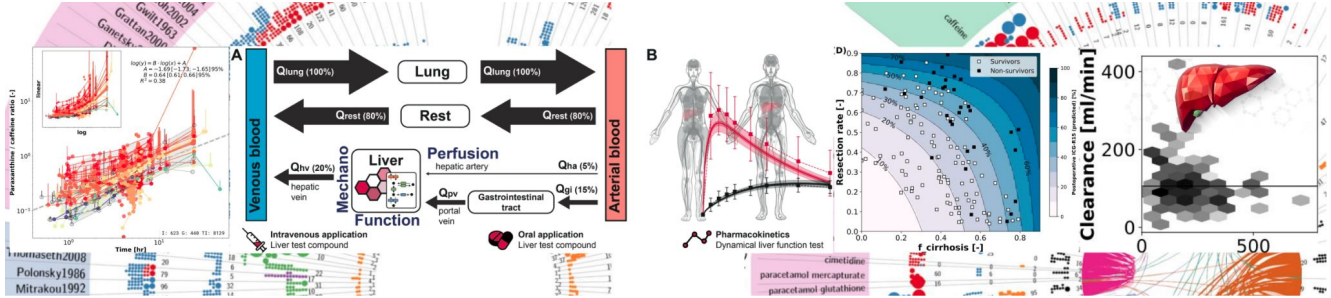


# Pharmacokinetics Modeling Course

## Interindividual Variability

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https://livermetabolism.com

# 🎯 Teaching Goals

By the end of this section, you should be able to:

1. Understand the concept of **interindividual variability** and its relevance in pharmacokinetics.
2. Identify key **factors influencing variability** in drug absorption, distribution, metabolism, and excretion (ADME).
3. Explain the role of **genetics, age, sex, body weight, and organ function** in pharmacokinetic variability.
4. Recognize the impact of **drug-drug interactions** and **lifestyle factors** (e.g. diet, smoking, alcohol) on pharmacokinetics.
5. Interpret pharmacokinetic data from **subpopulations** (e.g., pediatric, elderly, renally impaired).
6. Appreciate the importance of accounting for variability in **dose optimization** and **personalized medicine**.

# Large Interindividual Variability

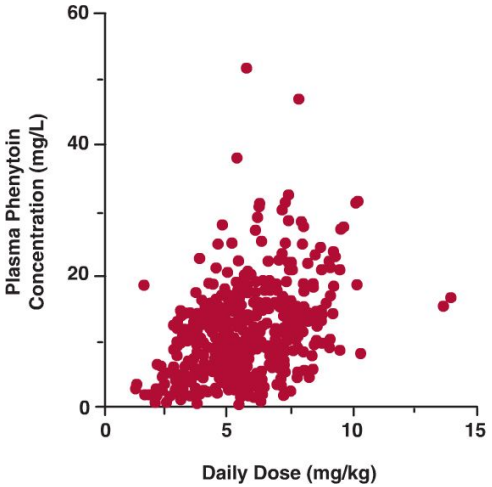



**FIGURE 1-7.** Although the average plasma concentration of phenytoin on chronic dosing tends to increase with the dosing rate, there is large variation in the individual values. (From: Lund, L. Effects of phenytoin in patients with epilepsy in relation to its concentration in plasma. In Davies DS, Prichard BNC, eds. Biological Effects of Drugs in Relation to Their Plasma Concentration. London and Basingstoke: Macmillan, 1973:227–238.)

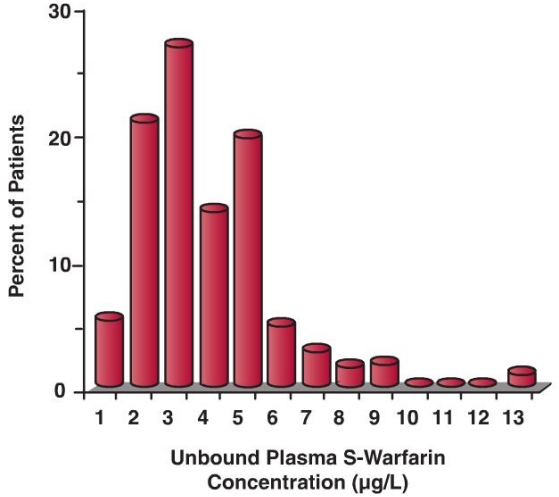
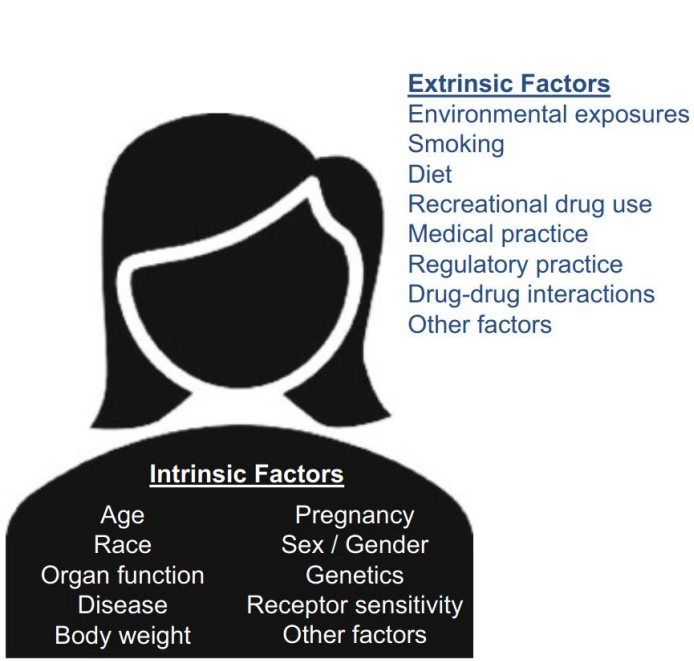



**FIGURE 1-8.** There is considerable interindividual pharmacodynamic variability in response to the oral anticoagulant warfarin as demonstrated by the substantial spread in the unbound concentration of the active S-isomer associated with a similar degree of anticoagulation in a group of 97 patients on maintenance therapy. (From: Scordo MG, Pengo V, Spina E, et al. Influence of CYP2C9 and CYP2C19 genetic polymorphisms of warfarin maintenance dose and metabolic clearance. Clin Pharmacol Ther 2002;72:702–710.)

Tozer TN, Rowland M. **Essentials of pharmacokinetics and pharmacodynamics.** Third edition

# Factors affecting variability



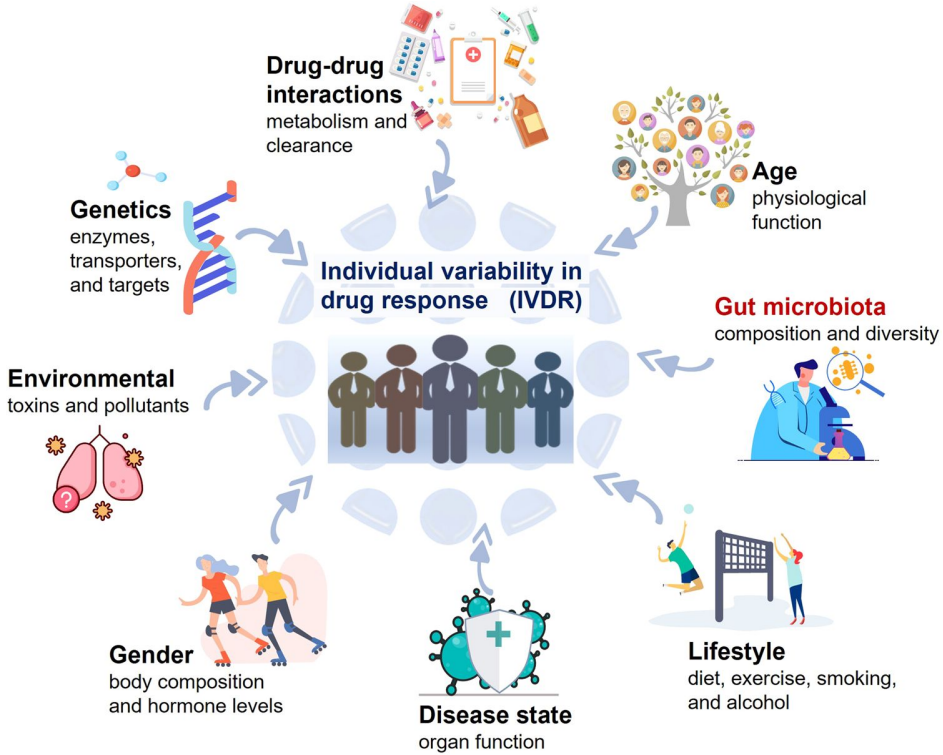
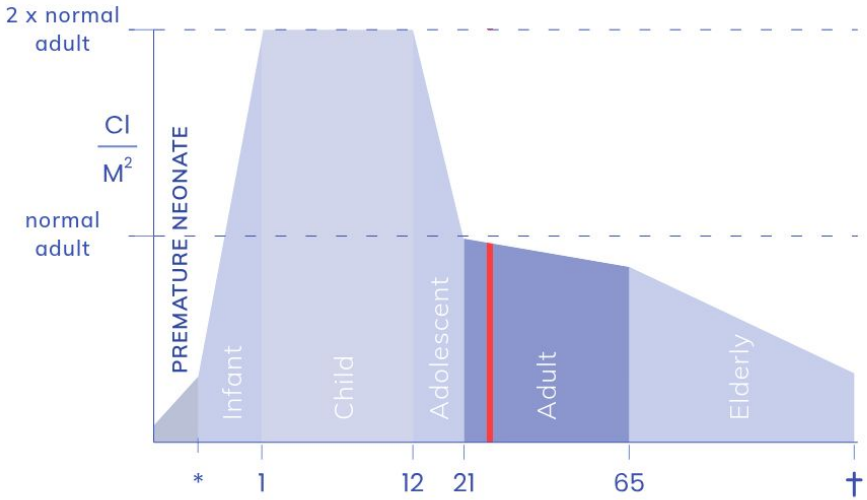



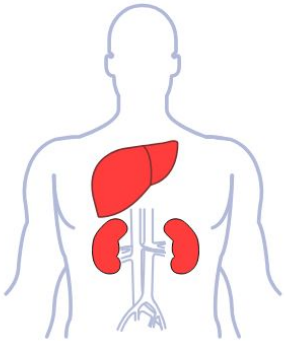

**Fig. 2** Intrinsic and extrinsic factors affecting drug disposition

Zhao, Q., Chen, Y., Huang, W. *et al.* Drug-microbiota interactions: an emerging priority for precision medicine. *Sig Transduct Target Ther* **8**, 386 (2023). https://doi.org/10.1038/s41392-023-01619-w

# 🏃 Dosing in Age 🏃

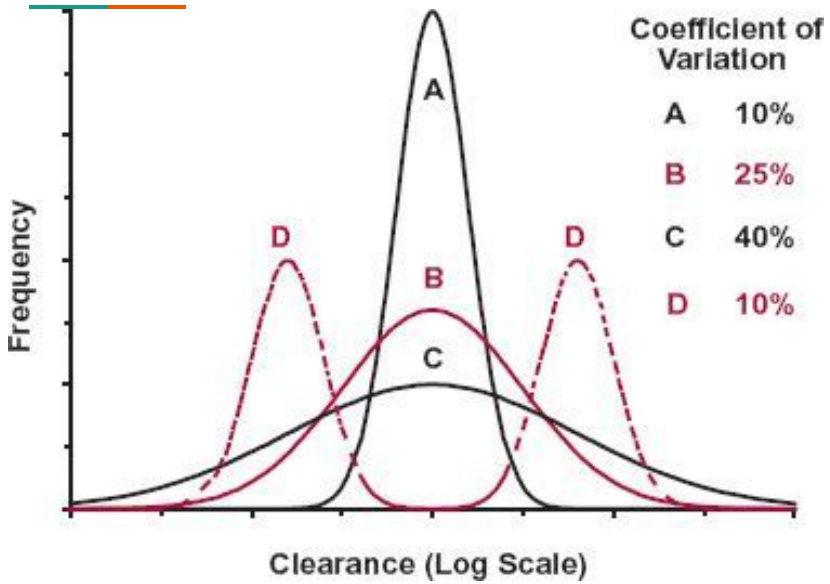
https://www.icp.org.nz/dosing-and-age/dosing-and-age



Age

# Quantifying Variability: Coefficient of Variation (CV)



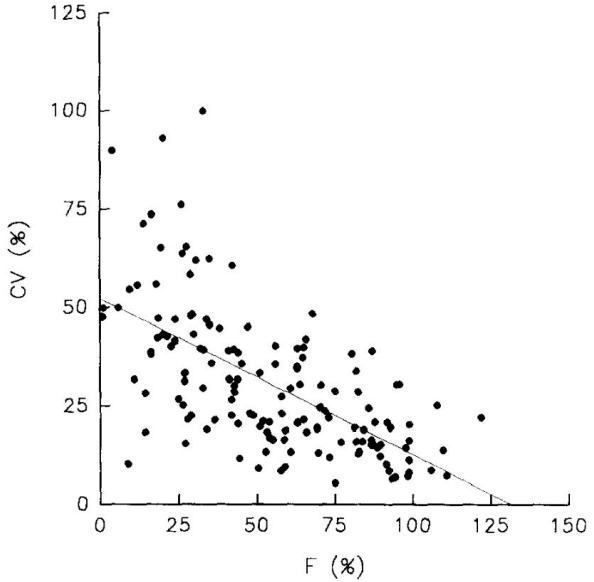




**Fig. 1.** Relationship between absolute bioavailability *(F)* and intersubject variability (CV) in absolute bioavailability for all studies evaluated ($n$ = 149). Data were obtained from a total of 143 references reporting absolute oral bioavailability data in *Clinical Pharmacology & Therapeutics* between 1970 and 1994. The total number of drugs studied was 100, the majority of which were cardiovascular system agents (38), central nervous system agents (25), and antiinfective agents (9).

Hellriegel ET, Bjornsson TD, Hauck WW. **Interpatient variability in bioavailability is related to the extent of absorption: implications for bioavailability and bioequivalence studies.** Clin Pharmacol Ther. 1996 Dec;60(6):601-7. doi: 10.1016/S0009-9236(96)90208-8. PMID: 8988062.

# Dose & Time Dependency

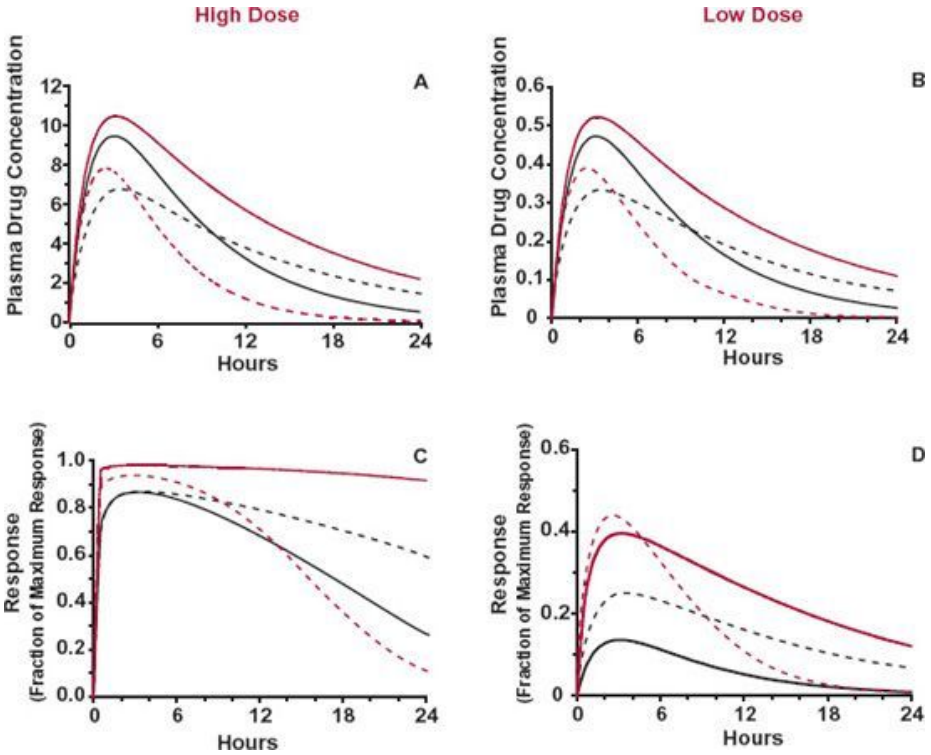



**FIGURE 12-5.** The interindividual variability in concentration and response varies with dose and time of observation. Shown are plasma concentrations (**A** and **B**) and responses (**C** and **D**) following large (*left*) and small (*right*) doses of a drug that displays **little interpatient variability in $C_{max}$, $t_{max}$, and maximum response, $E_{max}$. but large interpatient variability in half-life and concentration needed to produce 50% maximum response.** High dose (*top*): at $t_{max}$, the maximum response in all patients is produced with little variability in either $C_{max}$ or response. Greater variability in concentration and response is seen at later times. Low dose (*bottom*): at $t_{max}$, variability in $C_{max}$ is still low, but that in response is now considerable. Each line corresponds to a different patient.

# Variability in enzymes

**Table 1**
**Interindividual differences in hepatic CYP isoform activity[a]**

| | mRNA expression fold-difference[b] | Protein content fold-difference[c] | Intrinsic clearance fold-difference[d] | Substrate |
|---|---|---|---|---|
| CYP1A2 | 56 | 27 | 25 | Phenacetin |
| CYP2A6 | 146 | 38 | 53 | Coumarin |
| CYP2B6 | 95 | 27 | 170 | Bupropion |
| CYP2C8 | 20 | 11 | 40 | Paclitaxel |
| CYP2C9 | 8 | 12 | 47 | Tolbutamide |
| CYP2C19 | 88 | 24 | 28 | Omeprazole |
| CYP2D6 | 66 | 36 | 190 | Dextromethorphan |
| CYP2E1 | 43 | 15 | 22 | Chlorzoxazone |
| CYP3A4 | 126 | 129 | 645 | Midazolam |
| CYP3A5 | 20 | 100 | 458 | Midazolam |

[a]Adapted from data collected in 100 donors by Zhang et al. [2]. mRNA expression and protein determined in 100 samples, except for CYP2B6 ($n = 91$) and CYP2C19 ($n = 54$). Intrinsic clearance determined in 90 samples, except for CYP2B6 ($n = 82$), CYP2C9 ($n = 92$) and CYP2C19 ($n = 48$)
[b]Determined using quantitative reverse transcription polymerase chain reaction (qRT-PCR)
[c]Determined using liquid chromatography–mass spectrometry with stable isotope-labeled peptides
[d]Intrinsic clearance quantified in microsomal preparations normalized to corresponding P450 isoform protein content (μL/min/pmol P450)

# Variability in enzymes

- differences in individual protein amounts
- often dynamic (induction/repression)

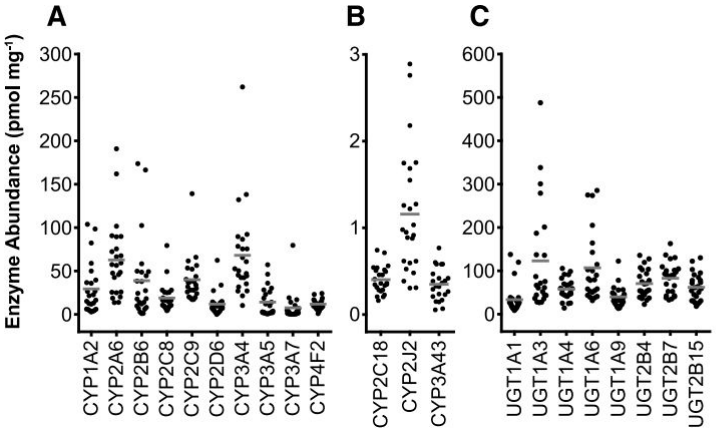



**Fig. 2.** A scatter plot of the measured abundance values of P450 (A and B) and UGT (C) enzymes. The number of samples is 24 for each enzyme except CYP2C9, CYP3A5, CYP3A7, CYP3A43, UGT1A3, UGT1A4, and UGT1A6 ($n$ = 23). Lines indicate population means of the sets of data.

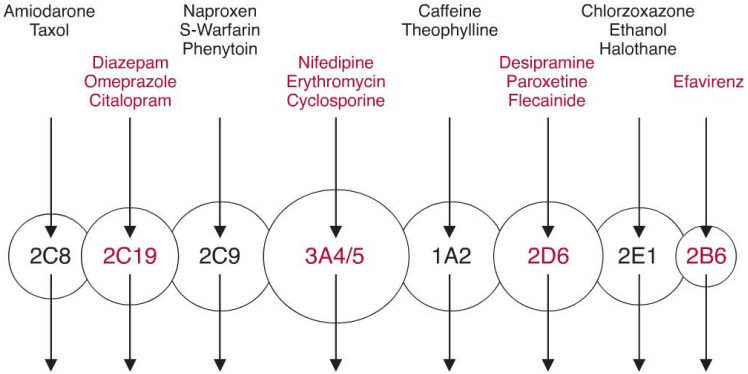


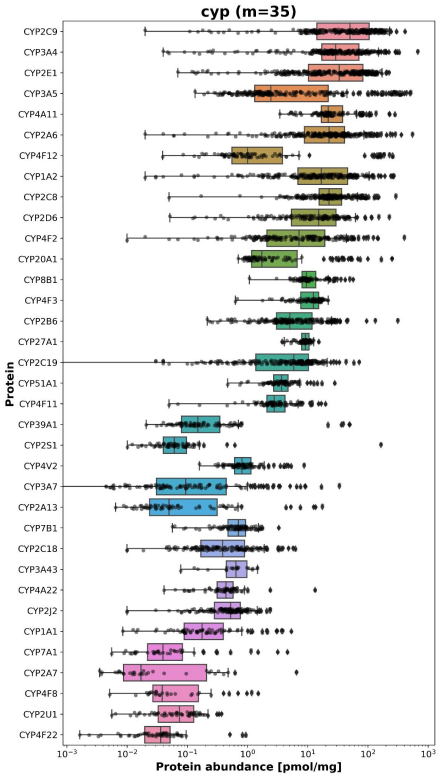

**FIGURE 5-3.** Graphic representation of the different forms of human cytochrome-P450 enzyme (*circles*) with different but often overlapping substrate specificities. The arrows indicate the single metabolic pathways. Representative substrates are listed above each enzyme.


Tozer TN, Rowland M. **Essentials of pharmacokinetics and pharmacodynamics.** Third edition.

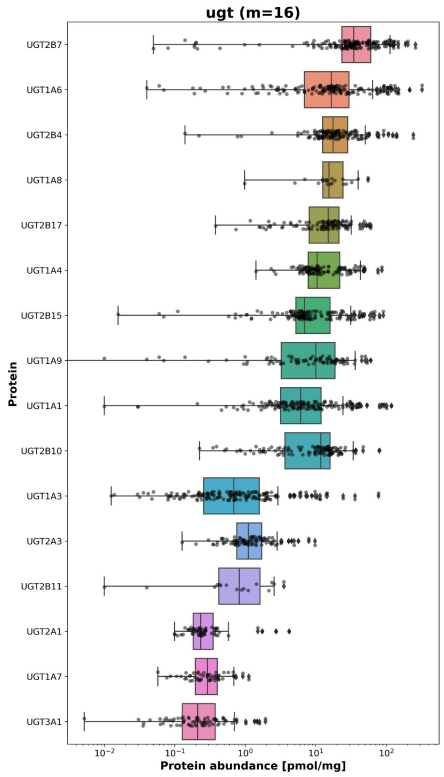
Achour B, Barber J, Rostami-Hodjegan A. **Expression of hepatic drug-metabolizing cytochrome p450 enzymes and their intercorrelations: a meta-analysis.** Drug Metab Dispos. 2014 Aug;42(8):1349-56. doi: 10.1124/dmd.114.058834. Epub 2014 May 30. PMID: 24879845.

# Large variability & multitude of isoforms (Human Liver)

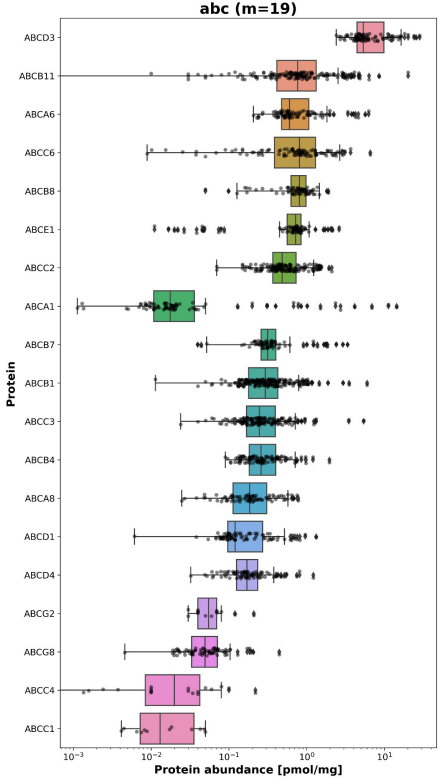
## Cytochrome P450 (CYP)



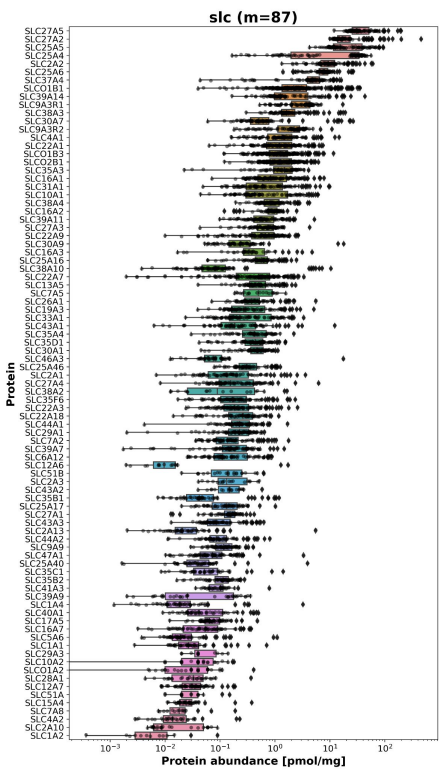

## UDP-glucuronosyltransferases (UGT)




## ATP-binding cassette (ABC)




## Solute Carrier (SLC)




Afruja Hossain, Sophie Silberhorn, Matthias König. **Protein distributions of drug metabolizing and transporting enzymes in the Human Liver.** In preparation.

# Pharmacogenomics

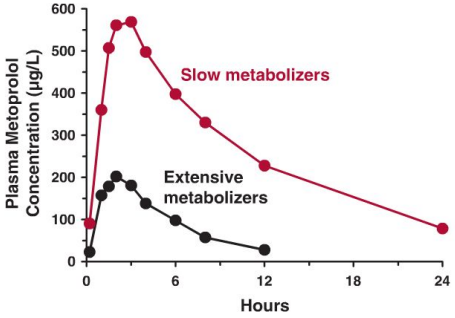



**FIGURE 13-3.** Plasma metoprolol concentrations after a single oral dose of 200-mg metoprolol tartrate were much higher in poor (*colored line*) than in extensive (*black line*) CYP2D6 metabolizers. Because metoprolol is a drug of high hepatic clearance, the difference between poor and extensive metabolizers is expressed in the large difference in oral bioavailability, because of differences in first-pass hepatic loss. (From: Lennard MS, Silas JH, Freestone S, et al. Oxidative phenotype—a major determinant of metoprolol metabolism and response. Reprinted by permission of New Eng J Med 1982;307:1558–1560.)

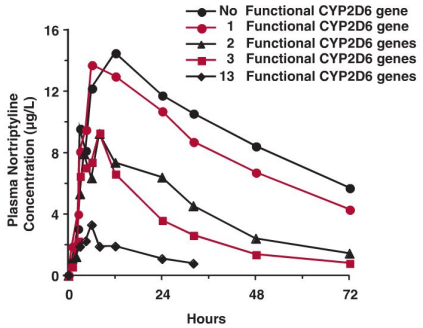



**FIGURE 13-2.** Strong genetic influence in the pharmacokinetics of nortriptyline is clearly demonstrated by the high correlation between the plasma concentration–time profile and the number of functional CYP2D6 genes possessed by an individual; the larger the number of functional genes, the higher is the clearance and the lower is the exposure profile following a single 25-mg dose of nortriptyline. (From: Dalén P, Dahl ML, Bernal Ruiz ML, et al. 10-Hydroxylation of nortriptyline in white persons with 0, 1, 2, 3, and 13 functional CYP2D6 genes. Clin Pharmacol Ther 1998;63:444–452.)

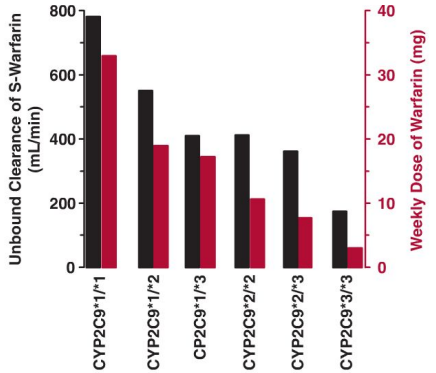



**FIGURE 13-4.** Genetics plays a significant role in the maintenance dose requirement of warfarin used in the treatment of various cardiovascular diseases. Shown are the unbound clearance of S-warfarin (*black*) in groups of patients with different CYP2C9 genotypes, all titrated and stabilized to a narrow target INR (International Normalization Ratio) range, a measure of anticoagulation, of between 2 and 3, and the mean weekly maintenance dose (obtained by summing the daily dose over 1 week, *in color*). Warfarin is administered as the racemate, with most of the therapeutic effect associated with the more active S-isomer, which is primarily eliminated by CYP2C9-catalyzed metabolism. Homozygous patients with two wild-type alleles (denoted by CYP2C9*1/*1) have the highest S-warfarin clearance and require the highest maintenance dose, and those with two of the most deficient alleles (CYP2C9*3/*3) have the lowest clearance and need the smallest maintenance dose. Heterozygous patients have intermediate clearance. However, as noted in Fig. 12-4 (Chapter 12, *Variability*), in addition to pharmacokinetic variability, there is also considerable interindividual variability in pharmacodynamics of this compound. (From: Scordo MG, Pengo V, Spina E, et al. Influence of CYP2C9 and CYP2C19 genetic polymorphisms of warfarin maintenance dose and metabolic clearance. Clin Pharmacol Ther 2002;72:702–710.)

# Pharmacogenomics: Examples

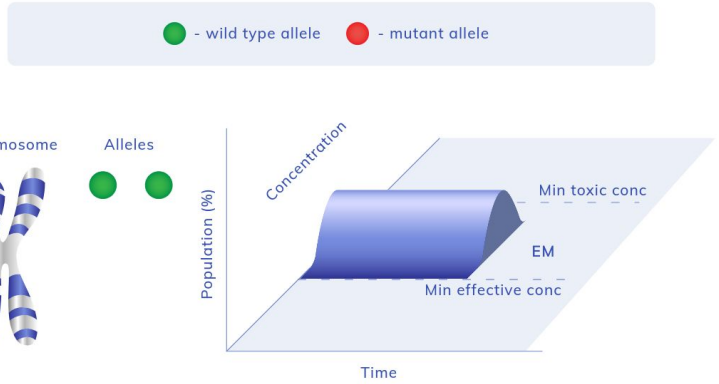
**TABLE 13-1 | Frequency of Genetic Polymorphisms Producing Slow Metabolism in Some Drug-Metabolizing Enzymes and Representative Substrates**

| Enzyme | Frequency of Poor Metabolizer | Drug Substrates[a] |
|---|---|---|
| **Phase I Reactions** | | |
| CYP2D6 | 5%–10% Caucasians | Bufurolol, codeine, dextromethorphan, encainide, flecainide, metoprolol, nortriptyline, timolol |
| | 3.8% Blacks | |
| | 0.9% Asians | |
| | 1% Arabs | |
| CYP2C9 | 1%–3% Caucasians | Celecoxib, fluvastatin, glyburide, *S*-ibruprofen, tolbutamide, phenytoin, *S*-warfarin. |
| CYP2C19 | 3%–5% Caucasians | Diazepam, lansoprazole, omeprazole, pantoprazole. |
| | 16% Asians | |
| Butylcholinesterase | Several abnormal genes; most common disorder 1 in 2500 | Succinylcholine |
| **Phase II Reactions** | | |
| Thiopurine *S*-methyltransferase | 0.3% Caucasians | Azathioprine, mercaptopurine. |
| | 0.04% Asians | |
| *N*-acetyltransferase (NAT2) | 60% Caucasians, African Americans | Amrinone, hydralazine, isoniazid, phenelzine, aminosalicylic acid. |
| | 10%–20% Asians | |
| Uridine diphosphate glucuronosyltranferase | | |
| 1A1 | 11% Caucasians | Irinotecan |
| | 1%–3% Asians | |
| 2B7 | 29% Caucasians | Flurbiprofen |
| | 7% Asians | |

Generally results in enhanced or prolonged effect following standard dose of drug.
[a]A major pathway for the elimination of compound.

# 🏃 Pharmacogenomics 🏃

https://www.icp.org.nz/pharmacogenetics/pharmacogenetics

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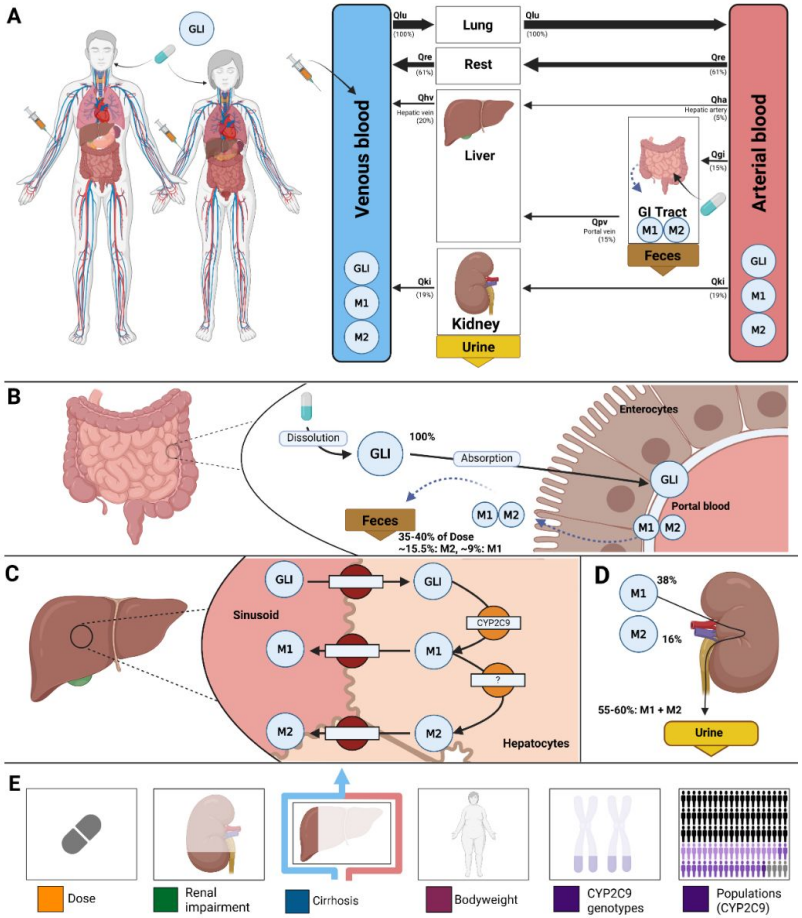
Genetic status:

- Extensive metabolism (EM)
- Intermediate metabolism (IM)
- Poor metabolism (PM)
- Ultrarapid metabolism (UM)

# Glimipiride



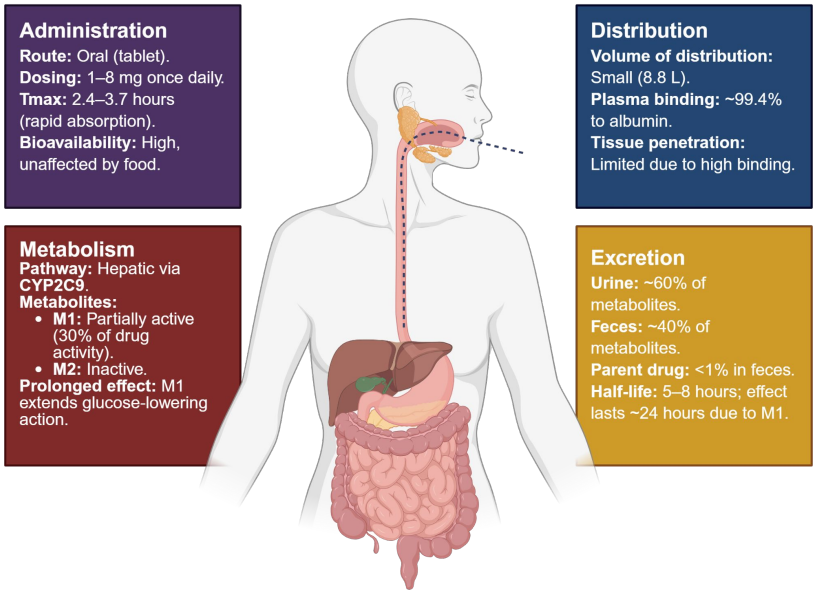




**Fig. 1 Whole-body PBPK model of glimepiride and key factors influencing its disposition. A)** Whole-body model illustrating glimepiride (GLI) administration (oral and intravenous), its systemic circulation via venous and arterial blood, and the key organs (liver, kidney, GI tract) involved in GLI metabolism, distribution, and excretion. **B)** Intestinal model showing dissolution and absorption of GLI by enterocytes. No enterohepatic circulation of M1 and M2 is assumed, but reverse transport via enterocytes is included. **C)** Hepatic model depicting CYP2C9-mediated metabolism of GLI to M1 and M2. **D)** Renal model highlighting the elimination of M1 and M2 via urine; unchanged GLI is not excreted renally. **E)** Key factors influencing glimepiride disposition accounted for by the model: liver function (cirrhosis), renal impairment, CYP2C9 genotypes, bodyweight, and administered dose.

# Glimepiride - CYP2C9 Genetic Variants

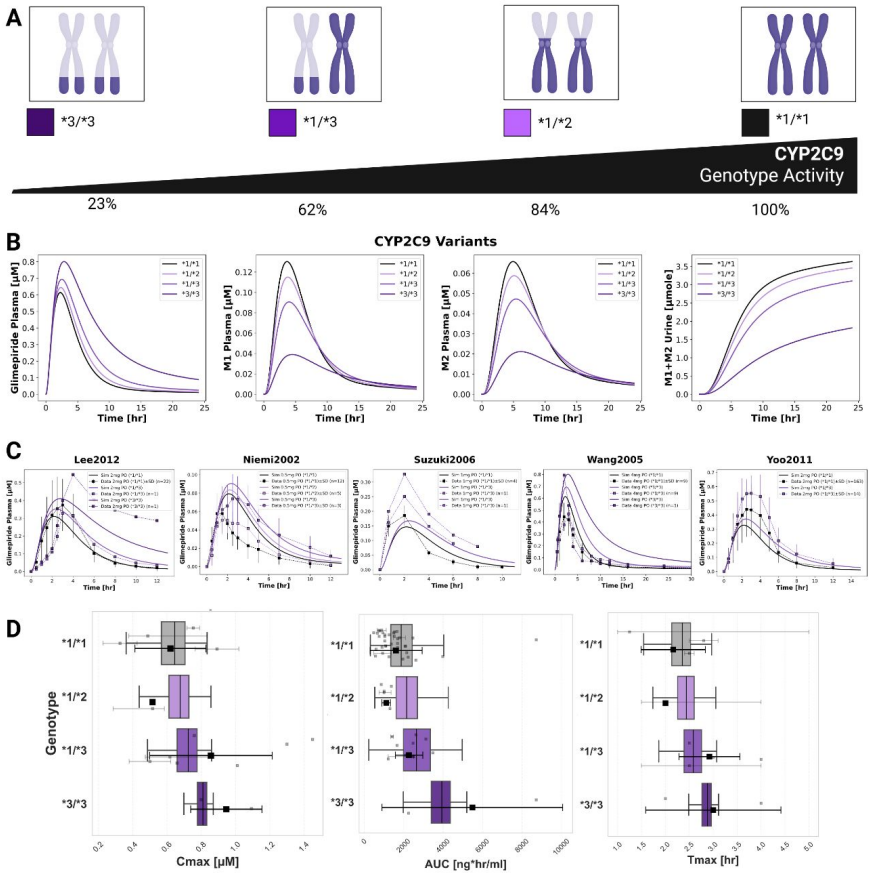



**Fig. 6 Impact of CYP2C9 genetic variants on glimepiride pharmacokinetics. A)** Illustration of key CYP2C9 genotypes (*1/*1, *1/*2, *1/*3, *3/*3) and their corresponding enzymatic activities. **B)** Simulated pharmacokinetic profiles of glimepiride, M1, M2, and cumulative M1+M2 urinary excretion, following a 4 mg oral dose, based on fixed enzyme activity values for different CYP2C9 genotypes. **C)** Comparison of simulated (solid lines, using fixed CYP2C9 activity values) versus observed (symbols) glimepiride plasma concentrations in individuals with different CYP2C9 genotypes across five clinical studies (Lee et al. [22], Niemi et al. [27], Suzuki et al. [30], Wang et al. [31], and Yoo et al. [8]). **D)** Boxplots comparing simulated glimepiride pharmacokinetic parameters derived from the probabilistic sampling approach (colored boxes) with observed clinical data (grey squares: individual data points; black squares: weighted arithmetic mean) across different CYP2C9 genotypes. Simulations for this panel correspond to a 4 mg oral dose. Observed data was aggregated from the clinical studies cited in panel C and dose-scaled to 4 mg where necessary.

# Glimepiride - Populations

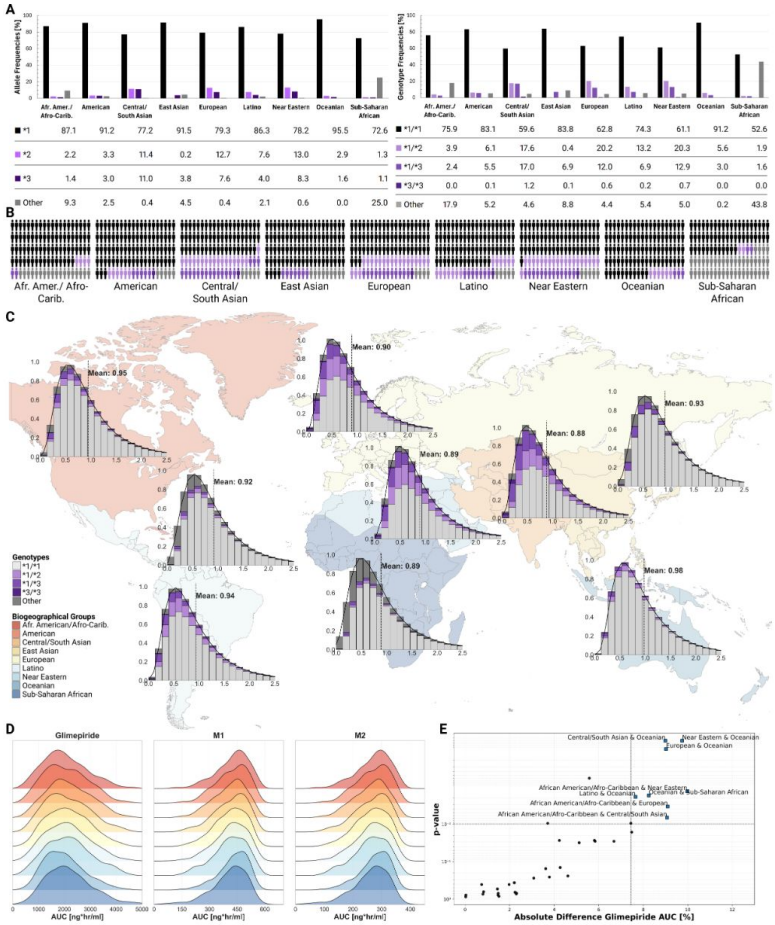
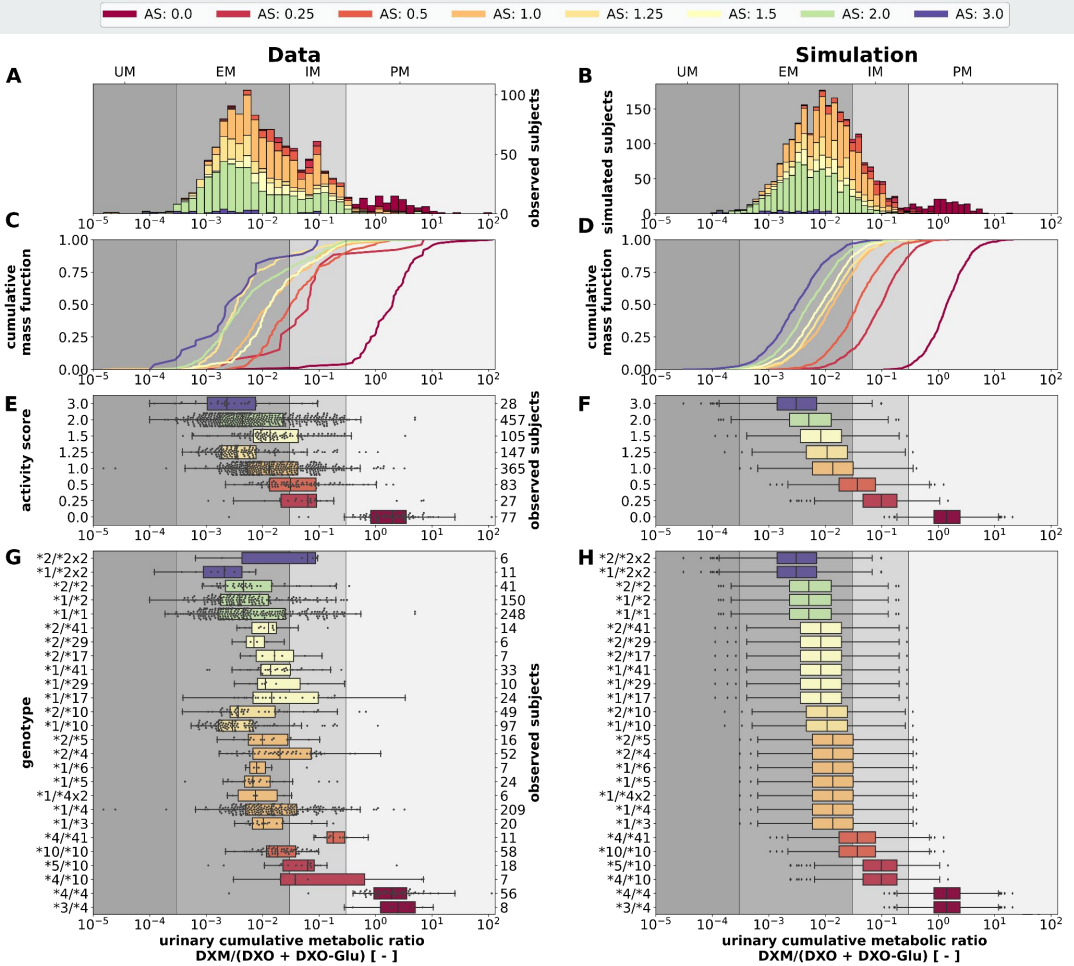



**Fig. 7 Global CYP2C9 genetic variability and population-level impact on glimepiride pharmacokinetics. A)** CYP2C9 allele and genotype frequencies across biogeographical groups [34], showing the distribution of key alleles and genotypes. **B)** Individual genetic variability representation within each biogeographical population. **C)** World map displaying population-specific CYP2C9 activity distributions derived from allele frequencies, with kernel density estimation (KDE) curves and mean enzymatic activity values shown for each biogeographical group. **D)** Ridgeline plots comparing glimepiride, M1, and M2 AUC distributions across biogeographical populations. **E)** Statistical comparison of population pairs showing the relationship between significance (p-value) and magnitude of pharmacokinetic differences, with some comparisons showing statistically significant but clinically modest differences in glimepiride AUC.

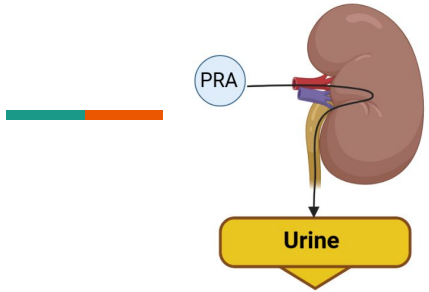
# Metabolic phenotyping

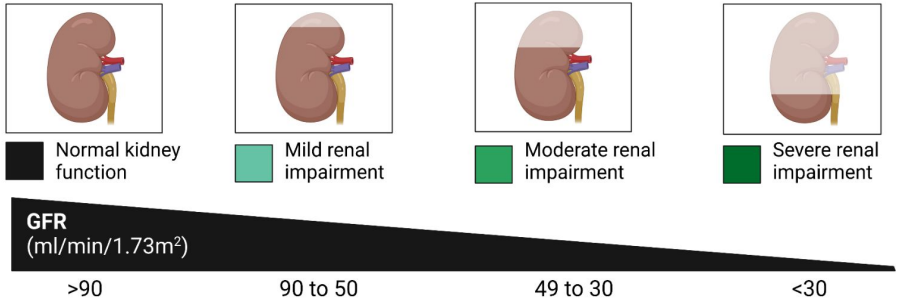
- Model predicts effect of CYP2D6 activity and genetic polymorphisms
- Urinary cumulative metabolic ratio (UCMR) for metabolic phenotyping

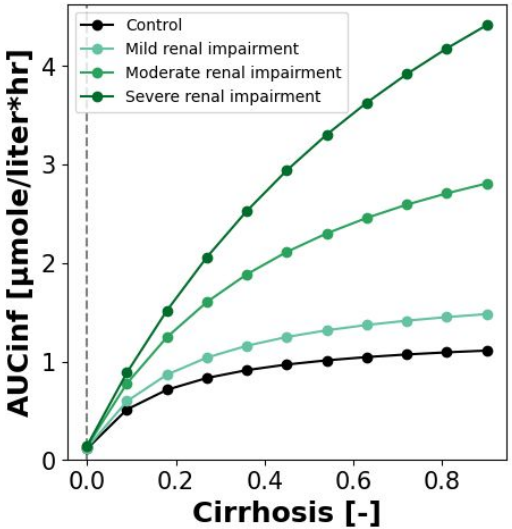
J.Grzegorzewski, J.Brandhorst, **M.König** ***Physiologically based pharmacokinetic (PBPK) modeling of the role of CYP2D6 polymorphism for metabolic phenotyping with dextromethorphan***
https://doi.org/10.1101/2022.08.23.504981
In print, Frontiers in Pharmacology

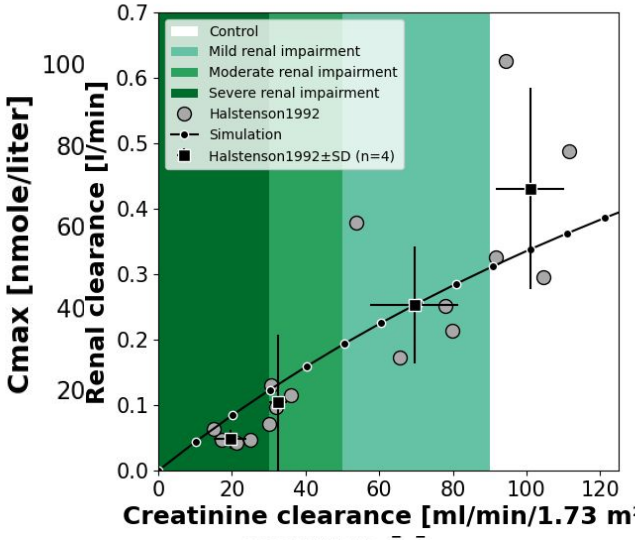


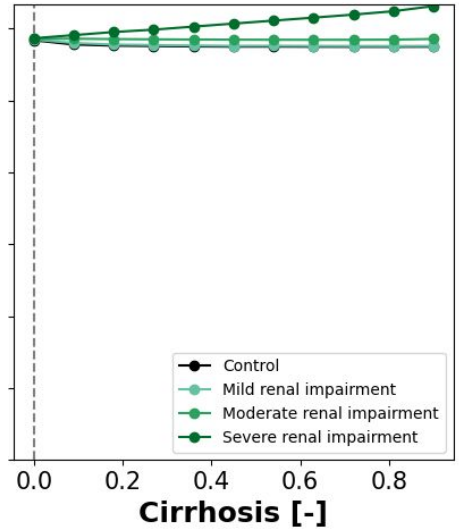
# Renal Impairment



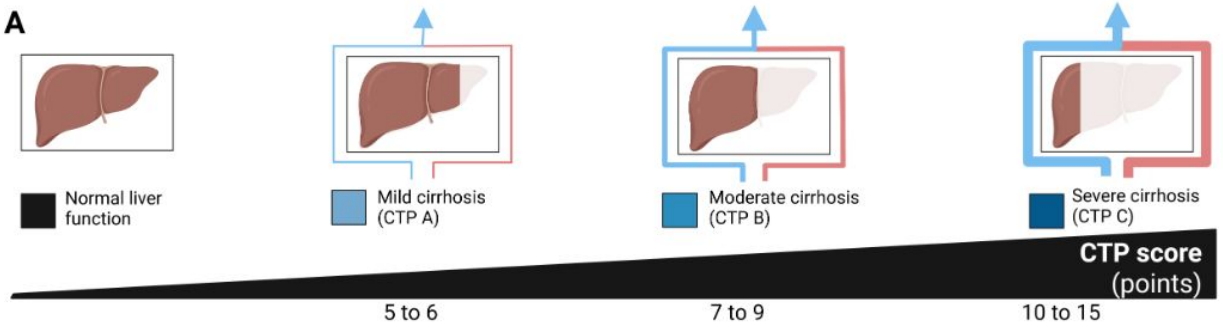



# Hepatic Impairment



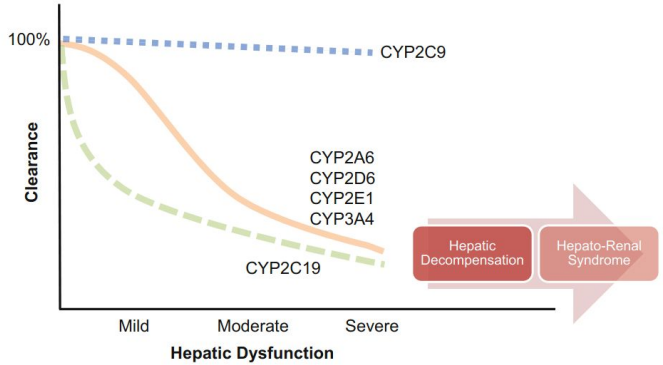



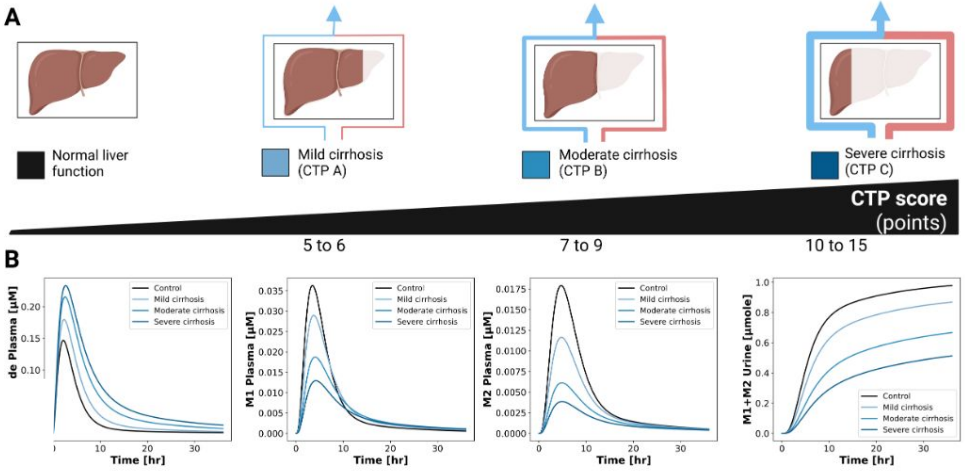

**Fig. 3** Sequential progressive model of hepatic dysfunction. The change in drug-metabolizing enzyme activity is nonuniform and isoform dependent

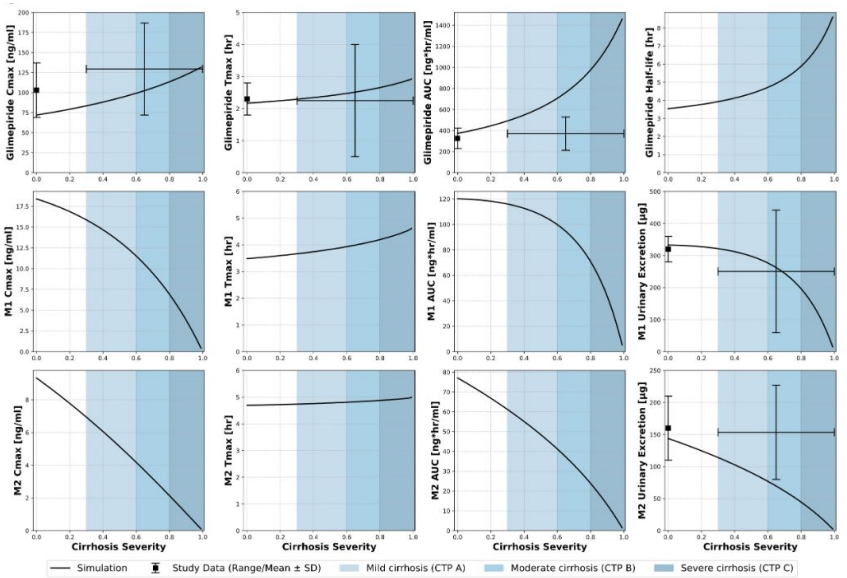
**Influence of liver disease on drug-metabolizing enzymes**

| Primary hepatic metabolic pathway | Drug(s) | Clearance ratio of hepatic impairment vs. healthy controls[a] | | | | | |
|---|---|---|---|---|---|---|---|
| | | Mild hepatic impairment | Reference | Moderate hepatic impairment | Reference | Severe hepatic impairment | References |
| CYP1A2 | Caffeine, duloxetine, tasimelteon | 0.83 (0.75, 0.90) | [282, 458] | 0.28 (0.15–0.55) | [282, 283, 458, 459] | 0.12 | [283] |
| CYP2A6 | Coumarin | 0.88 | [460] | 0.61 | [460] | 0.32 | [460] |
| CYP2B6 | Bupropion | 0.78 | [461] | – | | – | |
| CYP2C9 | Phenytoin | 1.00 | [462] | 0.96 | [462] | 1.07 (0.95, 1.19) | [462, 463] |
| CYP2C19 | Diazepam, esomeprazole, lansoprazole, mephenytoin, omeprazole, rabeprazole | 0.56 (0.34–0.73) | [282, 284–286, 464] | 0.36 (0.04–0.57) | [282, 284–286, 465, 466] | 0.41 (0.37–0.47) | [285, 286, 464] |
| CYP2D6 | Atomoxetine, debrisoquine, eliglustat, encainide, metoprolol, propranolol | 0.87 | [467] | 0.34 (0.13–0.56) | [287, 467, 468] | 0.26 | [287] |
| CYP2E1 | Chlorzoxazone | 0.73 | [282] | 0.25 | [282] | – | |
| CYP3A4/5 | Alfentanil, alprazolam, avanafil, colchicine, conivaptan, everolimus, ibrutinib, maraviroc, midazolam, naloxegol, rivaroxaban, sirolimus, tacrolimus | 0.72 (0.38–1.03) | [469–475] | 0.48 (0.14, 0.84) | [469, 471–479] | 0.34 (0.10–0.61) | [472, 473, 475, 479, 480] |
| UGT1A4 | Lamotrigine | – | – | 0.81 | [481] | 0.51 | [481] |
| CES | Oseltamivir | – | – | 0.83 | [482] | – | – |

[a]Mean and range listed. Clearance ratios calculated as $clearance_{disease}/clearance_{control}$, where clearance is the total clearance

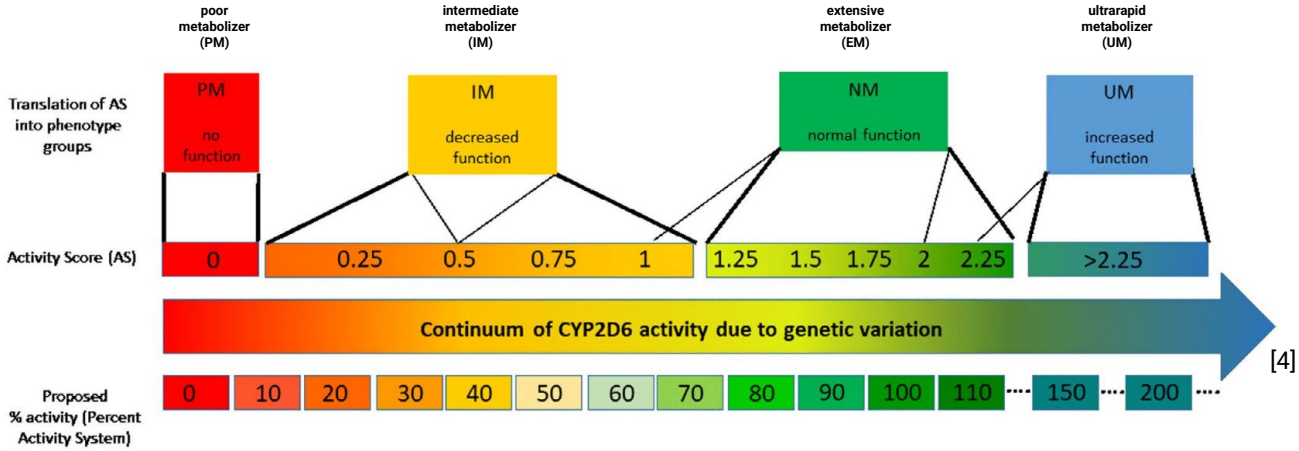
# Hepatic Impairment: Glimepiride



# CYP2D6 Polymorphism

- genetic variants have different activity values
- subjects carry combinations of these variants
- sum of individual activity values is the activity score (AS)




[4]

Activity Score (AS): $AS = \sum ActivityValue$

| | Activity Value | Allele |
|---|---|---|
| | 0 | *3,*4, *5, *6, *7, *8,*11,*12,*13,*15,*42,*44, … |
| | 0.25 | *10 |
| | 0.5 | *9,*10x2,*14,*17,*29,*41,*49,*50,*54,*55,*59 |
| | 1 | *1,*2,*9x2, *17x2, *33,*34,*35,*45,*46,*53, |
| | >1 | *1x2, *1x>2, *2x2, *1x>3, … |

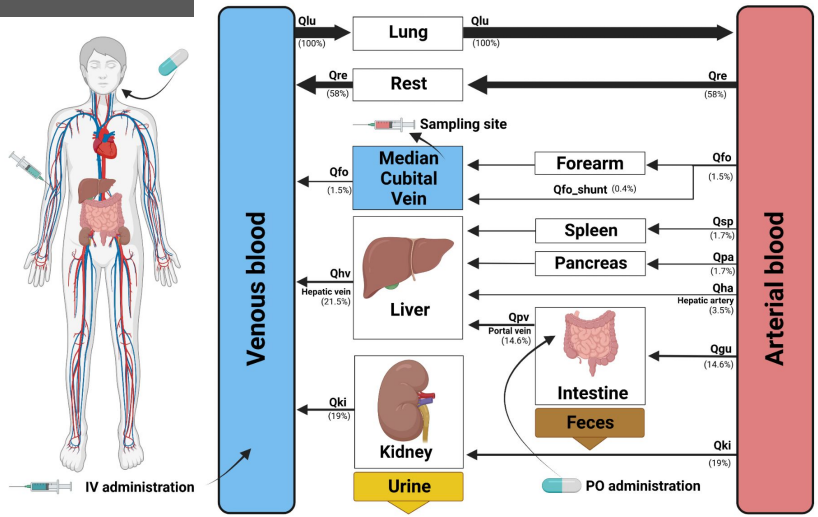
[5]


[4] K. E. Caudle et al., "Standardizing CYP 2D6 Genotype to Phenotype Translation: Consensus Recommendations from the Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group," Clin Transl Sci. vol. 13, no. 1, pp. 116–124, Jan. 2020, doi: 10.1111/cts.12692.

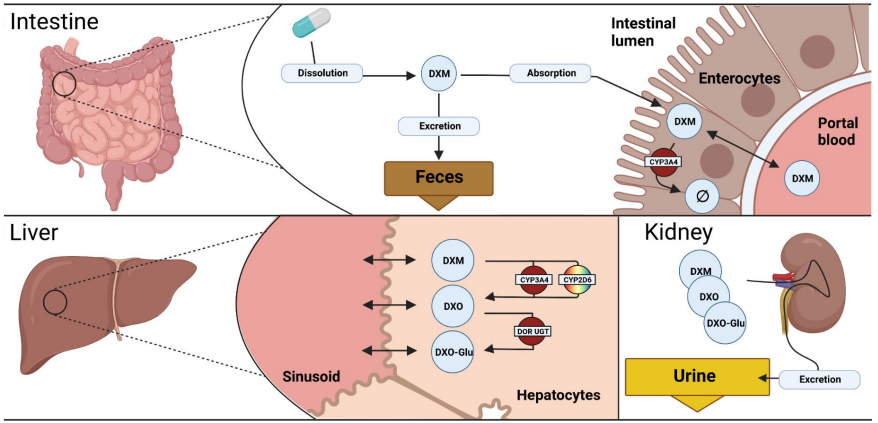
[5] M. Whirl-Carrillo[1], R. Huddart[1], L. Gong, K. Sangkuhl, C.F. Thorn, R. Whaley and T.E. Klein. "An evidence-based framework for evaluating pharmacogenomics knowledge for personalized medicine" *Clinical Pharmacology & Therapeutics* (2021) online ahead of print.

# Dextromethorphan - Genetic Polymorphisms CYP2D6

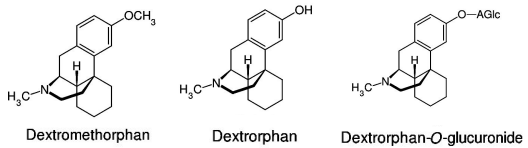
## Whole-body model




## Tissue models




## Substance/Metabolites



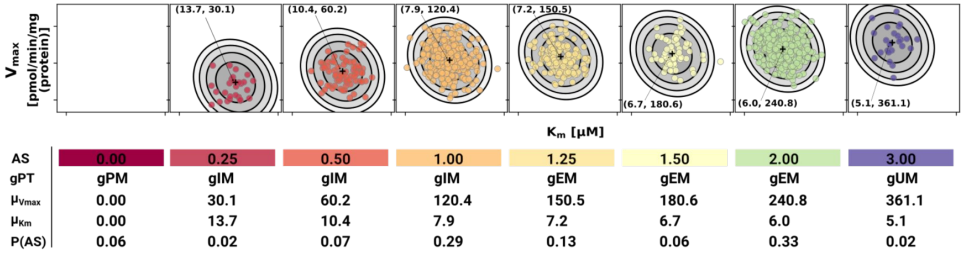

J.Grzegorzewski, J.Brandhorst, **M.König**
***Physiologically based pharmacokinetic (PBPK) modeling of the role of CYP2D6 polymorphism for metabolic phenotyping with dextromethorphan***
https://doi.org/10.1101/2022.08.23.504981 [in print, Frontiers in Pharmacology]

# Model of CYP2D6 Polymorphism and Variability

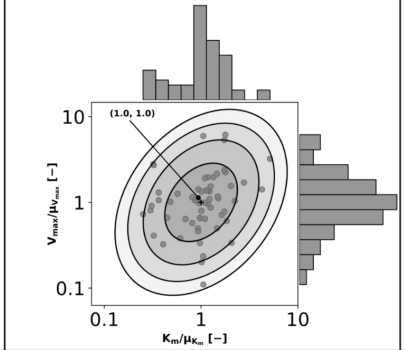
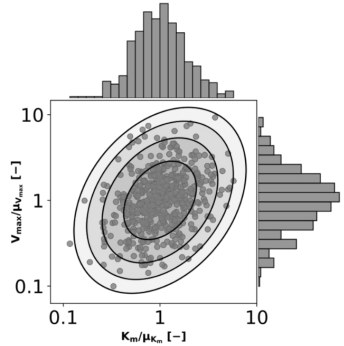
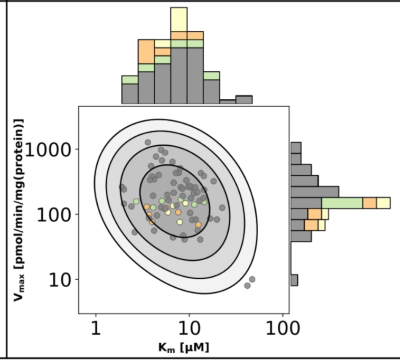
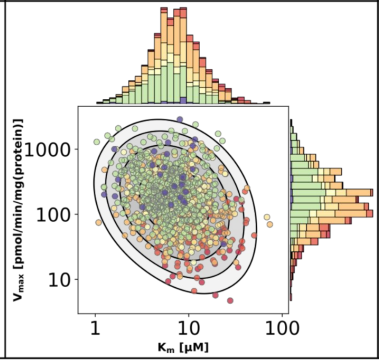
| Activity Value | Allele |
|---|---|
| 0 | *3,*4, *5, *6, *7, *8,*11,*12,*13,*15,*42,*44, … |
| 0.25 | *10 |
| 0.5 | *9,*10x2,*14,*17,*29,*41,*49,*50,*54,*55,*59 |
| 1 | *1,*2,*9x2, *17x2, *33,*34,*35,*45,*46,*53, |
| >1 | *1x2, *1x>2, *2x2, *1x>3, … |

Michaelis Menten: $v = \frac{V_{\max}[S]}{K_M + [S]}$

Activity Score (AS): $AS = \sum ActivityValue$



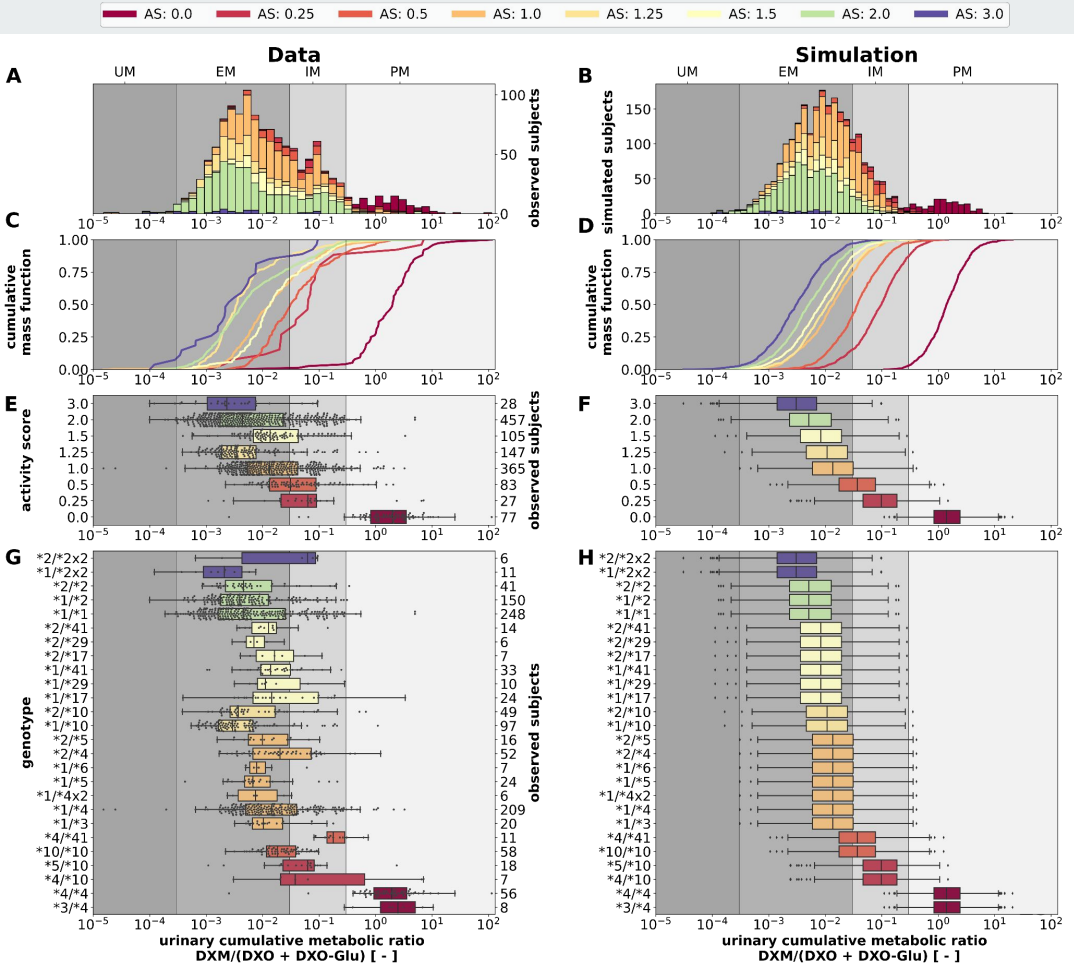

| AS | 0.00 | 0.25 | 0.50 | 1.00 | 1.25 | 1.50 | 2.00 | 3.00 |
|---|---|---|---|---|---|---|---|---|
| gPT | gPM | gIM | gIM | gIM | gEM | gEM | gEM | gUM |
| $\mu_{Vmax}$ | 0.00 | 30.1 | 60.2 | 120.4 | 150.5 | 180.6 | 240.8 | 361.1 |
| $\mu_{Km}$ | 0.00 | 13.7 | 10.4 | 7.9 | 7.2 | 6.7 | 6.0 | 5.1 |
| P(AS) | 0.06 | 0.02 | 0.07 | 0.29 | 0.13 | 0.06 | 0.33 | 0.02 |

| Enzyme | Data | Model |
|---|---|---|
| CYP3A4 |  |  |
| CYP2D6 |  |  |

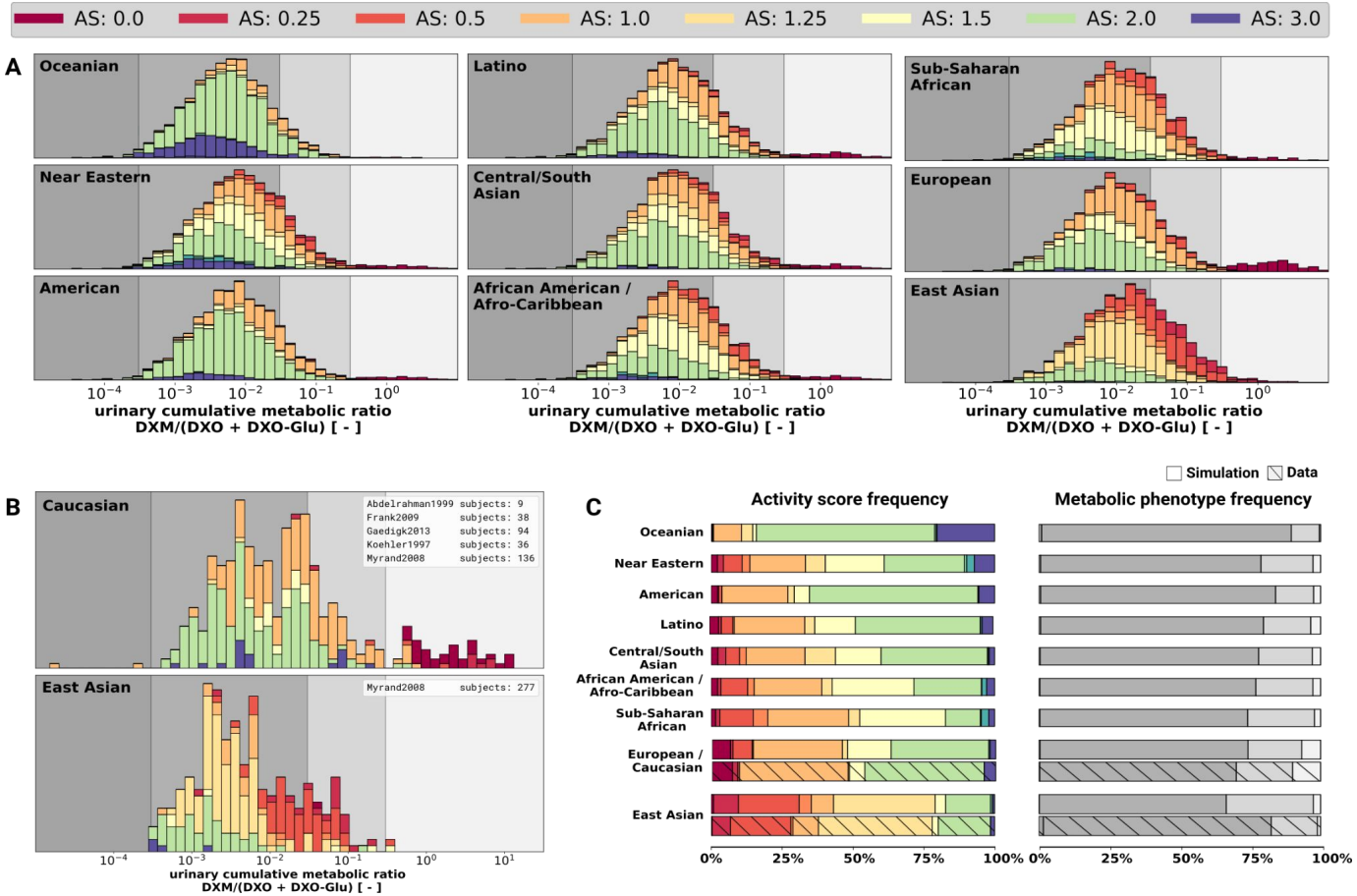
# Metabolic phenotyping

- Model predicts effect of CYP2D6 activity and genetic polymorphisms
- Urinary cumulative metabolic ratio (UCMR) for metabolic phenotyping

J.Grzegorzewski, J.Brandhorst, **M.König** ***Physiologically based pharmacokinetic (PBPK) modeling of the role of CYP2D6 polymorphism for metabolic phenotyping with dextromethorphan***
https://doi.org/10.1101/2022.08.23.504981
In print, Frontiers in Pharmacology



# Dextromethorphan - CYP2D6 Populations




J.Grzegorzewski, J.Brandhorst, **M.König** ***Physiologically based pharmacokinetic (PBPK) modeling of the role of CYP2D6 polymorphism for metabolic phenotyping with dextromethorphan*** https://doi.org/10.1101/2022.08.23.504981
In print, Frontiers in Pharmacology

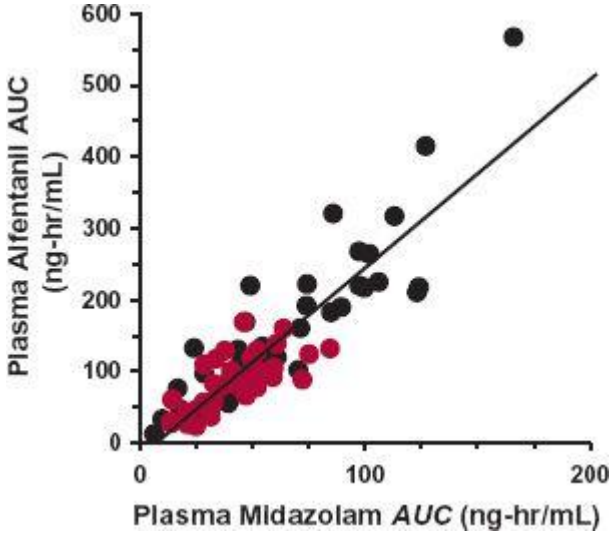



**FIGURE 12-3.** A high degree of cosegregation exists between midazolam and alfentanil exposure after intravenous () and oral () administration of these drugs to 12 subjects. Both drugs are primarily eliminated by CYP3A4 catalyzed metabolism, and reflect variation in the functional activity of this enzyme within this group of subjects. (From: Kharasch ED, Walker A, Hoffer C, et al. Sensitivity of intravenous and oral alfentanil and papillary miosis as minimally invasive and noninvasive probes for hepatic and first-pass CYP3A4 activity. J Clin Pharmacol 2005;45:1187–1197.)

https://basicmedicalkey.com/variability/