Genomics of adverse drug reactions

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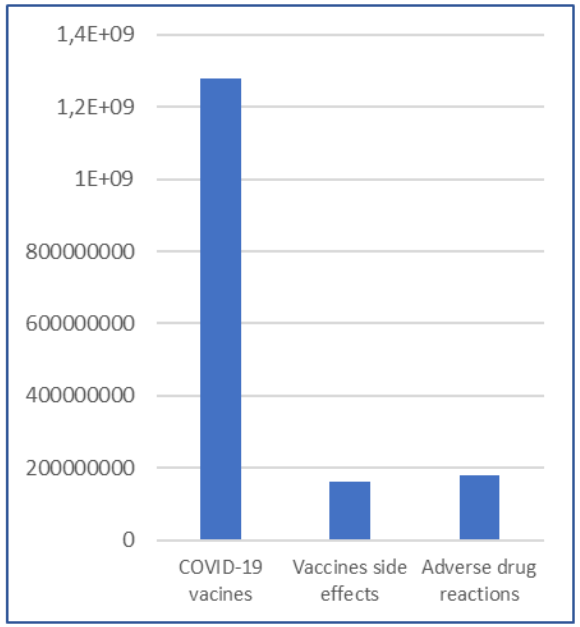
06-05-2021

A side effect is an unintended effect of a drug related to its pharmacological properties.

https://www.glasbergen.com/diet-health-fitness-medical/pharmaceutical-drugs-and-herbal-remedies/cartoons/page/5

Interest in Adverse Drug Reactions



Google	Results
COVID-19 vacines	1 280 000 000
Vaccines side effects	162 000 000
Adverse drug reactions	179 000 000

PubMed	Results
COVID-19 vacines	6024
Vaccines side effects	4825
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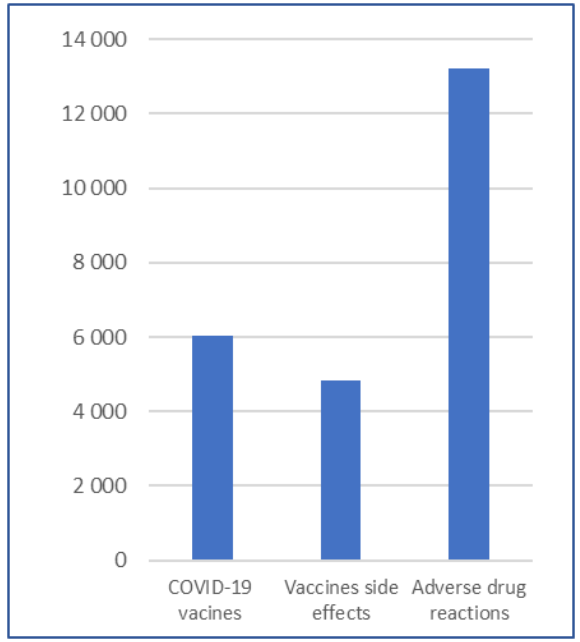
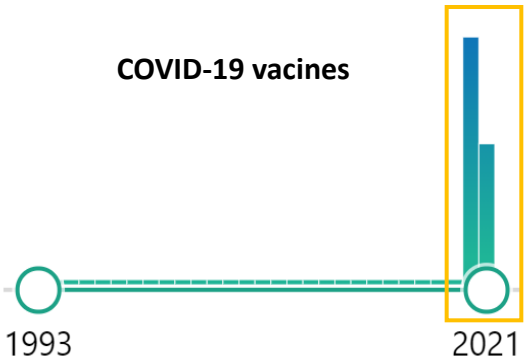
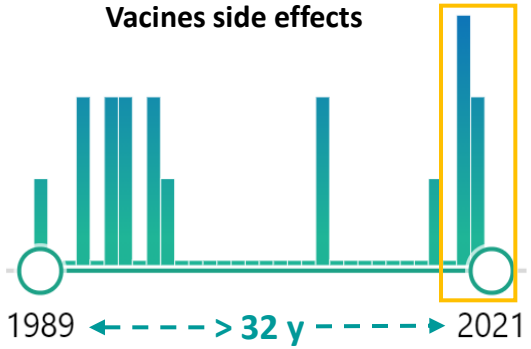
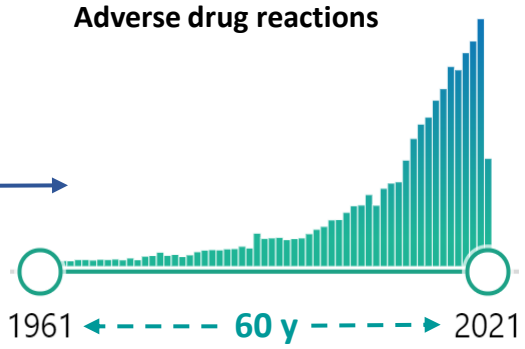








Reino Unido registou 30 casos de coágulos em 18,1 milhões de vacinados

A agência reguladora da saúde britânica identificou 30 casos de coágulos sanguíneos raros entre 18,1 milhões de pessoas que tomaram a vacina contra a covid-19 da Astrazeneca no Reino Unido, mas insiste no benefício daquele fármaco.

© Getty Images

Sete mortos no Reino Unido após vacinação com AstraZeneca

Sete pessoas morreram no Reino Unido de coágulos sanguíneos após receberem a vacina anti-covid-19 da AstraZeneca, mas as autoridades de saúde britânicas reforçam que os riscos são "muito pequenos" e aconselham a população a vacinar-se.

© Reuters

03/04/21 10:39 - HÁ 8 HORAS POR LUSA
MUNDO COVID-19

Noruega investiga mais duas mortes após toma da vacina da AstraZeneca

Ao todo são quatro as vítimas mortais, todas elas com um quadro clínico que incluía plaquetas baixas, coágulos de sangue nos vasos sanguíneos e hemorragias.

AO MINUTO: AstraZeneca? Esteja atento a estes sintomas (muito raros)

Acompanhe aqui AO MINUTO os mais recentes desenvolvimentos sobre a Covid-19 em Portugal e no Mundo.

AstraZeneca: EMA ainda a avaliar ligação entre vacina e tromboembolismos

A Agência Europeia do Medicamento (EMA) esclareceu hoje que ainda está a avaliar a possível ligação entre a vacina da AstraZeneca contra a covid-19 e a formação de tromboembolismos, após um responsável da instituição ter confirmado essa relação.

África do Sul suspende utilização da vacina J&J por "precaução"

A África do Sul suspendeu hoje a administração da vacina Johnson & Johnson como "medida de precaução", no seguimento da decisão da agência norte-americana do medicamento de interromper o seu uso enquanto se investigam casos de coágulos sanguíneos.

Confirma-se relação entre vacina da AstraZeneca e coágulos sanguíneos

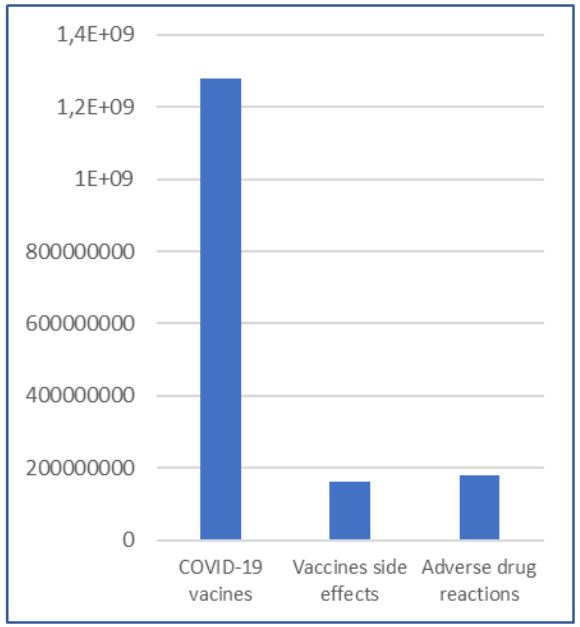
Especialistas da Agência do Medicamento estão reunidos para fazer uma nova avaliação à vacina.

Ministra da Saúde convoca reunião de urgência para debater AstraZeneca

Família de homem que morreu após vacina da AstraZeneca deixa apelo

A família de um homem de morreu depois de ter sido vacinado com a AstraZeneca diz-se "furiosa", mas apela à continuidade da vacinação. Ele foi "extraordinariamente azarado", indica.

Interest in Adverse Drug Reactions



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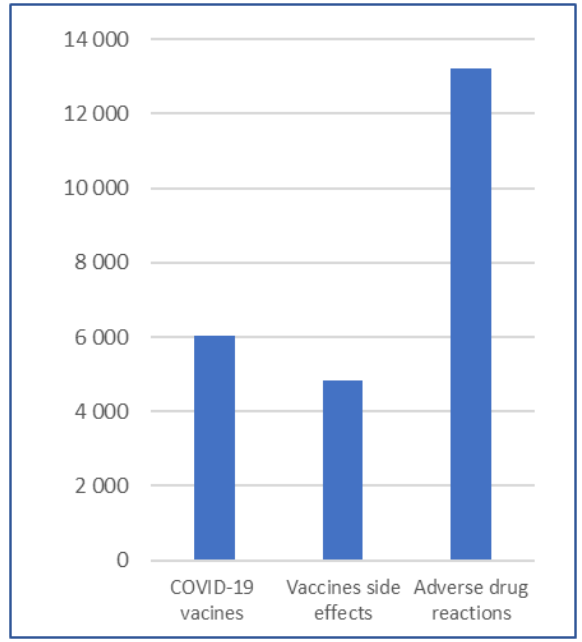

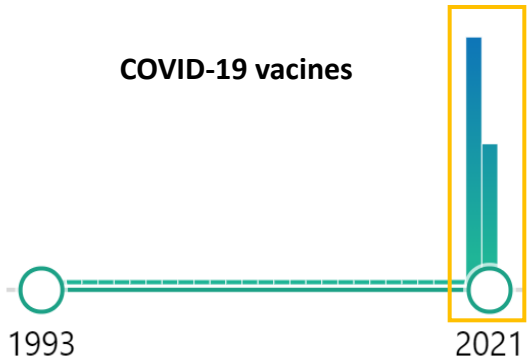

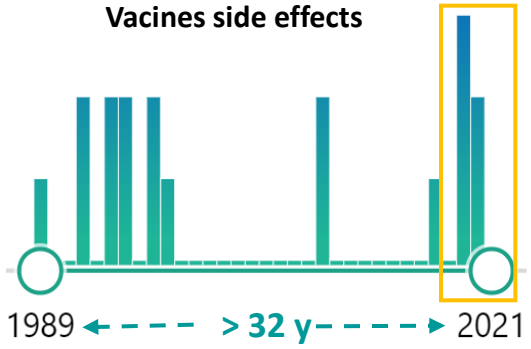

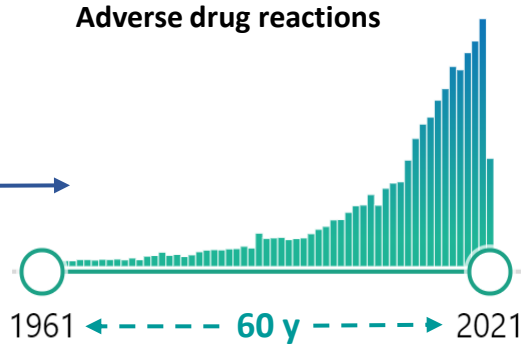

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Pharmacovigilance

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse reactions and other medicine-related problems.

Benefit-risk balance

At the time when a new medicine obtains a marketing authorisation, the active substance has been tested and the data have allowed a conclusion to be drawn that the benefits of the medicine outweigh its risks.

However, once the medicine has obtained a marketing authorisation, it will be used in normal healthcare settings for many patients who may differ from the study population, for example by age or additional diseases.

It is therefore important to identify any new or changing risk of a medicine as quickly as possible, and to take measures to minimise risk and promote safe and effective use.

https://www.ema.europa.eu/en/documents/leaflet/pharmacovigilance_en.pdf

Adverse Effects

… Any significant failure of expected pharmacological action. adverse events from drug withdrawal

Adverse effect term	Definition	Example(s)
Adverse event	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment	In a clinical trial for a topical emollient for psoriasis a road traffic accident could be a serious, unexpected, not study related adverse event
Adverse drug event	An injury resulting from the use of a drug	i) Intentional overdose ← Suicide, fentanyl ii) Medication error ← Polimedicated people iii) Adverse drug reaction
Medication error	A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer	Decrease in consciousness following accidental insulin overdose due to a prescribing or administration error
Adverse drug reaction **(ADR)** 	A response to a drug that is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function	Hypersensitivity reaction to allopurinol through standard clinical use of the drug

These reactions may be caused by the **drug** itself or one of its **metabolites**; from an **interaction** between 2 or more **drugs** or between a drug and **food**, or may be caused by an component of the product, such as **dye** or **preservative.**

The WHO definition has been criticized for excluding the (i) potential for contamination of a product, ADRs that include an element of error, and (ii) ADRs associated with pharmacologically inactive excipients in a product. (iii) The use of the term ‘drug’ also excluded the use of complementary and alternative treatments, such as herbal products.

"Right now I take a blue pill, a purple pill, an orange pill, a white pill, and a yellow pill. I need you to prescribe a green pill to complete my collection."

Cartoon ID: toon-3602

https://www.glasbergen.com/diet-health-fitness-medical/pharmaceutical-drugs-and-herbal-remedies/cartoons/page/1

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Why ADRs are important

- A wide range of drugs can produce ADRs
- ADRs are a major public health problem.
- The European Medicines Agency (EMA) received in EudraVigilance **2.002.814** reports related to **suspected ADR in 2019**, with a variable degree of severity.
- ADRs are responsible for **3,6% of the admissions at European hospitals.**
- Up to **10% of patients** experience an **ADR while hospitalized**.
- Around **0,5%** of the ADRs can be **fatal**.
- In **Portuga**l, the National Authority of Medicines and Health Products (INFARMED) received **11.585** ADR notifications in 2019, **56%** of which were classified as **severe**.

Classification of ADRs

Mos ADRs are **mild**, and disappear when the drug is stop or the dose is readjusted. An ADR is **serious** if the patient outcome is (1) death, (2) life-threatening, (3) requires hospitalization, (4) causes disability (significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life) (5) congenital abnormality, (6) requires intervention to prevent permanent impairment or damage (FDA).

Several different mechanisms are involved in ADR development. ADRs can also be spitted according their clinical presentation and predominant pathogenic processes in **Immune-mediated ADRs** (result principally from a deleterious immune reaction following drug exposure) and **no Immune-mediated ADRs .**

ADRs may be **local,** or **systemic**, affecting various organs and systems with different degrees of severity and can be classified according with the organ or system affected .

This heterogeneity raised the need of some systematization in the approach to ADRs.

The classic **Rawlins–Thompson** system divides ADRs into **2** main groups: **Type A** (extension of pharmacologic effect, often predictable, responsible for at least 2/3 of all ADRs: **Type B** (idioyosyncratic or immunologic reactions, rare and unpredictable)

The Rawlins–Thompson classification has change over the years in order to include ADRs that do not fit within the A and B groups

Classification of Adverse drug reactions

Type of reaction	Mnemonic	Features	Examples	Management
A: Dose-related	Augmented	• Common • Related to a pharmacological action of the drug • Predictable • Low mortality	• Toxic effects: Digoxin toxicity; serotonin syndrome with SSRIs • Side effects: Anticholinergic effects of tricyclic antidepressants	• Reduce dose or withhold • Consider effects of concomitant therapy
B: Non-dose-related	Bizarre	• Uncommon • Not related to a pharmacological action of the drug • Unpredictable • High mortality	• Immunological reactions: Penicillin hypersensitivity • Idiosyncratic reactions: Acute porphyria Malignant hyperthermia Pseudoallergy (eg, ampicillin rash)	• Withhold and avoid in future
C: Dose-related and time-related	Chronic	• Uncommon • Related to the cumulative dose	• Hypothalamic-pituitary-adrenal axis suppression by corticosteroids	• Reduce dose or withhold; withdrawal may have to be prolonged
D: Time-related	Delayed	• Uncommon • Usually dose-related • Occurs or becomes apparent some time after the use of the drug	• Teratogenesis (eg, vaginal adenocarcinoma with diethylstilbestrol) • Carcinogenesis • Tardive dyskinesia	• Often intractable
E: Withdrawal	End of use	• Uncommon • Occurs soon after withdrawal of the drug	• Opiate withdrawal syndrome • Myocardial ischaemia (β-blocker withdrawal)	• Reintroduce and withdraw slowly
F: Unexpected failure of therapy	Failure	• Common • Dose-related • Often caused by drug interactions	• Inadequate dosage of an oral contraceptive, particularly when used with specific enzyme inducers	• Increase dosage • Consider effects of concomitant therapy

Example: Severe allergic reaction to a COVID-19 vaccines
Thrombosis and thrombocytopenia afterr COVID-19 Vaccination

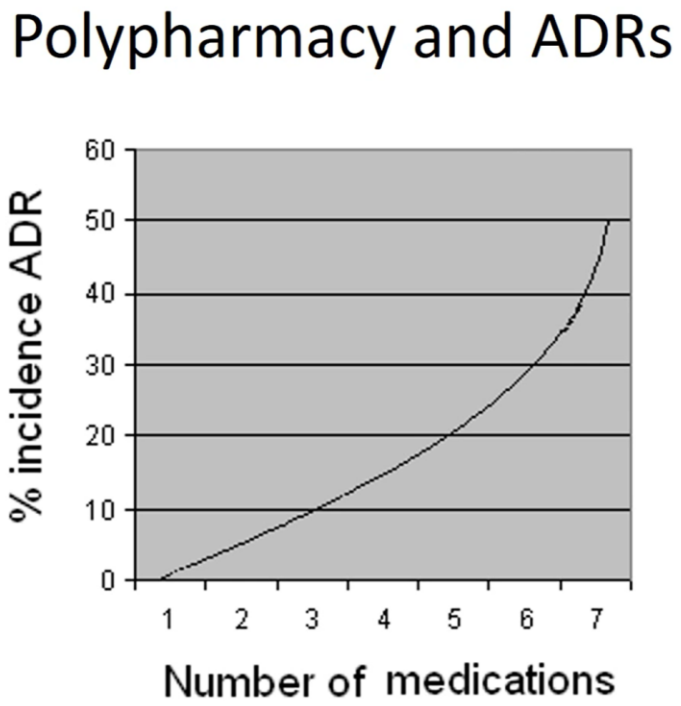
Ralph Edwards & Jeffrey K Aronson, 2000

PMID: 11072960

Factors affeting Susceptibility to ADRs

The reasons for the heterogeneity in inter-individual drug response are often not known, but there are a trilogy of implicated factors:

- **Environmental**
  - drug-drug (warfarin and fuconazol)
  - drug-food interactions (warfarin and citrus fruit)
- **Clinical**
  - Age (children and old people–higher risk)
  - co-morbidities (patients with renal or hepatic impairment show increased risk of ADR)
  - body mass index (Interferes with the drug distribution)
  - pregnancy (risk of teratogenic effect)
- **Genetic**
  - Genes involved in drug metabolism and detoxification
  - Genes involved in excretion (transportes)

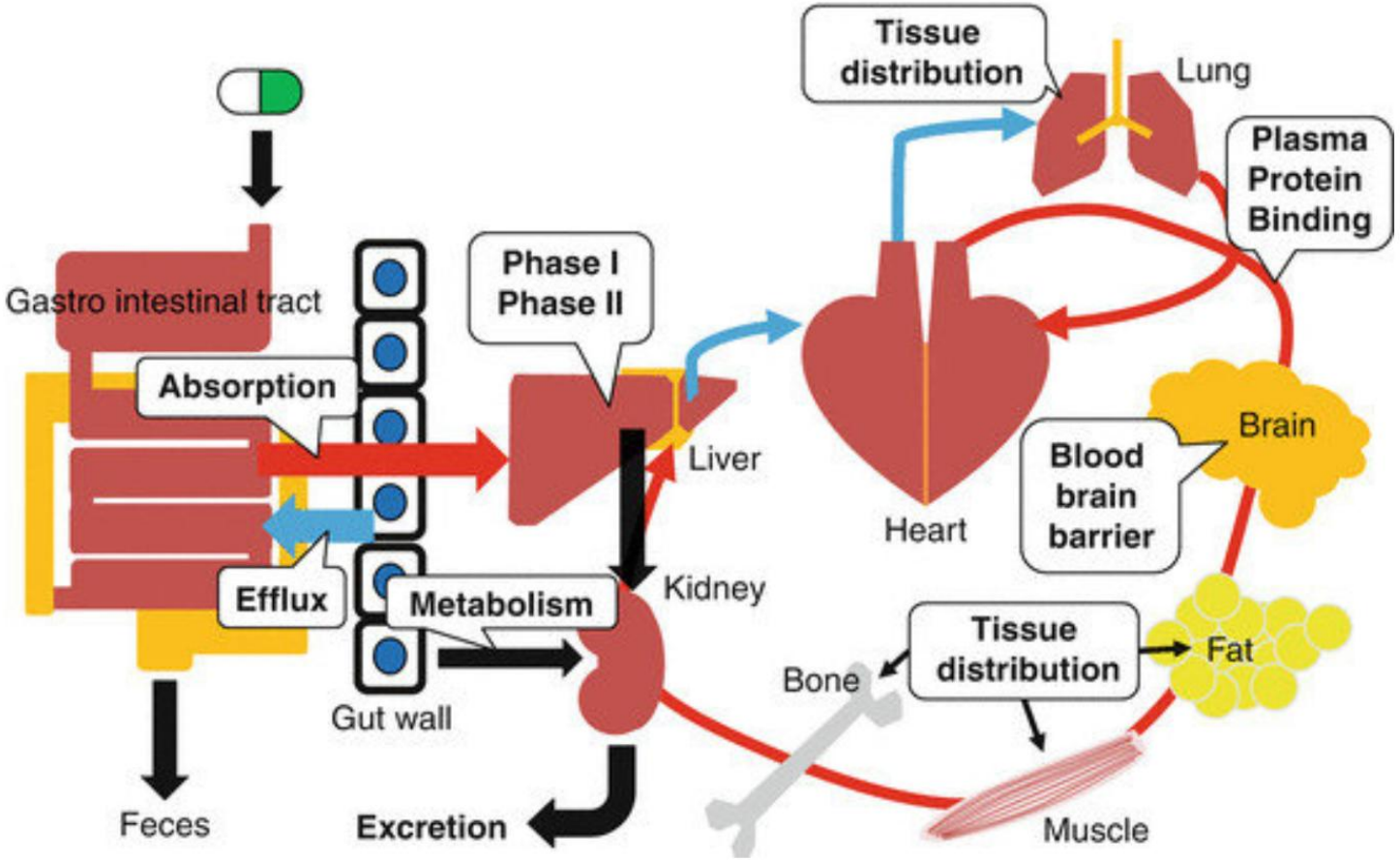


Pharmacokinetics / Pharmacodinamics

Pharmacokinetics
What the body does to the drug

Pharmacodynamics
What the drug does to the body

Pharmacokinetics

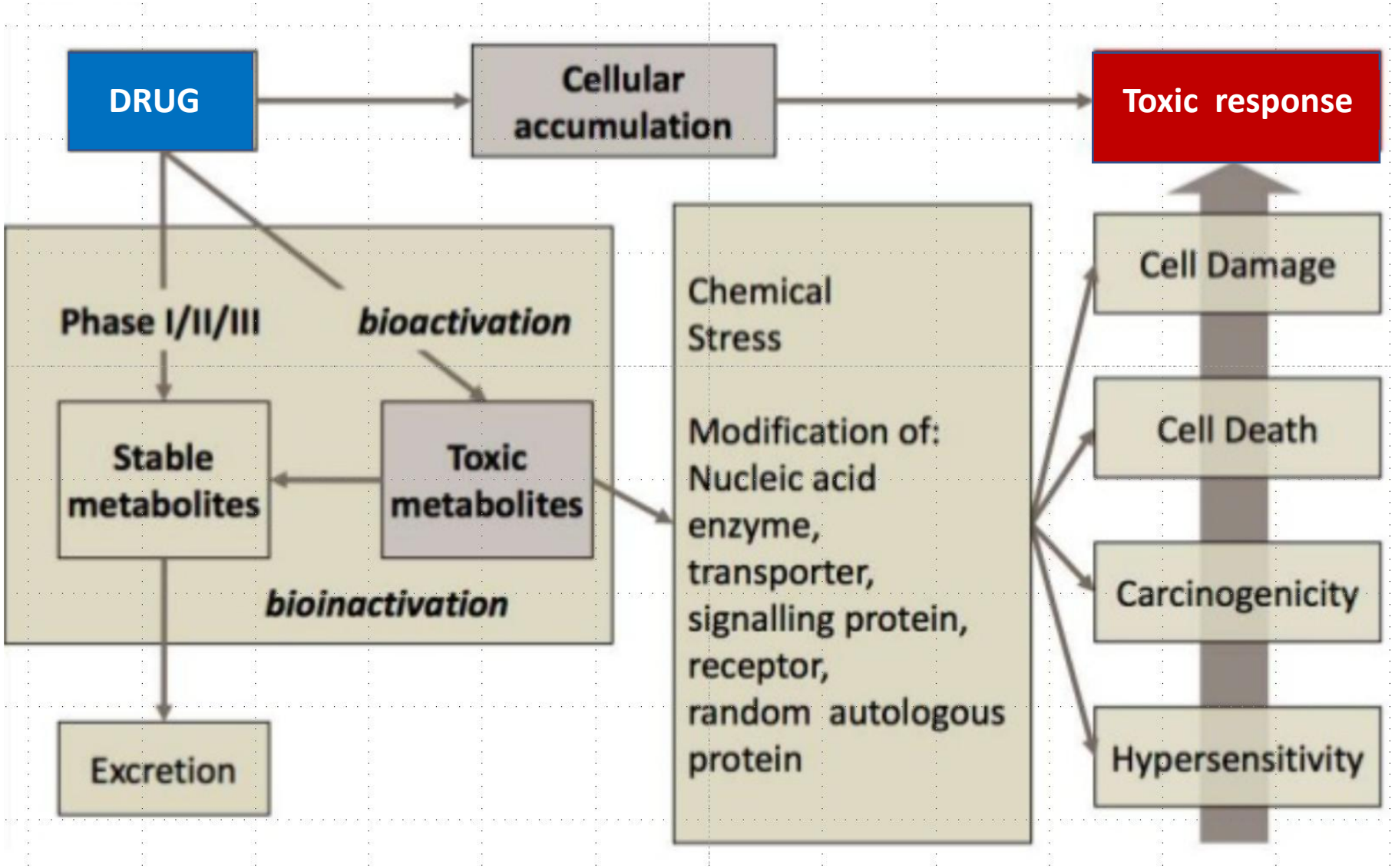


Pharmacodynamics

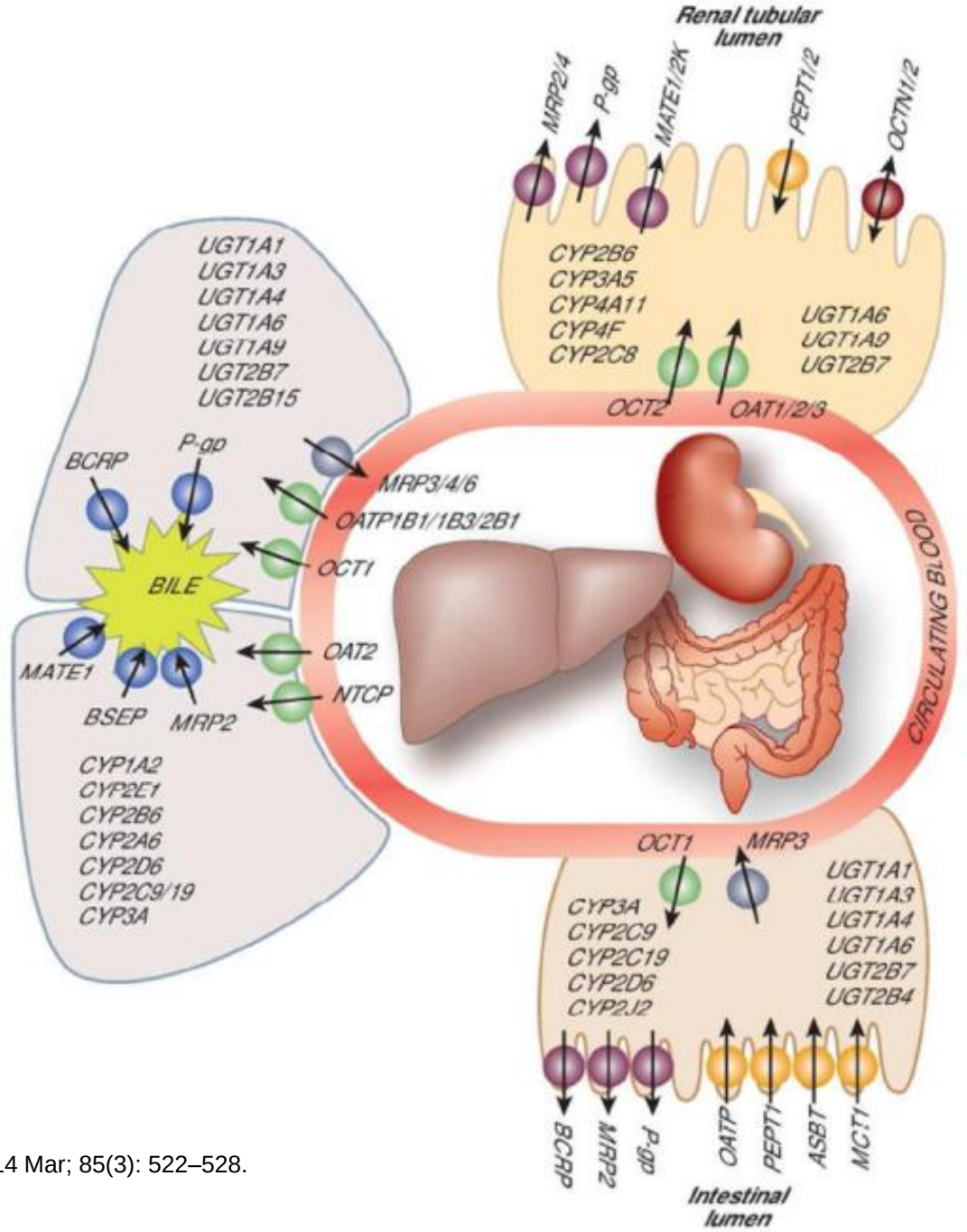
Predicting ADME Properties of Chemicals

https://link.springer.com/referenceworkentry/10.1007%2F978-94-007-6169-8_59-1

Physiological and Toxicological aspects of Drugs Metabolism



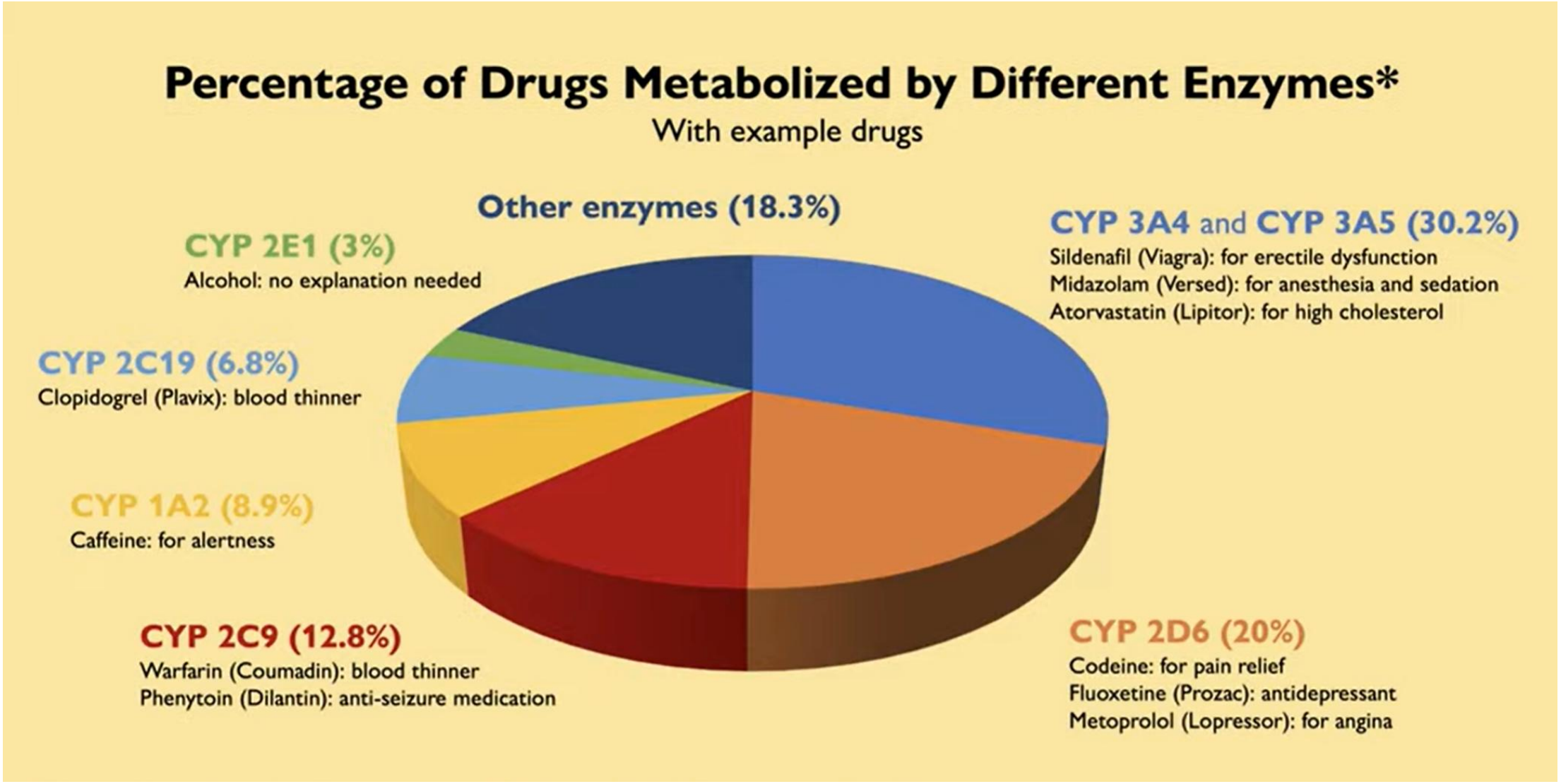
Liver enzymes



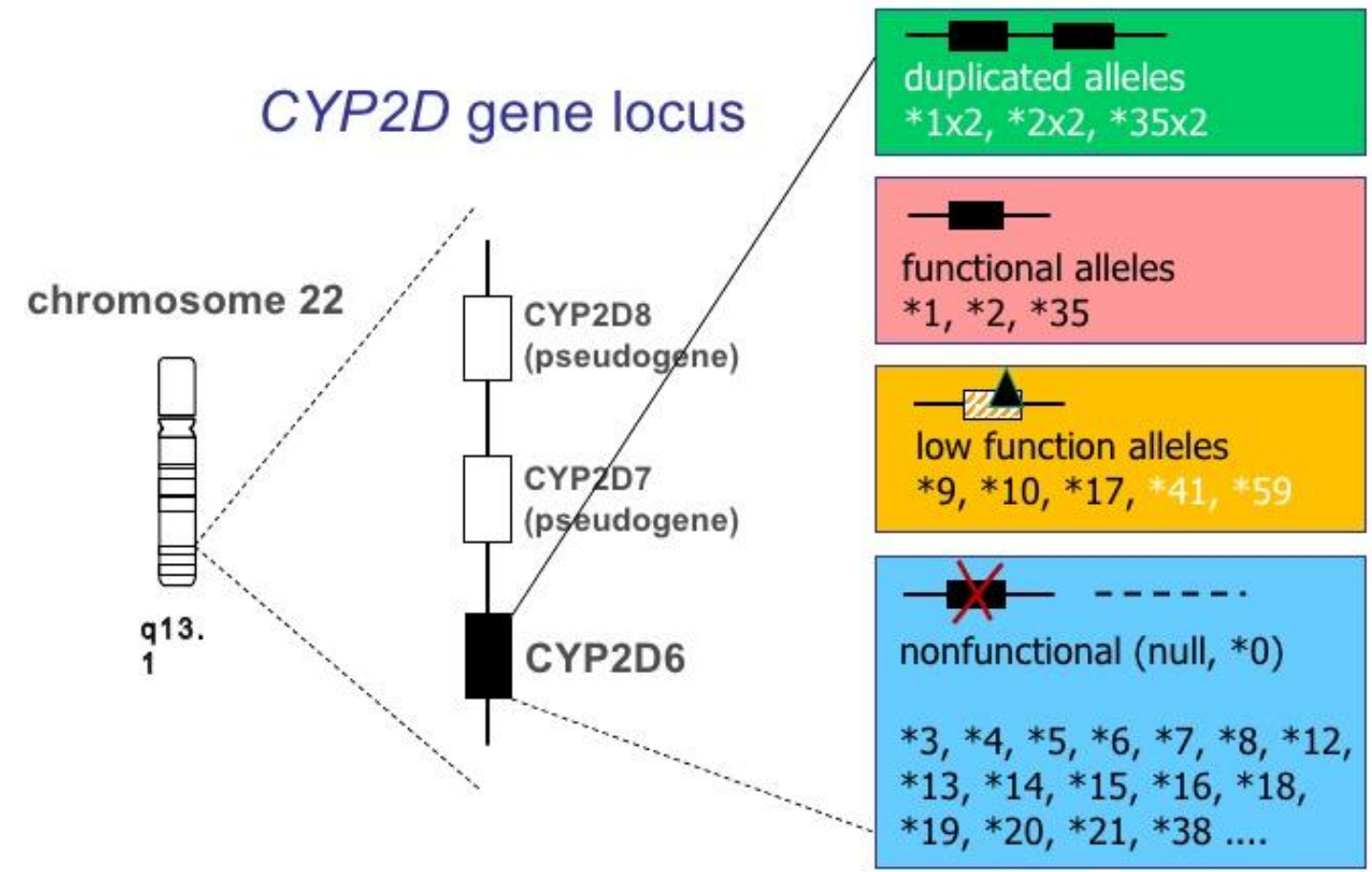
Transporters

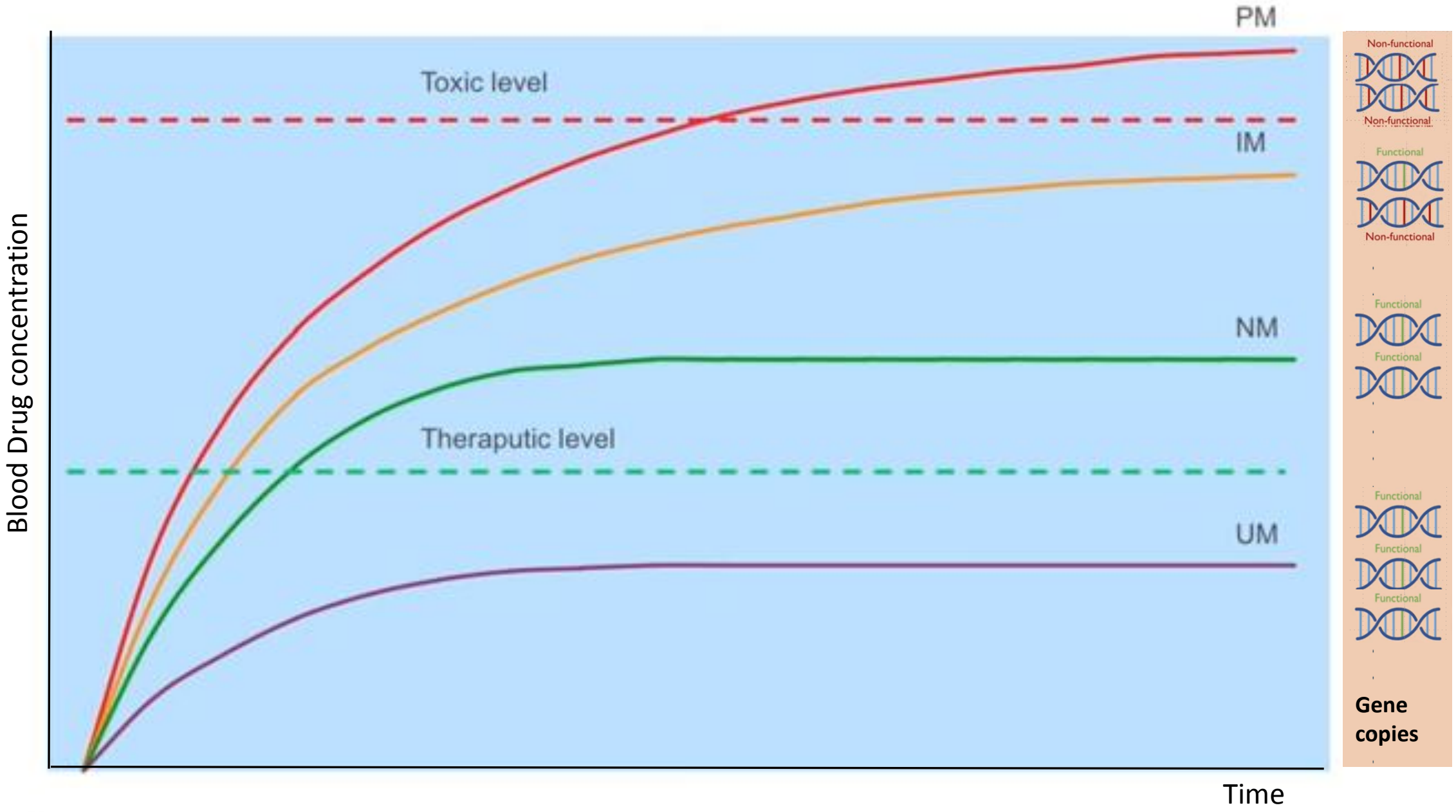
Kidney Int. 2014 Mar; 85(3): 522–528.

Enzymes of CYP450 Superfamily



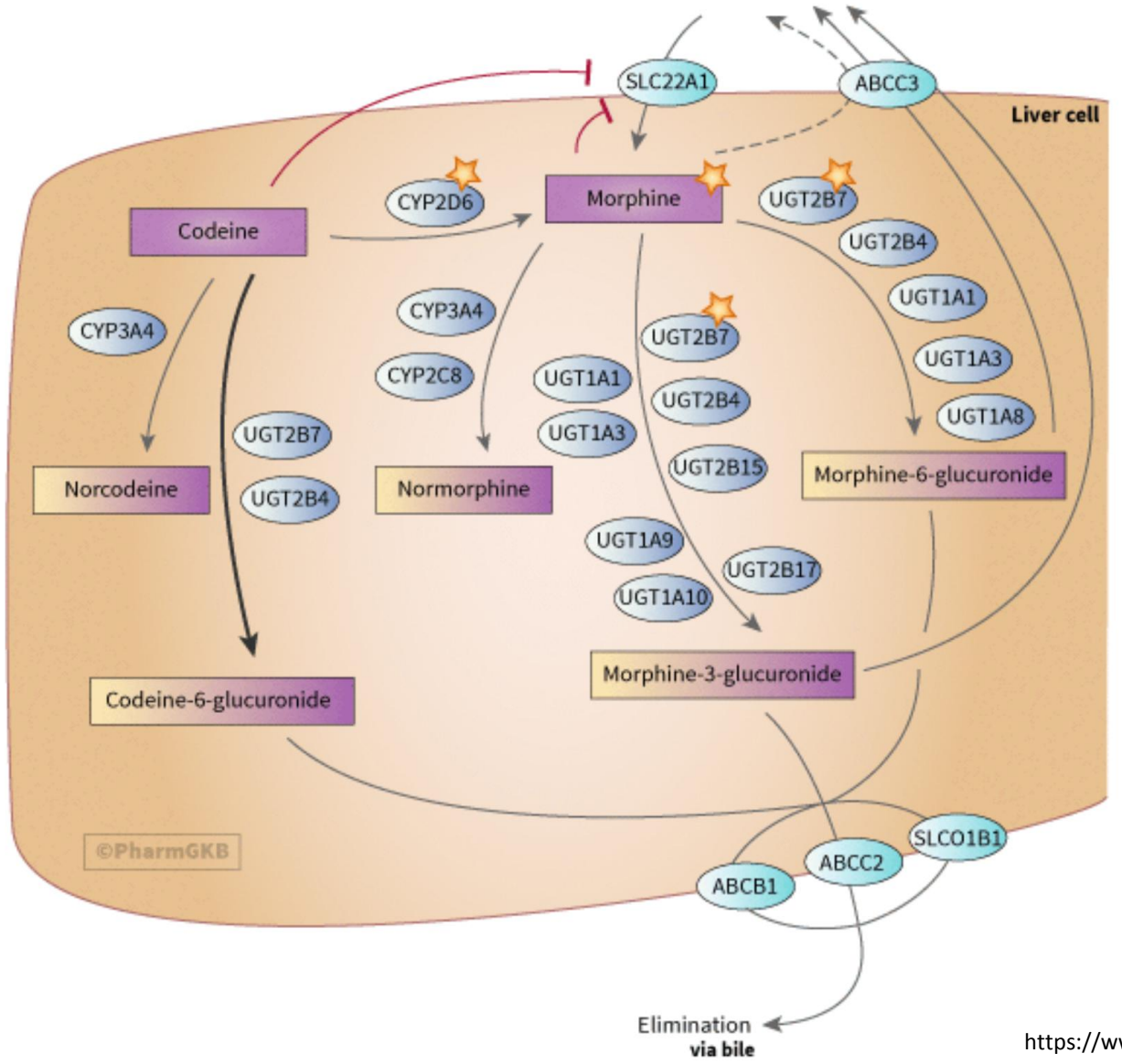
Molecular Basis of the *CYP2D6* Polymorphism



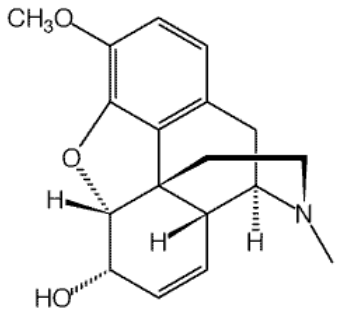


PM – Poor metabolizer; IM –Intermediate or extensive metabolizer; N- Normal Metabolizer; UM – Ultra rapid metabolizer

Codeine metabolism



https://www.pharmgkb.org/pathway/PA146123006



Codeina

Motherisk Update
Current Practice • Pratique courante

Safety of codeine during breastfeeding

Fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine

Parvaz Madadi Gideon Koren, MD, FRCPC James Cairns, MD David Chitayat, MD Andrea Gaedigk, PHD
J. Steven Leeder, PHARMD, PHD Ronni Teitelbaum, MSC Tatyana Karaskov, MD Katarina Aleksa, PHD

ABSTRACT

QUESTION Recently a newborn died from morphine poisoning when his mother used codeine while breastfeeding. Many patients receive codeine for postlabour pain. Is it safe to prescribe codeine for nursing mothers?

ANSWER When a mother is an ultrarapid metabolizer of cytochrome P450 2D6, she produces much more morphine when taking codeine than most people do. In this situation, newborns might be exposed to toxic levels of morphine when breastfeeding. Options to reduce this risk include discontinuing codeine after 2 to 3 days of use and being aware of symptoms of potential opioid toxicity in both mothers and newborns.

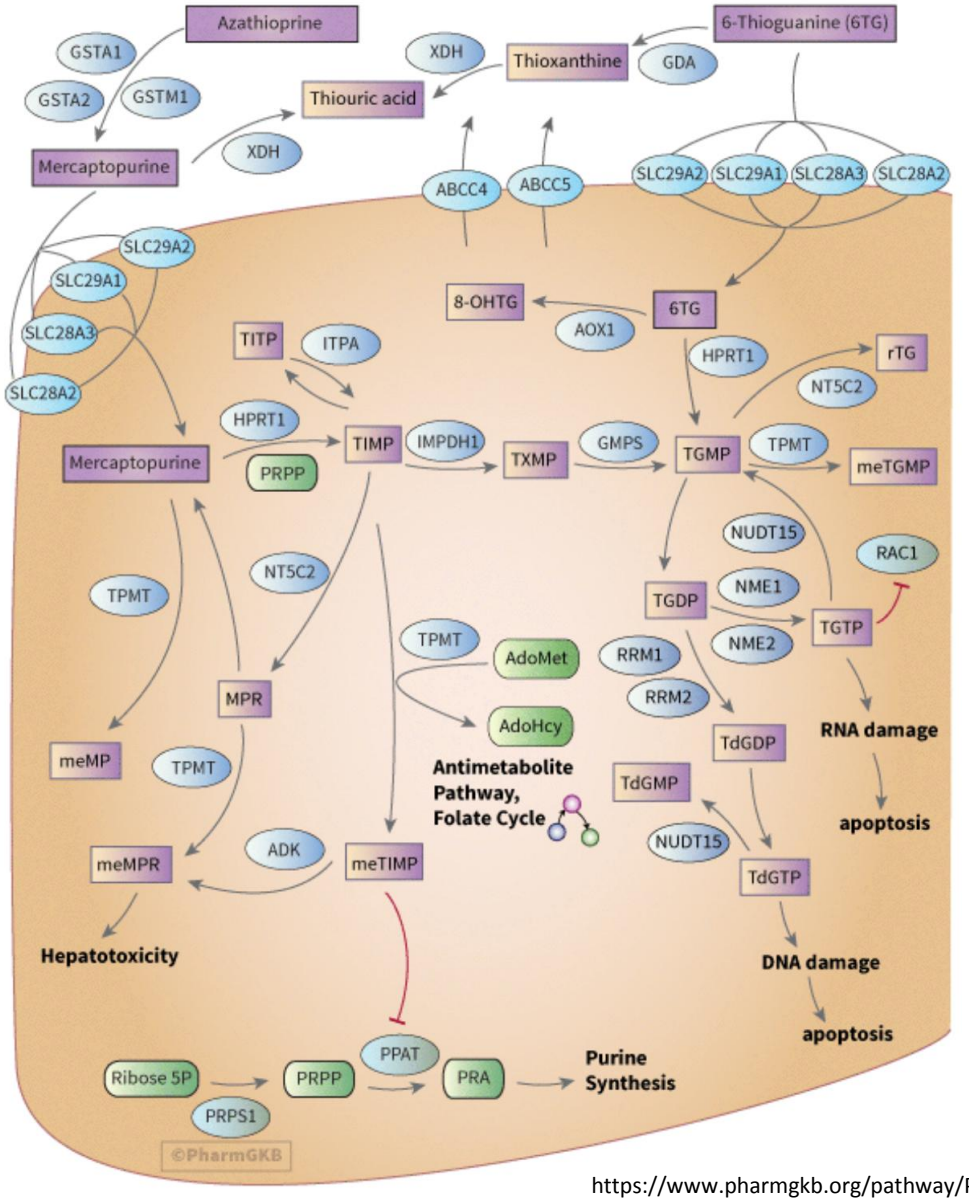
Thiopurines (6-MP, 6-TG and AZA) and TPMT

The **thiopurine drugs** are purine antimetabolites widely used in the treatment of (i) acute lymphoblastic leukemia, (2) autoimmune disorders (e.g., Crohn's disease and Rheumatoid Arthritis) and of (3) organ transplant recipients.

As inactive prodrugs, **6-mercaptopurine** (6-MP), **6-thioguanine** (6-TG) and **azathioprine** (AZA) require intracellular activation, catalyzed by multiple enzymes, to exert **cytotoxicity.** The first step in AZA activation is the release of 6-MP.

The active metabolites are metabolized and **inactivated by the enzyme thiopurine methyltransferase** (**TPMT**) and the enzyme **nudix hydrolase 15** (**NUDT15**).

Patients with reduced activity of either enzyme are exposed to higher levels of thioguanine and have a **higher risk of toxicity side effects**, including severe bone marrow suppression (myelosuppression).



https://www.pharmgkb.org/pathway/PA2040

PGx CPIC Guideline – Thiopurines and *TPMT*

CPIC UPDATE

Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on *TPMT* and *NUDT*15 Genotypes: 2018 Update

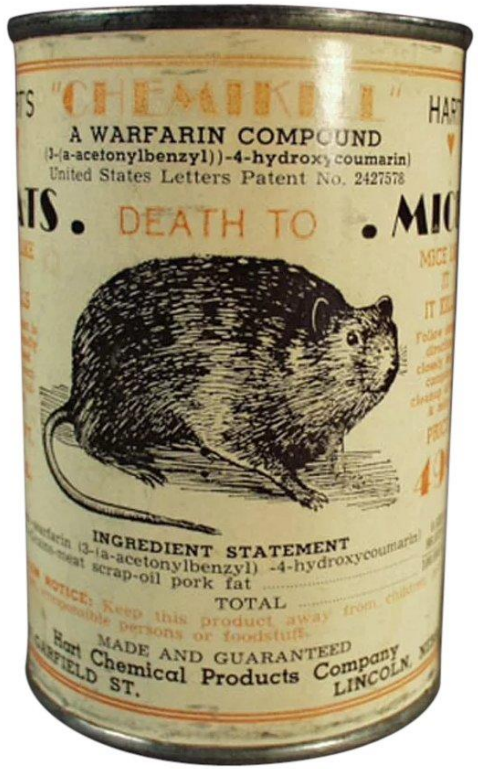
Mary V. Relling[1], Matthias Schwab[2,3,4], Michelle Whirl-Carrillo[5], Guilherme Suarez-Kurtz[6], Ching-Hon Pui[7], Charles M. Stein[8], Ann M. Moyer[9], William E. Evans[1], Teri E. Klein[4], Federico Guillermo Antillon-Klussmann[10,11], Kelly E. Caudle[1], Motohiro Kato[12], Allen E.J. Yeoh[13,14], Kjeld Schmiegelow[15,16] and Jun J. Yang[1]

Thiopurine methyltransferase (TPMT) activity exhibits a monogenic codominant inheritance and catabolizes thiopurines. *TPMT* variant alleles are associated with low enzyme activity and pronounced pharmacologic effects of thiopurines. Loss-of-function alleles in the *NUDT15* gene are common in Asians and Hispanics and reduce the degradation of active thiopurine nucleotide metabolites, also predisposing to myelosuppression. We provide recommendations for adjusting starting doses of azathioprine, mercaptopurine, and thioguanine based on *TPMT* and *NUDT15* genotypes (updates on www.cpicpgx.org).

https://cpicpgx.org/content/guideline/publication/thiopurines/2018/30447069.pdf

Warfarin

WARF _ **W**isconsin **A**lumni **R**esearch **F**oundation



Poison

rodenticide

Clinical Drug

anticoagulant 1954

Warfarin Metabolism

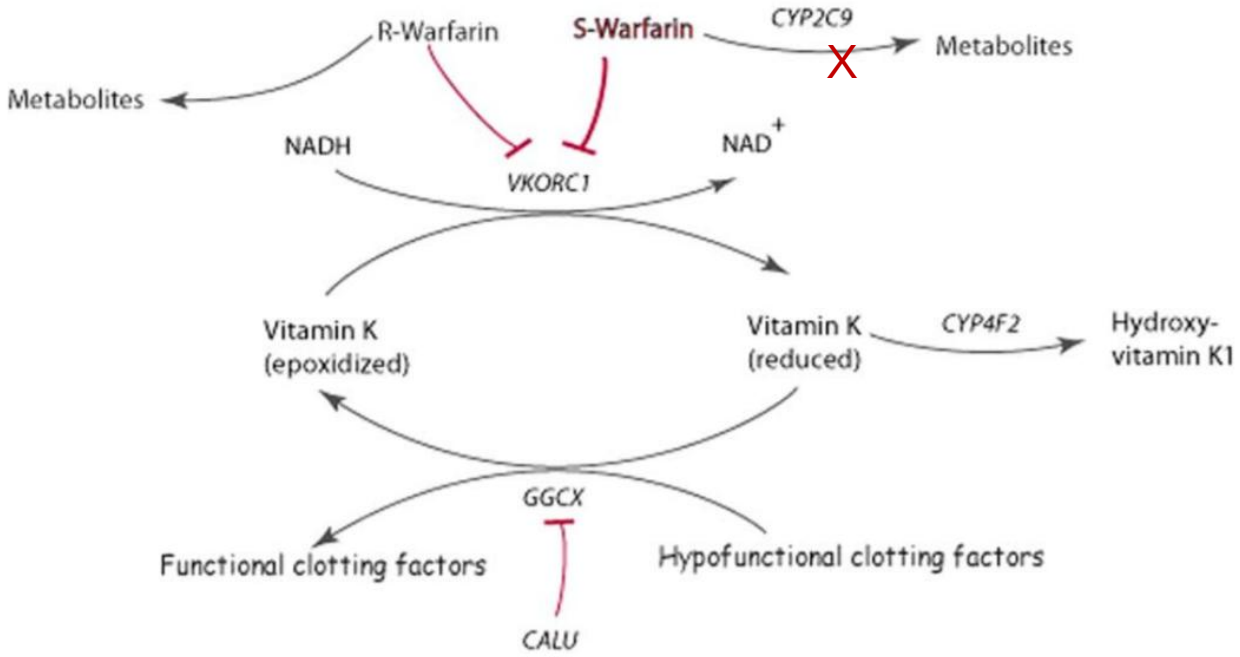


Figure 1 Schematic representation of warfarin metabolism and its mechanism of action. Warfarin is administered via a racemic mixture of the *R*- and *S*-stereoisomers. *S*-warfarin is 3–5 times more potent than *R*-warfarin and is metabolized predominantly to 7- and 6-hydroxyl metabolites via CYP2C9. Warfarin exerts its anticoagulant effect through inhibition of its molecular target VKORC1, which in turn limits availability of reduced vitamin K, leading to decreased formation of functionally active clotting factors. These clotting factors are glycoproteins that are posttranslationally carboxylated by gamma-glutamyl carboxylase (GGCX) to Gla-containing proteins. The endoplasmic reticulum chaperone protein calumenin (CALU) can bind to and inhibit GGCX activity. The metabolism of reduced vitamin K to hydroxyvitamin K1 is catalyzed by CYP4F2, which removes vitamin K from the vitamin K cycle (adapted from warfarin pharmacokinetics (PK) and pharmacodynamics (PD) pathways at PharmGKB, http://www.pharmgkb.org/do/serve?objId=PA451906&objCls=Drug#tabview=tab4).

Warfarin

		CYP2C9					
		*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
VKORC1	G/G	Normal responders 25.7% (n = 1016)	Normal responders 7.1% (n=282)	Sensitive responders 4.4% (n=174)	Sensitive responders 0.6% (n=22)	Sensitive responders 0.7% (n=27)	Highly sensitive responders 0.3% (n=10)
	G/A	Normal responders 29.3% (n=1161)	Sensitive responders 8.6% (n=339)	Sensitive responders 4.4% (n=174)	Sensitive responders 0.6% (n=24)	Highly sensitive responders 0.6% (n=25)	Highly sensitive responders 0.2% (n=9)
	A/A	Sensitive responders 12.2% (n=481)	Sensitive responders 3.2% (n=125)	Highly sensitive responders 1.6% (n=63)	Highly sensitive responders 0.3% (n=12)	Highly sensitive responders 0.2% (n=7)	Highly sensitive responders 0.1% (n=5)

Patients were divided into three warfarin sensitivity types on the basis of the *VKORC1* and *CYP2C9* genotypes

https://heart.bmj.com/content/103/22/1800

Clopidogrel metabolism

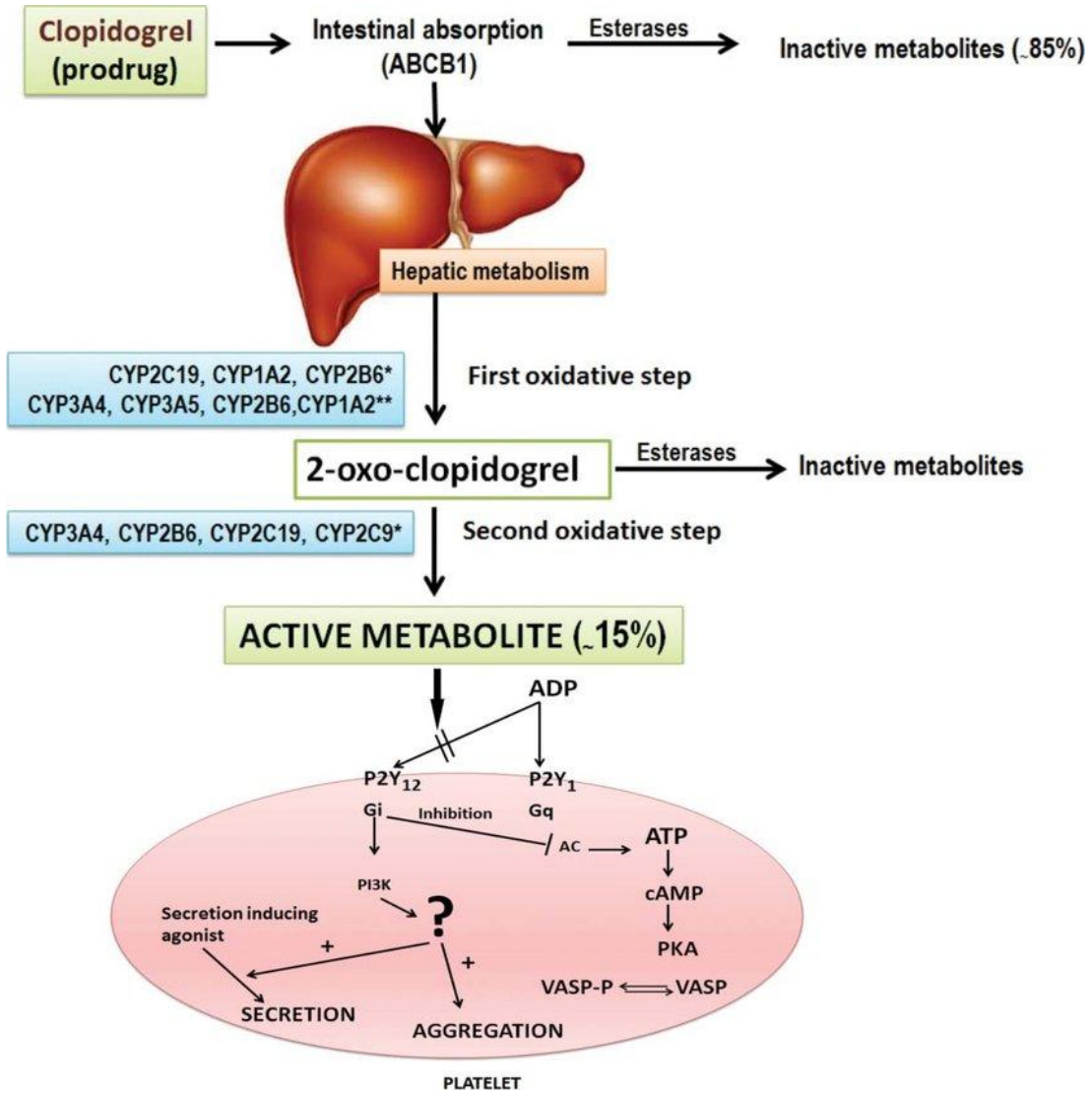
Clopidogrel, binds specifically and irreversibly to the **platelet** P2RY12 purinergic **receptor**, **inhibiting ADP-mediated platelet activation and aggregation**

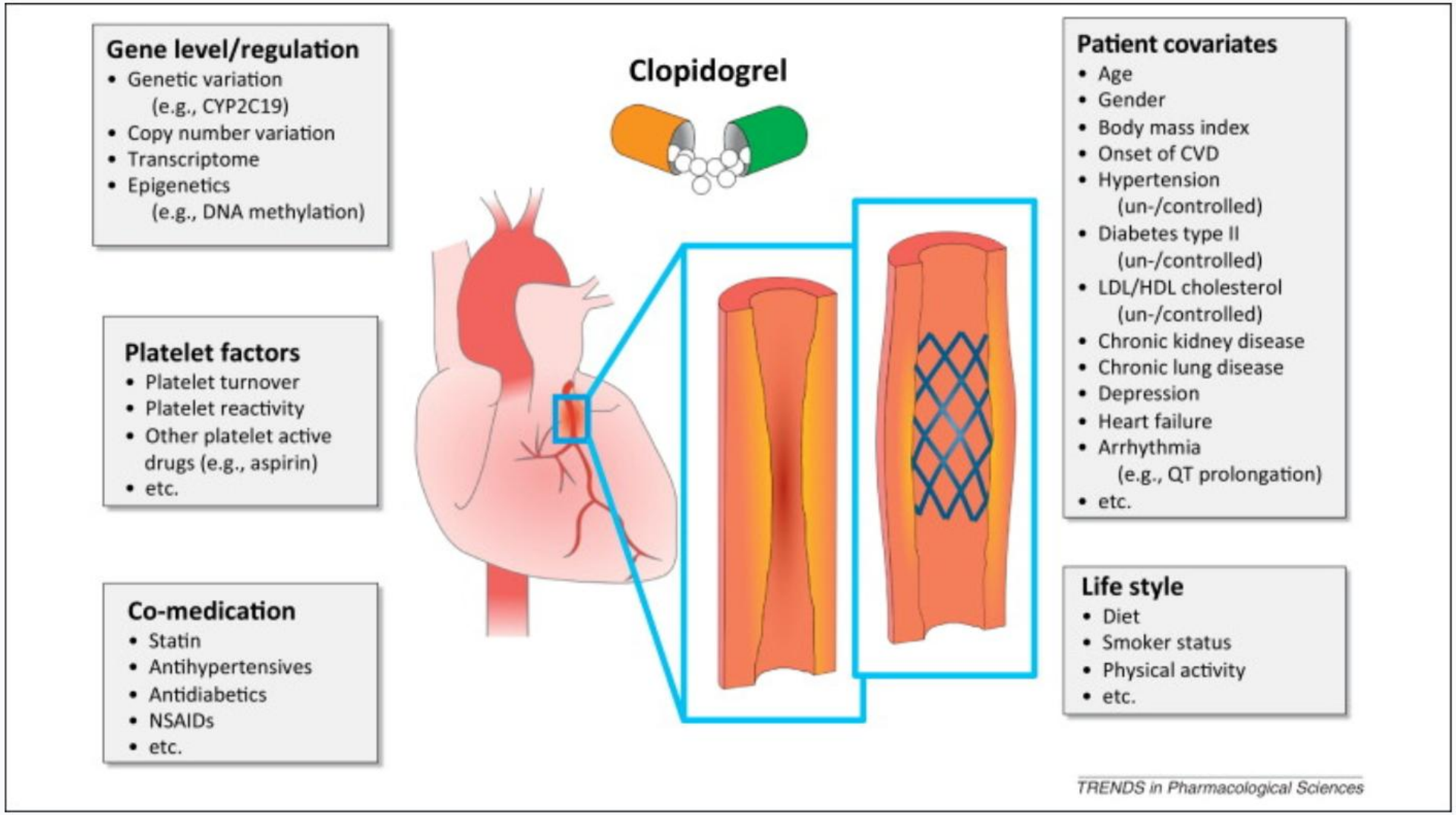
Clopidogrel is a **prodrug** that is absorbed in the intestine and activated in the l**iver**.

The conversion of clopidogrel to its active metabolite requires **two sequential oxidative steps**. 1st leads to formation of 2-oxo-clopidogrel, followed by the conversion of 2-oxo-clopidogrel to the active metabolite.

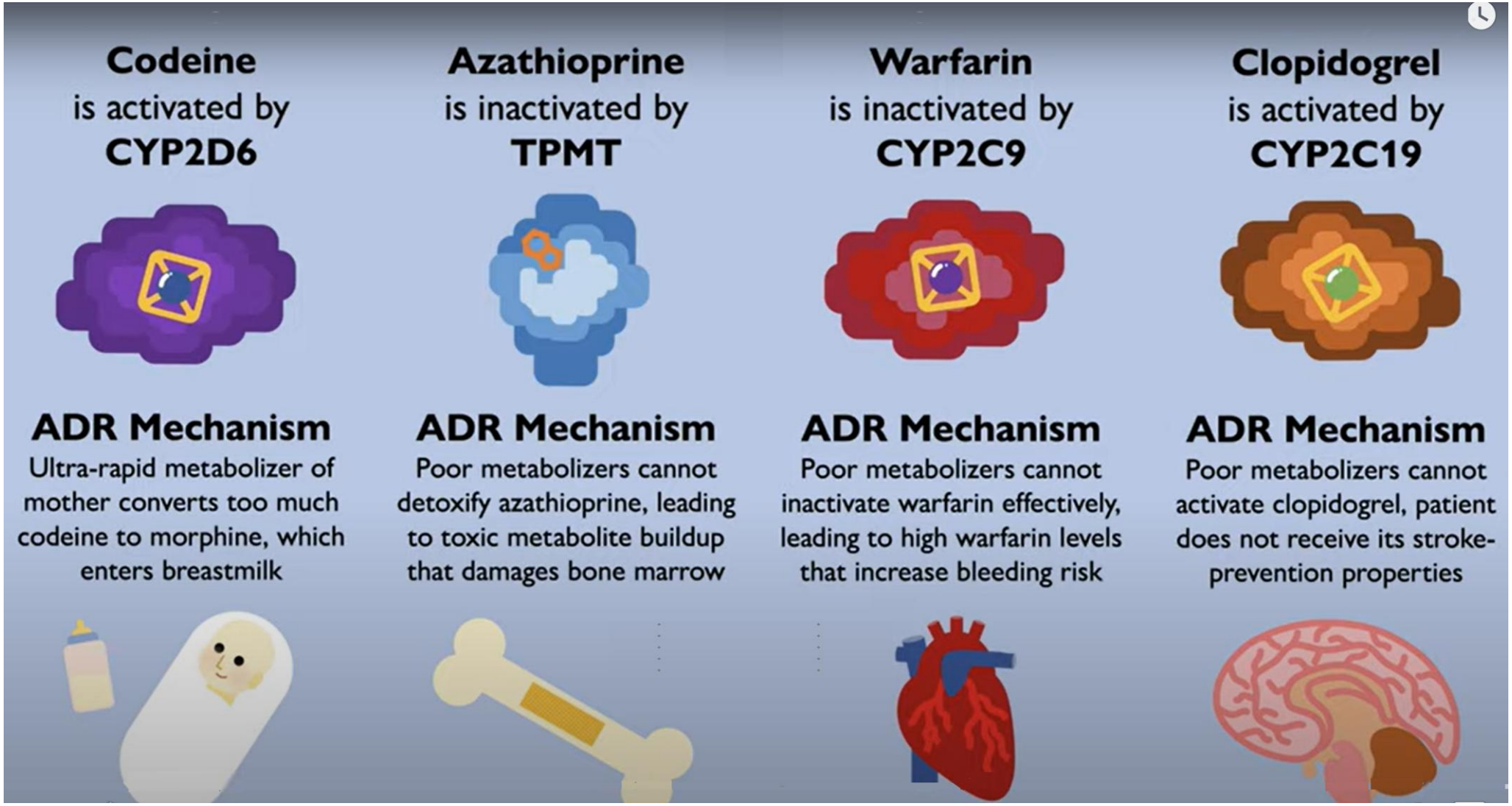
CYP2C19 is one of the hepatic cytochrome P450 enzymes involved in the formation of clopidogrel's active metabolite. Genetic polymorphisms of ***CYP2C19*** are associated **with impaired clopidogrel metabolism**

This **poor metabolizer phenotype** has also been

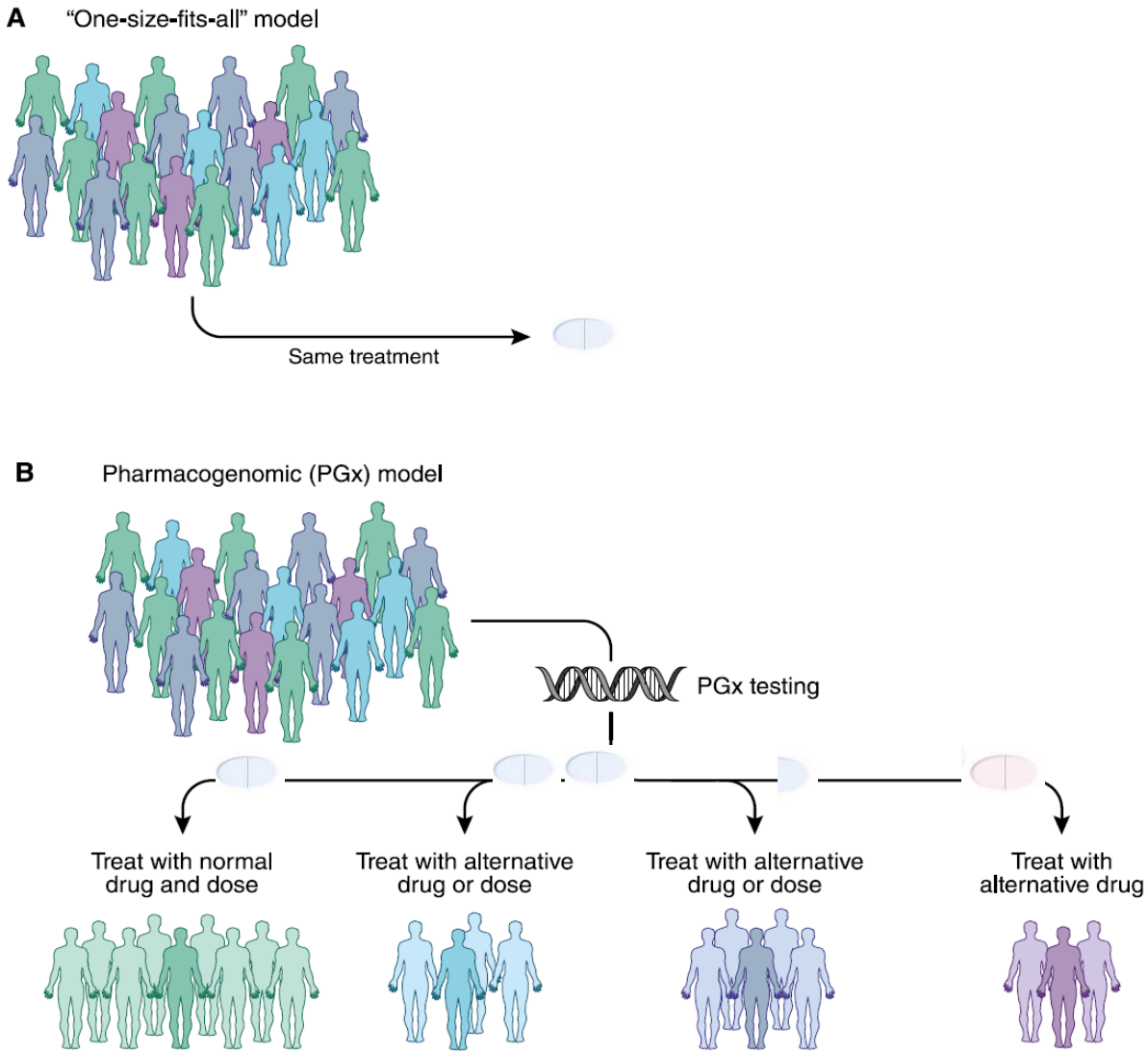



Gene level/regulation
• Genetic variation (e.g., CYP2C19)
• Copy number variation
• Transcriptome
• Epigenetics (e.g., DNA methylation)
Platelet factors
• Platelet turnover
• Platelet reactivity
• Other platelet active drugs (e.g., aspirin)
• etc.
Co-medication
• Statin
• Antihypertensives
• Antidiabetics
• NSAIDs
• etc.
Clopidogrel
Patient covariates
• Age
• Gender
• Body mass index
• Onset of CVD
• Hypertension (un-/controlled)
• Diabetes type II (un-/controlled)
• LDL/HDL cholesterol (un-/controlled)
• Chronic kidney disease
• Chronic lung disease
• Depression
• Heart failure
• Arrhythmia (e.g., QT prolongation)
• etc.
Life style
• Diet
• Smoker status
• Physical activity
• etc.
TRENDS in Pharmacological Sciences

Type A Adverse drug Reactions



What can be done ?



When to performe a PGx test ?

- When there is a specific guideline or recommendation from regulatory organisations (EMA / FDA) Ex: DPYD
- When the patient had a severe adverse drug reaction (ADR) or complication and there is a possibility that it is related with the treatment
- When there is a family history of ADR or known PGX variant that justifies the study
- When there is a need of adjusting dose (because the patient is not sensitive to the medication, the standard dose did not relieve the symptoms, or the patient presented exaggerated response to medication)
- To improve patients compliance of the treatment
- When patients had a past of several depression treatments failure
- When a preemptive PGx testing is available


Dave Simonds

TYPE B IDIOSYNCRATIC OR IMMUNOLOGIC ADVERSE DRUG REACTIONS

- Immunologic-mediated ADRs are included in Type B (not related to the dose, uncommon and unpredictable)
- They have an immune pathogenesis associated including Stevens–Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) (variants of the same condition).
- SJS/TEN is a rare but severe, and potentially fatal skin reaction. SJS patients show multifocal cutaneous and mucocutaneous erosive-ulcerative lesions and skin detachment.
- SJS/TEN are medical emergencies and an early diagnosis and appropriate management is crucial for patients survival.

- SJS/TEN is considered a delayed-type hypersensitivity reaction to drugs.
- SJS affects people from all etnicities, it is slightly more frequent in females than in and can occur at any age.
- Estimated prevalence at 1–2/million each year for SJS, and 0.4–1.2/million each year for TEN.
- More than 200 medications have been reported in association with SJS/TEN.
- There is a very strong genetic associations between some type B ADRs clinical presentations and individual HLA genetic loci within the major histocompatibility complex region on chromosome 6.

Examples of Type B reactions and Genetic Biomarkers

System	ADR	Causal drug	Indication	Associated genetic variant
Skin	Hypersensitivity **SJS / TEM/ DRESS/ maculopapular exanthem**	Carbamazepine	Epilepsy	*HLA-B*15:02* (Han Chinese)
		Phenytoin		*HLA-A*31:01* (Caucasian/Japanese)
				*HLA-B*15:02* (Han Chinese)
		Allopurinol	Gout	*HLA-B*58:01*
		Nevirapine	HIV	*HLA-C*04:01*
				*HLA-B*35:05* (Thai)
				*HLA-DRB1*01:01*
		Abacavir	HIV	*HLA-B*57:01*
Gastrointestinal	Hepatotoxicity **DILI**	Flucloxacillin	Gram +ve bacterial infection	*HLA-B*57:01*
		Co-amoxiclav	Bacterial infection	*HLA-A*02:01, DRB1*15:01-DQB1*06:02*
		Nevirapine	HIV	*HLA-DRB1:01:01*
		Minocycline	Bacterial infection	*HLA-B*35:02*
		Lapatinib	Breast cancer	*HLA-DQA1*02:01/HLA-DRB1*07:01*
	Pancreatitis	Azathioprine	Rheumatoid arthritis, Crohn's disease	*HLA-DRB1, HLA-DQB1*
Renal	Nephrotoxicity	5-aminosalicylic acid	Inflammatory bowel disease	*HLA-DRB1*03:01*
Hematological	Agranulocytosis	Clozapine	Schizophrenia	*HLA-B/HLA-DQB1*
		Sulfasalazine	Inflammatory joint/ bowel disease	*HLA-B*08:01, HLA-A*31:01*
		Antithyroid drugs	Hyperthyroidism	*HLA-B*27:05* (Caucasian)
				*HLA-B*38:02, HLA-DRB1*08:03* (Han Chinese)
				*DRB1*08032* (Japanese)
Musculoskeletal	Necrotizing autoimmune myopathy	Statins	Hypercholesterolemia	*HLA-DRB1*11:01*

Biomarkers of adverse drug reactions (2018) https://pubmed.ncbi.nlm.nih.gov/28950720/

Recommendations on HLA genotyping and drug hypersensitivity

1. ABACAVIR	***B*57:01***	FDA	All patients should be screened for the ***HLA-B*57:01*** allele prior to initiating therapy with abacavir or reinitiation of therapy with abacavir, unless patients have a previously documented ***HLA-B*57:01*** allele assessment. Abacavir is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in ***HLA-B*57:01***-positive patients
	B*57:01	EMA	Before initiating treatment with abacavir, screening for carriage of the ***HLA-B*57:01*** allele should be performed in any HIV-infected patient, irrespective of racial origin. Abacavir should not be used in patients known to carry the ***HLA-B*57:01*** allele
	B*57:01	CPIC	***HLA-B*57:01*** screening should be performed in all abacavir-naive individuals before initiation of abacavir-containing therapy. In abacavir-naive individuals who are ***HLA-B*57:01***-positive, abacavir is not recommended and should be considered only under exceptional circumstances when the potential benefit, based on resistance patterns and treatment history, outweighs the risk
2.ALLOPURINOL	***B*58:01***	EMA	The use of genotyping as a screening tool to make decisions about treatment with allopurinol has not been established. Routine testing for ***HLA-B*5801*** is not recommended in any patient. If the patient is a known carrier of ***HLA-B*58:01***, the use of allopurinol may be considered if the benefits are thought to exceed risks. Extra vigilance for signs of hypersensitivity syndrome or SJS/TEN is required, and the patient should be informed of the need to stop treatment immediately at the first appearance of symptoms
	B*58:01	CPIC	Allopurinol is contraindicated in patients who are carriers of ***HLA-B*5801*** (***HLA-B*5801/*X***, ***HLA-B*5801/HLA-B*5801***)
3. CARBAMAZEPINE	***B*15:02***	FDA	Prior to initiating carbamazepine therapy, testing for ***HLA-B*15:02*** should be performed in patients with ancestry in populations in which ***HLA-B*1502*** may be present. Carbamazepine should not be used in patients positive for ***HLA-B*15:02*** unless the benefits clearly outweigh the risks
	A*31:01	FDA	The risks and benefits of Tegretol therapy should be weighed before considering administering Tegretol in patients known to be positive for ***HLA-A*31:01***
	B*15:02	EMA	Individuals of Han Chinese and Thai origin should, whenever possible, be tested for the ***HLA-B*15:02*** allele prior to treatment with carbamazepine. Testing for the ***HLA-B*15:02*** allele in other Asian populations at genetic risk may be considered
	A*31:01	EMA	Routine testing for the ***HLA-A*31:01*** allele is not recommended. If European Caucasians or patients of Japanese descent are known to be positive for the ***HLA-A*31:01*** allele, the use of carbamazepine may be considered if the benefits are thought to exceed the risks
	B*15:02	CPIC	Regardless of the individual's ancestry or age, if the genetic testing results are "positive" for the presence of at least one copy of the ***HLA-B*15:02*** allele, it is recommended that a different agent be employed depending on the underlying disease, unless the benefits clearly outweigh the risk
4. PHENYTOIN	***B*15:02***	FDA	Consideration should be given to avoid phenytoin as an alternative for carbamazepine in patients positive for ***HLA-B*15:02***
	B*15:02	CPIC	Regardless of the ***CYP2C9*** genotype and individual's ancestry or age, if the ***HLA-B*15:02*** test result is "positive", the recommendation is to consider administering an anticonvulsant other than carbamazepine and phenytoin unless the benefits of treating the underlying disease clearly outweigh the risks. Alternative medications such as oxcarbazepine, eslicarbazepine acetate and lamotrigine have some evidence linking SJS/TEN with the ***HLA-B*15:02*** allele; thus, caution should be exercised in choosing alternatives to phenytoin

Vancomycin induced DRESS

- DRESS = **D**rug **R**eaction with **E**osinophilia and **S**ystemic **S**ymptoms syndrome was first named in 1996.
- DRESS syndrome is a rare ADR characterised by a severe skin reaction, fever, eosinophilia, or other haematological abnormalities and involvement of other organs mainly the liver.
- There is a delayed onset. Symptoms appear 2–6 weeks after the begining otreatment with the causative drug In past it was associated to a high mortality rate due to visceral organ involvement although nowadays it is much lower around 1-2%.
- Estimated incidence: between 1 in 1000 and 1 in 10,000 exposures

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HLA-A*32:01 is strongly associated with vancomycin-induced drug reaction with eosinophilia and systemic symptoms

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ADR-PREVENT

Collaboration project involving INSA – INFARMED and several hospitals , for the study of Adverse Drug Reactions that occur in the Portuguese population. Includes: Risk factors, pharmacogenomics and predictive models for prevention

What we are planning to do

1. Identification of most frequent ADRs, classification by clinical use, groups, by demographic categories, by level of ADR severity and by type of reaction (depending on the physiological system affected);
2. Establishment of a national biobank of ADR patient samples associated with the National Pharmacovigilance System (SNF);
3. Definition of panel for testing genetic variants associated with risk of ADR;
4. Identification of variants associated with ADR in the study population;
5. Development of predictive risk algorithms for ADR, including anthropometric, clinical and genetic susceptibility, using datamining approaches.

Precision medicine in 2030— seven ways to transform healthcare

	Where we are today	Where we will be in 2030
Clinical applications		
Genomics for disease	Primarily limited to rare disease and select cancers.	Genomics is routine. Genetic causes and targeted therapies are discovered for many “common” diseases. Microbiome measures are routinely included.
Pharmacogenomics (PGx)	Common in cancer and within select applications of older medications at select sites.	Genome-aware EHRs make PGx easy and automatically update rules from central guidelines. New PGx associations discovered from clinical data.
Genomics for healthy individuals	In research, whole-genome sequencing and search for mutations in one of the ACMG59 genes, present in about 3% of people. Variant interpretation is hard.	ACMG59 grows to > 200, variant interpretation improved by huge, diverse sequenced populations. Cell-free DNA becomes a mainstay of cancer screening
EHRs	Episodic capture from healthcare without robust genomics support. EHR data is essentially not portable.	Genome- and device- enabled. Data can be easily moved between EHRs and to participant apps.
Environmental influences on health	Patient-reported habits and exposures	Geocode-based exposure linkage Real time monitoring of multiple environmental exposures Precision nutrition

Denny JC, Collins FS. Precision medicine in 2030-seven ways to transform healthcare. Cell. 2021 Mar 18;184(6):1415-1419.. PMID: 33740447

"I've been taking this medication for 45 years and the side effects turned me into an old man!"

Thank you!