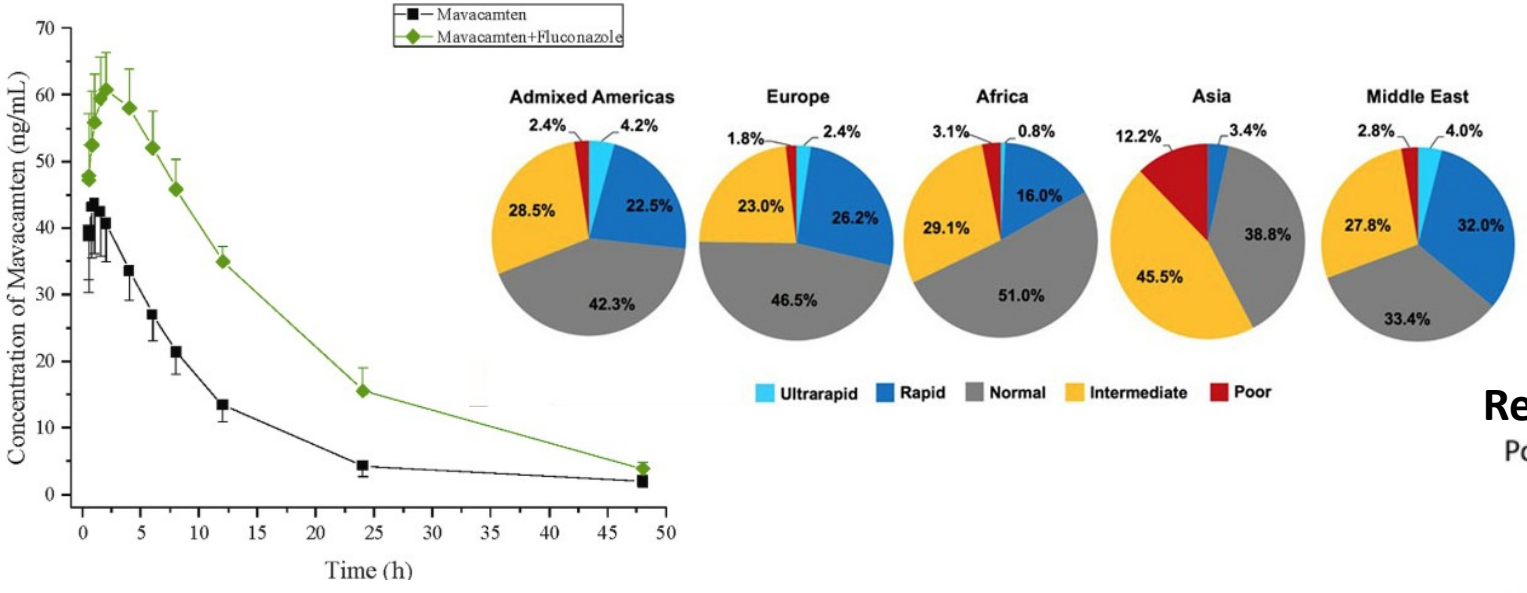
| Features | Values |
|---|---|
| gnomAD exome: | 0.0026 |
| gnomAD genome: | 0.0001 |
| gnomAD exome (non cancer): | 0.0174 |
| gnomAD v4 Genome: | 0.0007 |
| gnomAD v4 Exome: | 0.0015 |
| dbSNP rsid: | rs5030868 |
| Clinvar Germline: | Pathogenic/Likely pathogenic ★★☆☆ |

| | | | |
|---|---|---|---|
| ABCB1 | CYP2C9 | GGCX | POR |
| ABCG2 | CYP2D6 | HLA-A | RYR1 |
| BCHE | CYP3A4 | HLA-B | SLCO1B1 |
| CACNA1S | CYP3A5 | MT-RNR1 | TPMT |
| CYP2B6 | CYP4F2 | MTHFR | TYMS |
| CYP2C cluster | DPYD | NAT2 | UGT1A1 |
| CYP2C19 | G6PD | NUDT15 | VKORC1 |

*Oncologie et soins de support* *Infectiologie et immunologie* *Système cardiovasculaire* *Neuropsychiatrie* *Anesthésie et douleur*




## Exemple du CAMYZOS (Mavacamten)




Li Q, Liu YN, Chen C, Xu RA, Xie S, Zhan R. **Effects of CYP2C19 inhibitors on mavacamten pharmacokinetics in rats based on UPLC-MS/MS**. Chem Biol Interact. 2023 Aug 1;380:110531. doi: 10.1016/j.cbi.2023.110531. Epub 2023 May 6. PMID: 37150496.

**Génotypage**

Ex : CYP2C19 *2 / *3

**Phénotype**

CYP2C19 poor metabolizer

**Recommandations** ViDAL Hoptimal

Poor metabolizer :

- starting daily dose 2.5 mg once daily
- Contra-indications with strong CYP3A4 inhibitors
- Maximum daily dose is 5 mg once daily

Non poor metabolizer :

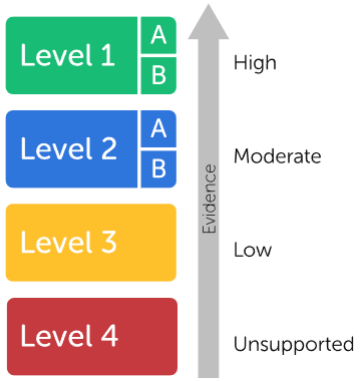
- starting daily dose 5 mg once daily
- Contra-indications with strong CYP2C19 and CYP3A4 inhibitors
- Maximum daily dose is 15 mg once daily

# Société savantes qui émettent des recommandations

CPIC® Clinical Pharmacogenetics Implementation Consortium

**DPWG**
Dutch Pharmacogenetics Working Group

RNPGx
RÉSEAU FRANCOPHONE DE PHARMACOGÉNÉTIQUE




Clinical Pharmacology & Therapeutics

Review | Open Access

**French-Speaking Network of Pharmacogenetics (RNPGx) Recommendations for Clinical Use of Mavacamten**

Louis Lebreton, Jean-Christophe Boyer, Claire Lafay-Chebassier, Benjamin Hennart, Sarah Baklouti, Séverine Cunat, Paul Vilquin, Yves Medard, Elodie Gautier-Veyret ... See all authors

First published: 25 November 2024 | https://doi.org/10.1002/cpt.3502

| LEVEL | PHARMACOGENOMIC TEST | DETAILS |
|---|---|---|
| Essential | CYP2C19 *2 (rs4244285) and *3 alleles (rs4986893) | Stratification for starting and maximum dose prescription, as well as dose adjustment based on drug–drug interactions |
| Advisable | CYP2C19 *17 alleles (rs12248560) | Dose adjustment (efficiency) |
| Possibly helpful | CYP2C19 rs12769205 (*35), rs28399504 (*4), rs56337013 (*5), rs3758581 (*6), rs72558186 (*7), rs41291556 (*8), rs17884712 (*9), rs140278421 (*22), rs118203757 (*24), Deletions (*36 et *37) | Adverse drug reaction associated with overexposure after genotyping CYP2C19 *2 and *3 alleles |

# Institutions qui précisent les pratiques dans les RCP de médicaments

FDA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ansm
Agence nationale de sécurité du médicament et des produits de santé

swissmedic

| PGX LEVEL | SOURCE | TITLE | GENES | DRUGS |
|---|---|---|---|---|
| Testing Required | EMA | Annotation of EMA Label for mavacamten and CYP2C19 (Dosing Info, Prescribing Info) | CYP2C19 | mavacamten |
| Informative PGx | FDA | Annotation of FDA Label for mavacamten and CYP2C19 (FDA Biomarker) | CYP2C19 | mavacamten |
| Informative PGx | HCSC | Annotation of HCSC Label for mavacamten and CYP2C19 | CYP2C19 | mavacamten |

RÉSEAU FRANCOPHONE DE PHARMACOGÉNÉTIQUE

Association loi 1901, Fondé en 2006
71 membres
Bureau 2025-2027 :
Pr Nicolas PICARD, Limoges (Président)
Dr Sylvie QUARANTA, Marseille (vice-présidente)
Pr Marie-Anne LORIOT, HEGP (past-président)
Dr Hugo ALARCAN, Tours (Trésorier)
Dr Jean-Christophe BOYER, Nîmes
Dr Estelle AYME-DIETRICH, Strasbourg
Dr Louis LEBRETON, Bordeaux


- Se positionner en tant que **société savante de recours** v
à-vis des institutions, autorités de santé ou de tutelles
- Rédiger des **recommandations** / ensemble des aspects du
domaine

Thésaurus ABM
Saisine HAS RIHN (Panel NGS)
Évaluation de tests compagnon par la HAS

Clinical Pharmacology & Therapeutics

Review | Open Access

**French-Speaking Network of Pharmacogenetics (RNPGx) Recommendations for Clinical Use of Mavacamten**

Louis Lebreton, Jean-Christophe Boyer, Claire Lafay-Chebassier, Benjamin Hennart, Sarah Baklouti, Séverine Cunat, Paul Vilquin, Yves Medard, Elodie Gautier-Veyret, Clara Laffitte-Redondo, Céline Verstuyft, Abd El Kader Ait Tayeb, Vincent Haufroid, Julien Wils, Fabien Lamoureux, Alexandre Evrard, Julie Davaze-Schneider, Mouna Ben-Sassi, Nicolas Picard, Sylvie Quaranta, Estelle Ayme-Dietrich, the French-Speaking Network of Pharmacogenetics (RNPGx)

First published: 25 November 2024 | https://doi.org/10.1002/cpt.3502

Review > Therapie. 2024 Nov-Dec;79(6):709-717. doi: 10.1016/j.therap.2024.05.006. Epub 2024 Jun 5.

**[Pharmacogenetics of aminoglycoside ototoxicity: State of knowledge and practices – Recommendations of the Francophone Network of Pharmacogenetics (RNPGx)]**

[Article in French]
Louis Lebreton [1], Benjamin Hennart [2], Sarah Baklouti [3], Aurélien Trimouille [4], Jean-Christophe Boyer [5], Laurent Becquemont [6], Claire-Marie Dhaenens [7], Nicolas Picard [8]

Affiliations + expand
PMID: 38876950 DOI: 10.1016/j.therap.2024.05.006

> Therapie. 2017 Apr;72(2):269-284. doi: 10.1016/j.therap.2016.09.011. Epub 2017 Jan 3.

**Pharmacogénétique des immunosuppresseurs : état des connaissances et des pratiques – recommandations du Réseau national de pharmacogénétique (RNPGx)**

[Article in French]
Jean-Baptiste Woillard [1], Laurent Chouchana [2], Nicolas Picard [3], Marie-Anne Loriot [4]; Réseau national de pharmacogénétique (RNPGx)

# GT « analyses PGx à partir de WES WGS »

- Contexte de réalisation
- Analyse bio-informatique
- Mise à disposition des résultats

# GT « analyses PGx à partir de WES WGS »

RNPGX — RÉSEAU FRANCOPHONE DE PHARMACOGÉNÉTIQUE

- Contexte de réalisation
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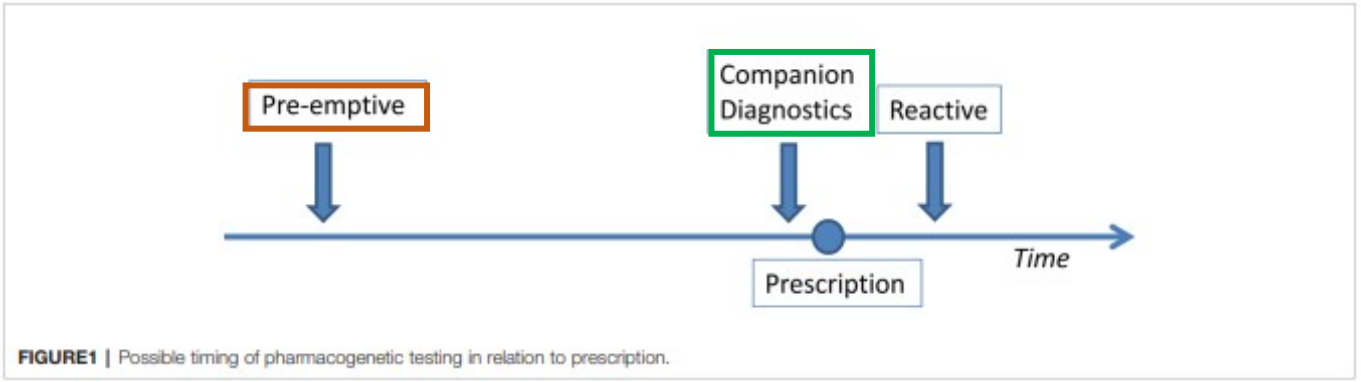



**FIGURE1** | Possible timing of pharmacogenetic testing in relation to prescription.

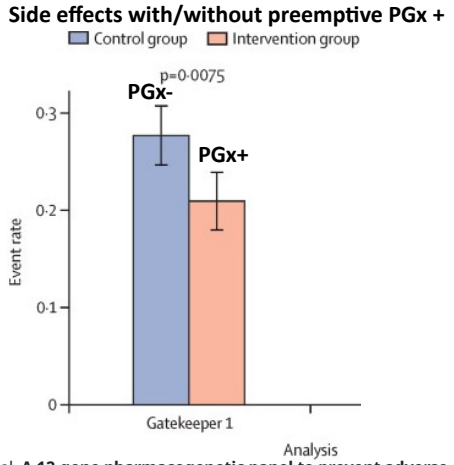
**Companion diagnostic** → Co-prescription Maladie rare/Cancer – PGx ? (PFMG ? Dépistage néonatal ?)

**Pre emptive** → Carte pharmacogénétique

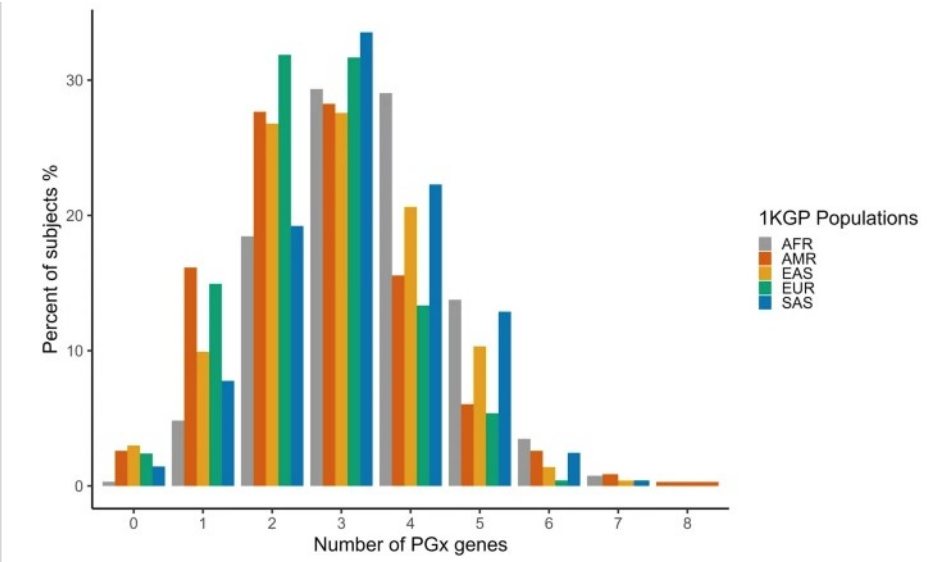
PHARMACOGENETIC ID CARD

| Felix Muster (name) | | 1976-09-16 (date of birth (y/m/d)) | male (gender) |
|---|---|---|---|
| **GENE** | **GENOTYPE** | **EFFECT** | **EXAMPLES OF AFFFECTED DRUGS** |
| ABCB1 | CGC/TTT | drug-dep. alt. efficacy | |
| COMT | low/im | slow metabolism | |
| CYP1A2 | *1F/*1F | very fast metabolism | clozapine, coffeine, zolmitriptane, ropinirol |
| CYP2B6 | *1/*6 | slow metabolism | efavirenz, bupropion, methadone, pethidine |
| CYP2C9 | *1/*1 | normal metabolism | |
| CYP2C19 | *1/*1 | normal metabolism | |
| CYP2D6 | *1/*2 | normal metabolism | |
| CYP3A4 | *1/*1 | normal metabolism | |
| CYP3A5 | *3/*3 | normal metabolism | |
| CYP4F2 | C/T | slow metabolism | |
| DPYD | *1/*1 | normal metabolism | |
| OPRM1 | A/G | drug-dep. alt. efficacy | morphine |
| POR | *28/*28 | fast metabolism | |
| SLCO1B1 | *1a/*1a | normal drug efficacy | |
| TPMT | *1/*1 | normal metabolism | |
| VKORC1 | G/A | increased drug efficacy | acenocoumarol, phenprocoumon, warfarin |

Genetic analyses may not detect all known mutations of a gene. List of affected drugs is not comprehensive. Consequences of pharmacogenetics on medication should be discussed with consulting physician.




Swen JJ, et al. **A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study.** Lancet. 2023 Feb 4;401(10374):347-356. doi: 10.1016/S0140-6736(22)01841-4. Erratum in: Lancet. 2023 Aug 26;402(10403):692. doi: 10.1016/S0140-6736(23)01742-7. PMID: 36739136.




Number of PGx genes with atypical drug response as determined by CPIC. Distribution of pharmacogenes with a predicted non-typical response across the entire 1KGP dataset.

Sherman CA, Claw KG, Lee SB. **Pharmacogenetic analysis of structural variation in the 1000 genomes project using whole genome sequences.** Sci Rep. 2024 Oct 1;14(1):22774. doi: 10.1038/s41598-024-73748-3. PMID: 39354004; PMCID: PMC11445439.

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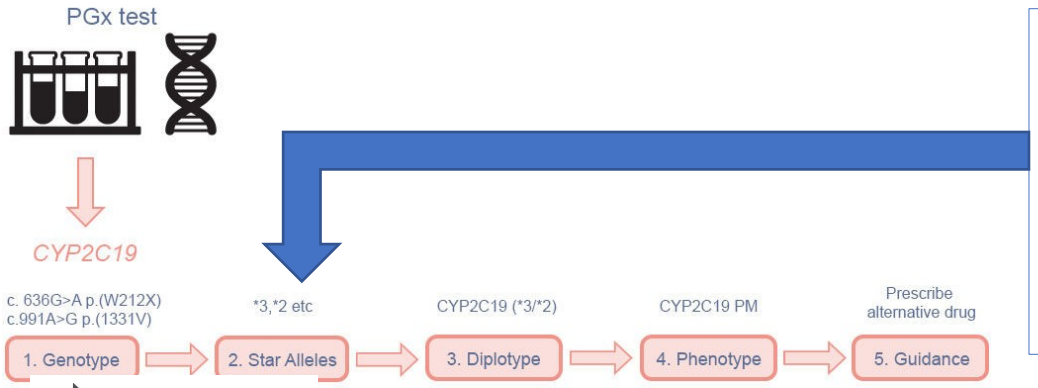
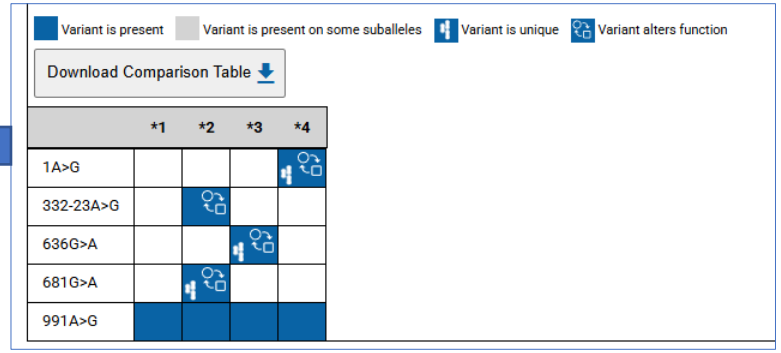
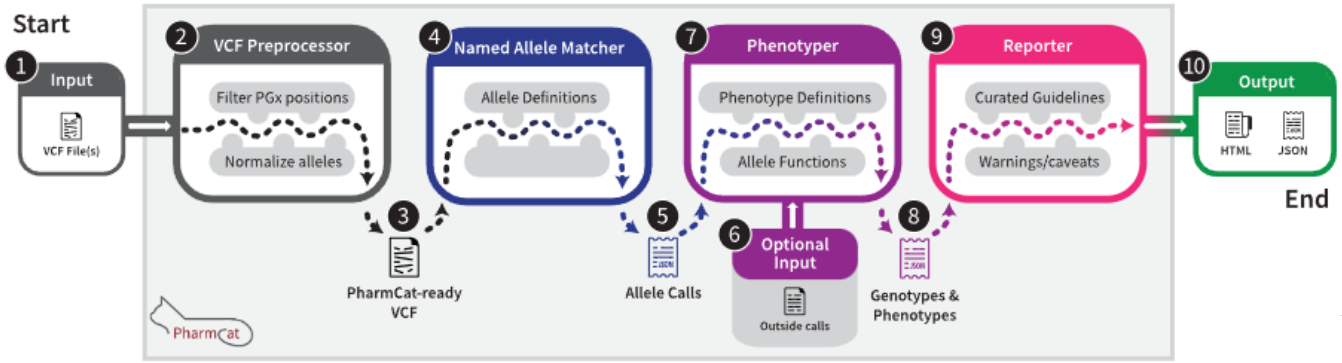



How PharmCat Works




clopidogrel

| Source | Genes | Implications | Recommendation | Classification |
|---|---|---|---|---|
| CPIC Guideline Annotation<br>Population:<br>CVI ACS PCI<br>Alternate Drug | Genotype<br>CYP2C19:*1/*2<br>Phenotype<br>Intermediate Metabolizer | CYP2C19: Reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events | Avoid standard dose (75 mg) clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication.<br>Other Considerations<br>For cardiovascular indications of acute coronary syndrome (ACS) and/or percutaneous coronary intervention (PCI). ACS and/or PCI includes patients undergoing PCI for an ACS or non-ACS (elective) indication. | Strong |

**Ex autres programmes :**

sbslee/**pypgx**

A Python package for pharmacogenomics (PGx) research

ALDY

# GT « analyses PGx à partir de WES WGS »

Contexte de réalisation | Analyse bio-informatique | Mise à disposition des résultats

## Cahier des charges

| | | Aldy | Stargazer | PharmCAT | StellarPGx | PyPGx | Cyrius | Astrolabe Constellation | PharmVIP | Pano | Optitype / hlaty | xHLA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | https://github.com/0xTCG/aldy | https://stargazer.gs.washington.edu/stargazerweb/ | https://github.com/PharmGKB/PharmCAT?tab=readme-ov-file | https://github.com/SBIMB/StellarPGx | https://github.com/sbslee/pypgx | https://github.com/Illumina/Cyrius | https://github.com/twesigomwedavid/cyp2d6-gt-algorithms/blob/master/README.md | | | https://github.com/FRED-2/OptiType https://github.com/nf-core/hlatyping/tree/master | https://github.com/humanlongevity/HLA |
| **Type d'analyse** | Targeted | | | | | Pris en charge | | Pris en charge | | | | |
| | WES | | | | | Pris en charge | | Pris en charge | | | | |
| | WGS | | | | | Pris en charge | | Pris en charge | | | | |
| | Short read | | | | | Pris en charge | | Pris en charge | | | | |
| | Long Read | | | | | Pris en charge | | Pris en charge | | | | |
| **Contenu de l'analyse** | Version(s) du génome | | | | | GRCh37 et GRCh38 | | GRCh37 et GRCh38 | | | | |
| | Listing gènes | | | | | ABCB1,ABCG2,ACYP2,ADRA2A,A | | CYP2D6 | | | | |
| | Core Panel RNPGx | | | | | | | | | | | |
| | AMP Tier1 PharmGKB | | | | | | | | | | | |
| | Variants rares (à définir) | | | | | | | | | | | |
| | SV CYP2D6 | | | | | Prédit | | | | | | |
| | SV CYP2B6 | | | | | | | | | | | |
| | UGT1A1 *28 | | | | | | | | | | | |
| | TYMS | | | | | Non pris en charge | | | | | | |
| | Locus HLA | | | | | | | | | | | |
| | possibilité de corriger un génotype manuellement | | | | | | | | | | | |
| | possibilité de corriger un phénotype manuellement (en cas de variant délétère sans * allèle assigné) | | | | | | | | | | | |
| **Flexibilité du contenu de l'analyse ?** | | | | | | | | | | | | |
| **Caractéristiques input** | Format(s) | | | | | .bam ou .vcf | | .bam .vcf | | | | |
| | Témoins nécessaires ? | | | | | | | | | | | |
| **Caractéristiques output** | Star alleles | | | | | oui | | oui | | | | |
| | recommandations PGx | | | | | | | non | | | | |
| Autres | actualisation des recos | | | | | | | | | | | |
| | maintenance | | | | | | | | | | | |
| | ergonomie | | | | | | | | | | | |
| | Mito ? | | | | | | | | | | | |

# GT « analyses PGx à partir de WES WGS »

Contexte de réalisation

Analyse bio-informatique

Mise à disposition des résultats

## Cahier des charges

## Bibliographie / Essais

### PyPGx (SV)

Article | Open access | Published: 01 October 2024

**Pharmacogenetic analysis of structural variation in the 1000 genomes project using whole genome sequences**

Carissa A. Sherman, Katrina G. Claw & Seung-been Lee

*Scientific Reports* **14**, Article number: 22774 (2024) | Cite this article

### Aldy sur WES WGS

Front Oncol. 2023 Jul 4;13:1199741. doi: 10.3389/fonc.2023.1199741

**Computational pharmacogenotype extraction from clinical next-generation sequencing**

Tyler Shugg [1,†], Reynold C Ly [2,†], Wilberforce Osei [1], Elizabeth J Rowe [1], Caitlin A Granfield [2], Ty C Lynnes [2], Elizabeth B Medeiros [2], Jennelle C Hodge [2], Amy M Breman [2], Bryan P Schneider [3], S Cenk Sahinalp [4], Ibrahi Numanagić [5], Benjamin A Salisbury [6], Steven M Bray [6], Ryan Ratcliff [6], Todd C Skaar [1,*]

Author information | Article notes | Copyright and License information

PMCID: PMC10352904 PMID: 37469403

### Stargazer / Stellar / Aldy / Cyrius

CTS Clinical and Translational Science

ARTICLE | Open Access

**Benchmarking pharmacogenomics genotyping tools: Performance analysis on short-read sequencing samples and depth-dependent evaluation**

Andreas Halman, Sebastian Lunke, Simon Sadedin, Claire Moore, Rachel Conyers

First published: 09 August 2024 | https://doi.org/10.1111/cts.13911 | Citations: 1

Access Univ. Bordeaux

### Stargazer / Aldy / Astrolabe (gène CYP2D6)

Article | Open access | Published: 03 August 2020

**A systematic comparison of pharmacogene star allele calling bioinformatics algorithms: a focus on *CYP2D6* genotyping**

David Twesigomwe, Galen E. B. Wright, Britt I. Drögemöller, Jorge da Rocha, Zané Lombard & Scott Hazelhurst

*npj Genomic Medicine* **5**, Article number: 30 (2020) | Cite this article

ENA European Nucleotide Archive

| **GeT-RM Characterization Study References** (see "Study refs" tab) | **Coriell ID #** https://www.coriell.org/ | **URL to access BAM and FASTQ files from the European Nucleotide Archive (ENA) (unhide columns D-G for more info)** | ***CYP1A1*** | ***CYP1A1*** References | ***CYP1A2*** | ***CYP1A2*** References | ***CYP2A6*** | ***CYP2A6*** References | ***CYP2B6*** |
|---|---|---|---|---|---|---|---|---|---|
| 2,3,4 | HG01190 | http://www.ebi.ac.uk/ena/( | *1/*1 | 2 | *1A/*1A | 2 | *1/*1 | 2 | *1(*5)/*1(*27) |
| 2,3,4,9 | NA06991 | http://www.ebi.ac.uk/ena/( | *1/*1 | 2 | *1F/*1F | 2 | *1/*1 | 2 | *1/*6 |
| 2,4,7 | NA06993 | | | | | | | | *1/*1 |
| 2,3,4,6 | NA07000 | http://www.ebi.ac.uk/ena/( | | | | | | | *1/*1 |
| 2,3,4 | NA07019 | http://www.ebi.ac.uk/ena/( | *1/*4 | 2 | *1A/*1F | 2 | *1/*1 | 2 | *1(*5) or *1(*22) |
| 2,3,4 | NA07029 | http://www.ebi.ac.uk/ena/( | *1/*1 | 2 | *1A/*1F | 2 | *1/*1 | 2 | *6/(*27) |
| 2,3,4 | NA07048 | | | | | | | | *1/*1 |
| 2,3,4 | NA07055 | http://www.ebi.ac.uk/ena/( | *1/*5 | 2 | *1F/*1F | 2 | *1/*1 | 2 | *6/(*27) |
| 2,3,4,7 | NA07056 | http://www.ebi.ac.uk/ena/( | *1/*1 | 2 | *1A/*1A | 2 | *1/*1 | 2 | *6/(*22) |
| 2,3,4 | NA07348 | http://www.ebi.ac.uk/ena/( | *1/*1 | 2 | *1F/*1F | 2 | *1/*1 | 2 | *1/*1 |
| 2,3,4 | NA07357 | http://www.ebi.ac.uk/ena/( | *1/*1 | 2 | *1F/*1F | 2 | *1/*1 | 2 | *1/*1 |
| 1,2,3,4,7,8 | NA07439 | | *1/*1 | 2 | *1F/*1L | 2 | *1/*1 | 2 | *1/*6 |
| 2,3,4 | NA10831 | http://www.ebi.ac.uk/ena/( | *1/*1 | 2 | *1A/*1F | 2 | *1/*2 | 2 | *1/*1 |

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Cahier des charges

Bibliographie / Essais

## Pharmacogenetics (PGx) Working Group 12

**Topics :**

-scope of WG12 and definitions of terms

-choice of priority diseases and indications

-single markers versus profiling vs polygenic drug respon

-technology platforms for testing

-data needs and user perspective on GDI

- creating standardized ways of collecting/storing/report phased single nucleotide and structural variants

-exploring relevance of genetic diversity in PGx testing

-design a “Pan-European” PGx array

-combine PGx with other genetic information (e.g., ethnicity, blood groups/HLA, FH, PRS, etc.)

-translating genetic test results into actionable prescription advice

-setting up trials for evidence

-costs and reimbursement programs for PGx testing

-implementation hurdles across various health care systems

-setting up PGx education/courses for healthcare officials and general public

-exploring collaboration with international efforts and societies

- stimulate development of systems to share PGx information across the entire healthcare chain

## PGx implementation

Recommandations d’analyse bio-informatique en PGx

Recommandations cibles PGx de référence (Pr PICARD)

Expertise PGx pertinente par maladie rare / cancer (PFMG / DNN)

Mise à disposition de l’information PGx

# Merci de votre attention

RNPGx

RÉSEAU FRANCOPHONE DE PHARMACOGÉNÉTIQUE

BioInfoDiag