Pharmacogenetics and Pharmacogenomics

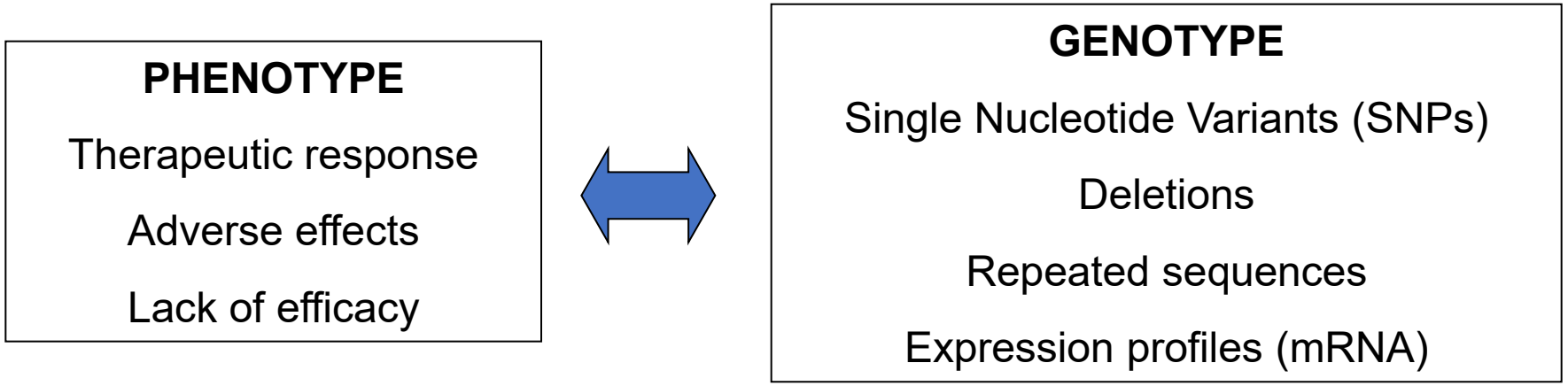
Pharmacogenetics and pharmacogenomics are related fields that study how an individual's genetic profile influences their response to medications.

While they're often used interchangeably, **pharmacogenetics** generally focuses on the impact of individual genes on drug response, while **pharmacogenomics** considers the broader context of the entire genome.

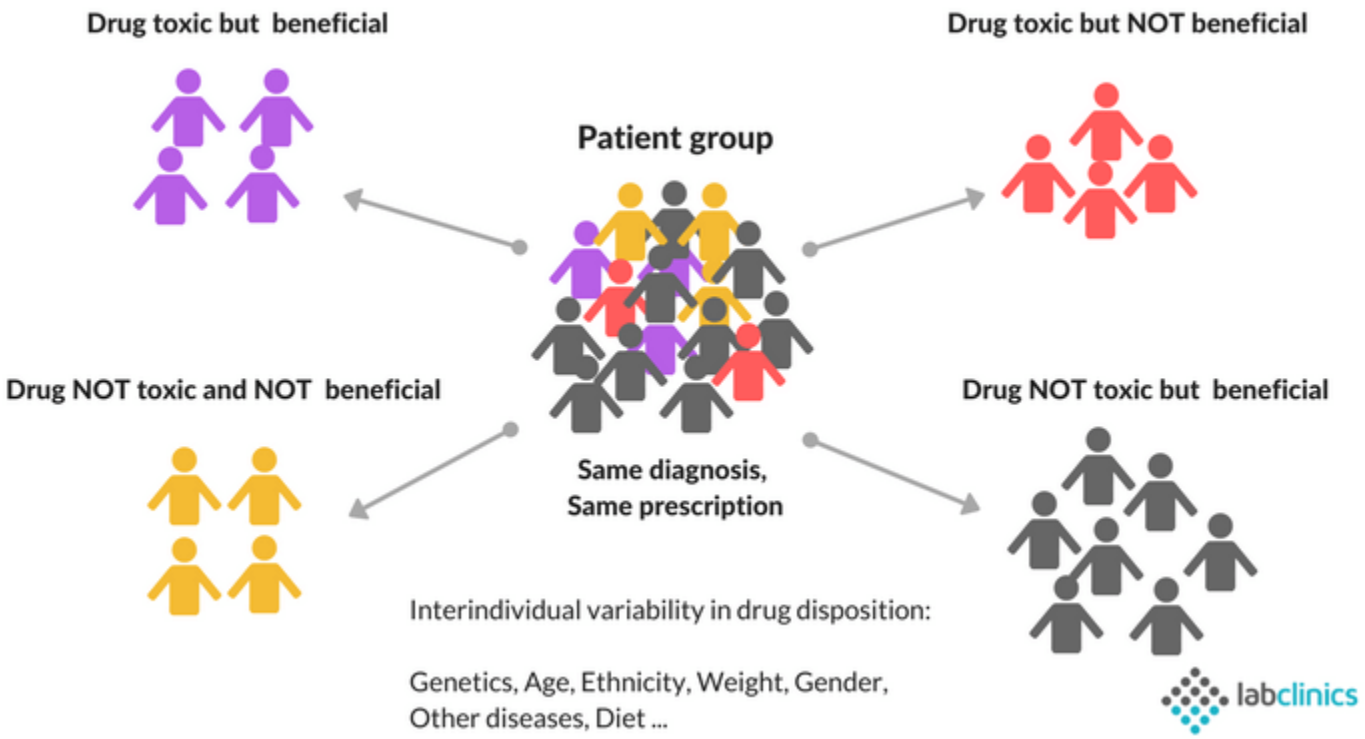
Both fields contribute to personalized medicine by helping to tailor drug treatments to individual genetic profiles, potentially leading to safer and more effective therapies.

AIMS of pharmacogenetic research

- to associate a specific PHENOTYPE (therapeutic response, adverse drug effects, inefficacy, resistance) with one particular GENOTYPE

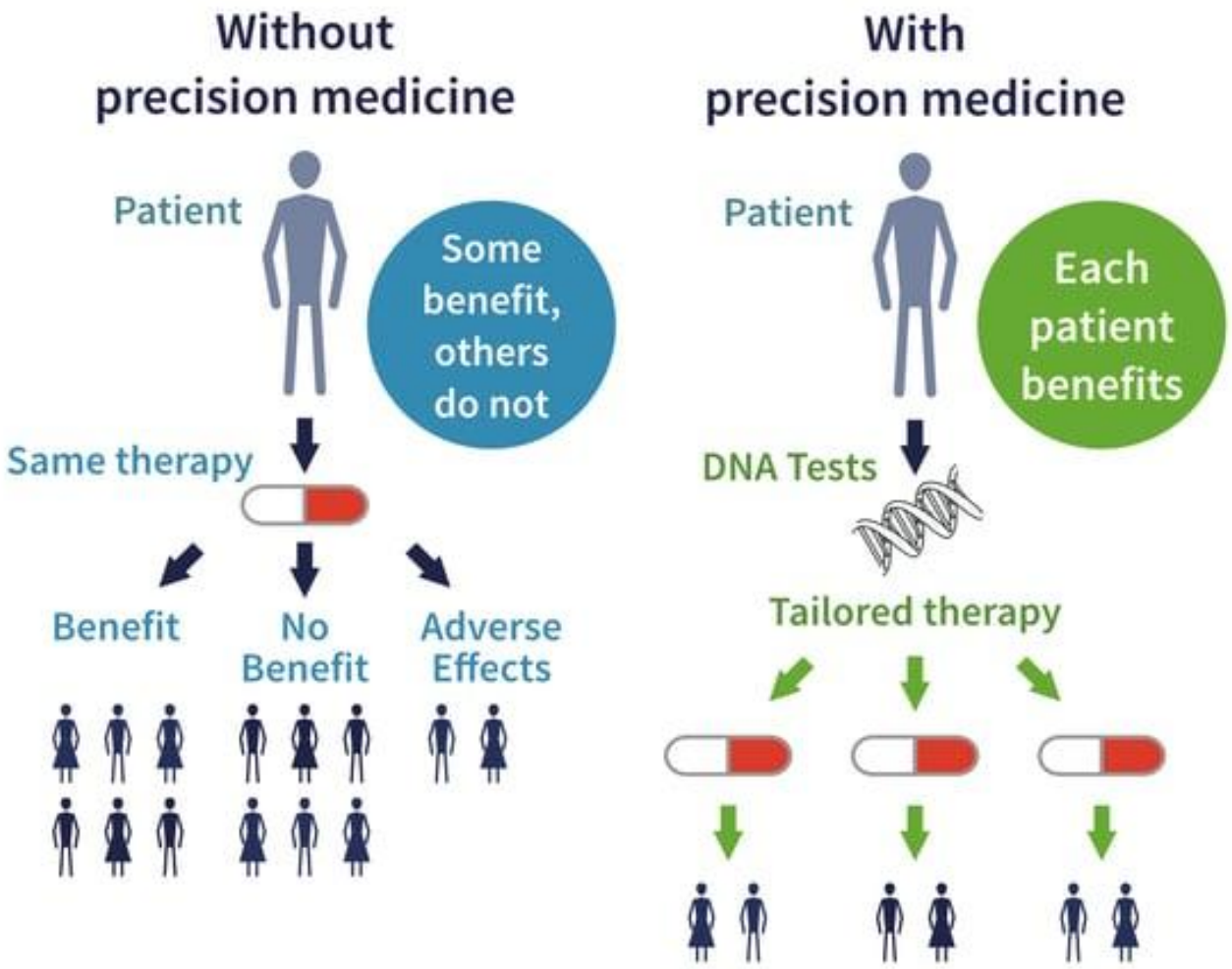


Interindividual variability in drug response



- Therapeutic effect
- Therapeutic failure
- Adverse reactions

PERSONALIZED MEDICINE: WHY?



ADR: Adverse Drug Reaction

Recently, the new European legislation has modified the **definition of adverse reaction**, now understood as "***Harmful and unintended effect resulting from the use of a medicinal product***" (EU Directive 84/2010) which includes damages from drugs resulting from:

- - Use not in accordance with the indications contained in the marketing authorization (off-label use)
- - Therapeutic errors, including accidental overdose
- - Improper use
- - Abuse of the drug
- - Association with exposure for professional reasons
- -**Lack of efficacy**

Article 1

Amendments to Directive 2001/83/EC

Directive 2001/83/EC is hereby amended as follows:

1. Article 1 is amended as follows:

(a) point 11 is replaced by the following:

'11. Adverse reaction: A response to a medicinal product which is noxious and unintended.';

Classifications of ADRs

- 1958, Wayne: ADRs predictable and unpredictable
- 1973, Levine: ADRs dose dependent and not-dose dependent, acute, subacute and chronic
- Rawlins e Thompson: ADRs type A (Augmented), type B (Bizarre), type C (Chronic), type D (Delayed), type E (End of use) and type F (Failure)
- Aronson e Fermer: three-dimensional classification DoTS, which takes into account for each ADR: Dose-dependence (Do), Time of onset of the reaction (T) and Patient susceptibility (S)

Rawlins e Thompson

(Adverse drug reactions: definitions, diagnosis, and management. Lancet 2000; 356: 1255-9.)

Table 5.1 Extended Rawlins–Thompson classification of adverse drug reactions

Type of reaction	Features	Examples
Type A: Augmented pharmacological effect	Common Predictable effect Dose-dependent Low morbidity Low mortality	Bradycardia associated with a beta-adrenergic receptor antagonist
Type B: Bizarre effects not related to pharmacological effect	Uncommon Unpredictable Not dose-dependent High morbidity High mortality	Anaphylaxis associated with a penicillin antibiotic
Type C: Dose-related and time-related	Uncommon Related to the cumulative dose	Hypothalamic pituitary–adrenal axis suppression by corticosteroids
Type D: Time-related	Uncommon Usually dose-related Occurs or becomes apparent some time after use of the drug	Carcinogenesis
Type E: Withdrawal	Uncommon Occurs soon after withdrawal of the drug	Opiate withdrawal syndrome
Type F: Unexpected failure of therapy	Common Dose-related Often cause by drug interactions	Failure of oral contraceptive in presence of enzyme inducer

- **Predictable (dose-dependent)**
- **Impredictable (not dose-dependent)**

Da: https://www.farmacovigilanzasif.org/

idiosyncrasy – farmacogenetic ADRs

Idiosyncrasy is an unusual, dangerous and sometimes lethal adverse reaction to a drug that:

- is due to genetic causes (e.g. altered or absent enzymes) and does not result from an immune system response
- unlike allergy, does not require sensitization for a first exposure to a substance
- the manifestations are different from drug to drug and often repeat the effects of overdose

Idiosincrasy	Allergy
Present at birth	It can occur in any period of life (>25-40 years old)
does not require sensitization	Requires sensitisation, even cross-sensitivity
It is related to the individual genetic characteristic	The level of antigens is important for the sensibilization
Symptoms are dose-dependent	Symptoms are not dose-dependent
Symptoms are drug-specific and similar to over dose	Symptoms are uniform
The drugs responsible are not similar to the antigens	The drugs responsible are similar to the antigens
Antagonists can be used	Standard drugs (adrenaline, cortison, antiistaminc) can be used

Lack of response to medications

Table 1. Response rates of patients to a major drug for a selected group of therapeutic areas[1]

Therapeutic area	Efficacy rate (%)
Alzheimer's	30
Analgesics (Cox-2)	80
Asthma	60
Cardiac Arrythmias	60
Depression (SSRI)	62
Diabetes	57
HCV	47
Incontinence	40
Migraine (acute)	52
Migraine (prophylaxis)	50
Oncology	25
Osteoporosis	48
Rheumatoid arthritis	50
Schizophrenia	60

Spear, B.B., Heath-Chiozzi, M., & Huff, J. (2001).
Clinical application of pharmacogenetics. TRENDS in Molecular Medicine, 7(5), 201-204.

- **The 20-40% of patients does not respond to antidepressant**
- **The 40% of patients is resistent to anti-anti-asthmatics drugs**
- **The 30% of patients does not repsond to antiulcer drugs**
- **The 28 % of patients does not respond to ipolipidemic drugs**

Come segnalare una reazione avversa

Le segnalazioni di sospette reazioni avverse (ADR, Adverse Drug Reaction in inglese) da farmaci e da vaccini consentono di rilevare potenziali segnali di allarme relativi all'uso dei medicinali così da renderli più sicuri, a beneficio di tutti i pazienti.

La normativa europea sulla farmacovigilanza richiede a tutti gli operatori sanitari e ai cittadini di segnalare qualsiasi sospetta *reazione avversa* (grave e non grave, nota e non nota).

Una sospetta reazione avversa può essere segnalata secondo una delle seguenti modalità:

- compilando la scheda di segnalazione e inviandola via e-mail al **Responsabile di farmacovigilanza** della propria struttura di appartenenza, *oppure* al **Titolare dell'Autorizzazione all'Immissione in Commercio (AIC)** del medicinale che si sospetta abbia causato la *reazione avversa*.
- direttamente on-line sul sito AIFA

Per le sospette reazioni avverse che si verificano dopo l'assunzione di integratori alimentari, prodotti erboristici, preparazioni magistrali (per esempio a base di cannabis per uso medico), medicinali omeopatici (non registrati come medicinali) e altri prodotti di origine naturale, la segnalazione può essere effettuata attraverso il sistema online di fitovigilanza VigiErbe (www.vigierbe.it).

Segnala online una reazione avversa a farmaci e/o vaccini

Link correlati

Moduli di segnalazione di reazioni avverse >

Responsabili di farmacovigilanza >

Normativa sulla farmacovigilanza >

Segnala online su VigiErbe (sistema di fitovigilanza)

Sicurezza dei farmaci >

Farmacovigilanza >
La Rete Nazionale di Farmacovigilanza (RNF) >
Come segnalare una reazione avversa >
Responsabili di farmacovigilanza >
Sistema europeo Eudravigilance >
Accesso alle segnalazioni - ADRreports >
Fondi regionali >
Segnali di sicurezza >
Misure di gestione del rischio >
Monitoraggio addizionale >

Condividi

Sono un operatore sanitario

Sono un operatore sanitario (medico ospedaliero, medico specialista, medico di medicina generale, farmacista, infermiere, etc.) e voglio segnalare i disturbi che io o i miei pazienti abbiamo avuto in seguito all'assunzione di medicinali.

Sono un cittadino

Sono un cittadino e voglio segnalare i disturbi che io, i miei famigliari o i miei conoscenti abbiamo avuto in seguito all'assunzione di medicinali.

Come segnalare una reazione avversa

Le segnalazioni di sospette reazioni avverse (ADR, Adverse Drug Reaction in inglese) da farmaci e da vaccini consentono di rilevare potenziali segnali di allarme relativi all'uso dei medicinali così da renderli più sicuri, a beneficio di tutti i pazienti.

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Segnala online una reazione avversa a farmaci e/o vaccini

Link correlati

Moduli di segnalazione di reazioni avverse >

Responsabili di farmacovigilanza >

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Misure di gestione del rischio >
Monitoraggio addizionale >

Condividi

Normativa di Farmacovigilanza

Il **Regolamento europeo 1235/2010** sulla farmacovigilanza ha introdotto strumenti e procedure per migliorare l'efficacia del monitoraggio della sicurezza dei farmaci e il loro uso razionale. Inoltre, ha promosso la trasparenza del processo decisionale e definito modalità per aumentare la partecipazione dei cittadini. Tali modifiche hanno avuto un notevole impatto sui ruoli e sulle responsabilità di tutti i soggetti coinvolti nella farmacovigilanza: le agenzie regolatorie, l'industria farmaceutica, gli operatori sanitari e i cittadini.

Le **Direttive del Parlamento europeo e del Consiglio 2010/84/UE del 21 luglio 2012 e 2012/26/UE del 25 ottobre 2012**, che modificano, per quanto riguarda la farmacovigilanza, la direttiva 2001/83/CE sui medicinali per uso umano, hanno rafforzato il quadro giuridico per la sorveglianza dei medicinali nell'Unione Europea rendendolo più robusto per garantire una maggiore sicurezza dei pazienti e una miglior tutela della salute pubblica.

All'interno dell'EMA opera il "Comitato di valutazione dei rischi per la farmacovigilanza" (PRAC) in cui sono rappresentati tutti gli Stati membri. Il PRAC si occupa di tutti gli aspetti della gestione dei rischi derivanti dall'utilizzo dei medicinali per uso umano, tra cui l'individuazione, la valutazione, la riduzione e la comunicazione del rischio di reazione avverse. Il PRAC fornisce raccomandazioni al Comitato per i Medicinali per Uso Umano (CHMP) e al Gruppo di Coordinamento (CMDh) su qualsiasi situazione emergente in farmacovigilanza e in relazione ai sistemi di gestione dei rischi, monitorandone l'efficacia.

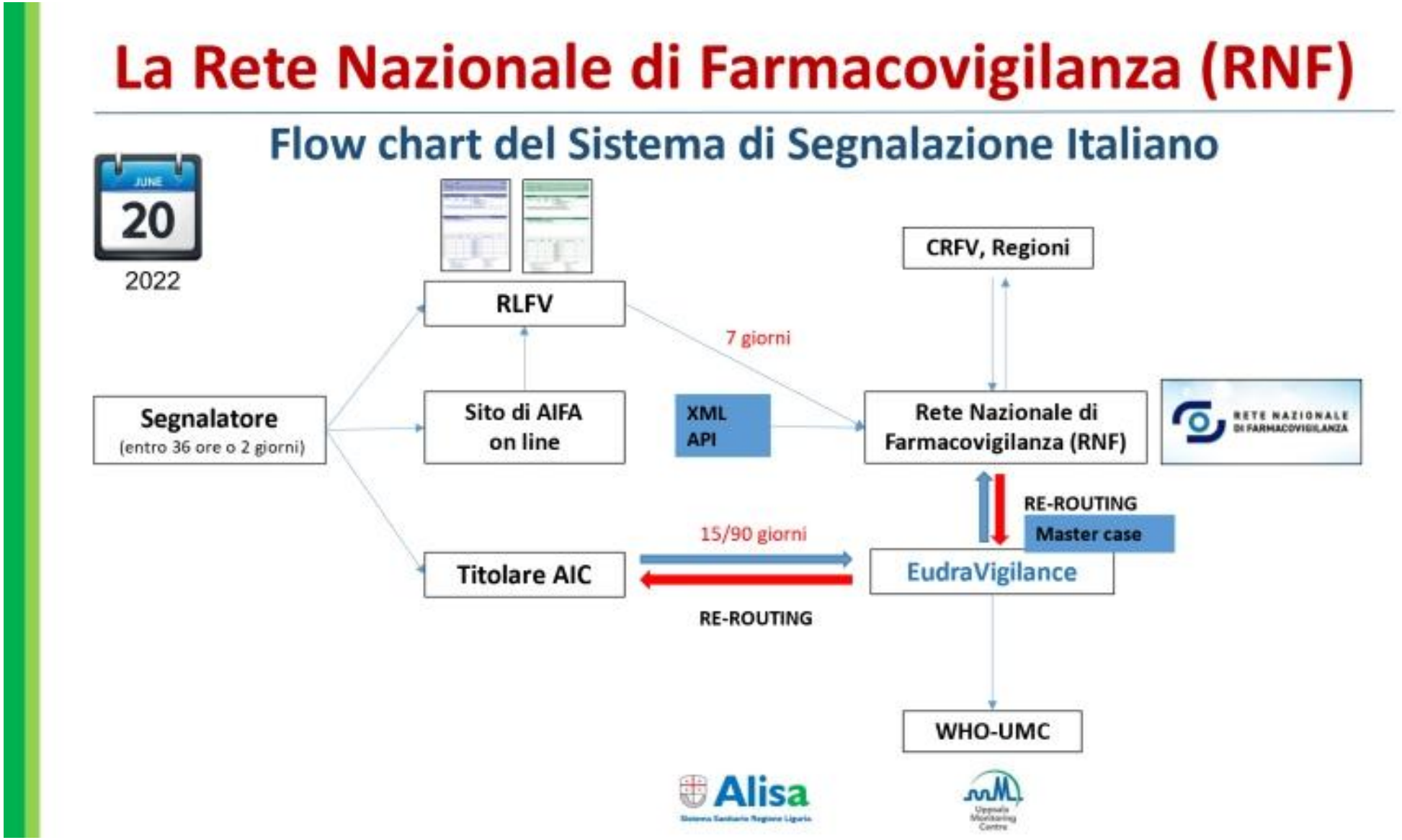
La normativa oggi in vigore definisce "reazione avversa" "ogni effetto nocivo e non voluto conseguente all'uso di un medicinale". Di fatto, con tale definizione sono oggetto di segnalazione anche le reazioni avverse derivanti da errore terapeutico, abuso, misuso, uso off label, sovradosaggio ed esposizione professionale*.

Tutte le segnalazioni di reazioni avverse confluiscono nel database europeo Eudravigilance e sono accessibili al pubblico in forma di dati aggregati https://www.adrreports.eu/vet/it/index.html. La normativa di farmacovigilanza prevede la possibilità di imporre ai titolari dell'Autorizzazione all'Immissione in Commercio (AIC), al momento della concessione della stessa o successivamente, di condurre ulteriori studi sulla sicurezza e/o sull'efficacia del farmaco, ad esempio per fornire rassicurazioni sull'assenza di problemi di sicurezza relativi a una specifica reazione avversa o per studiare l'uso del farmaco in pazienti che non sono stati inclusi negli studi clinici (studio di sicurezza post-autorizzazione PASS).

La legislazione fornisce disposizioni anche su procedure e/o tematiche specifiche inerenti le attività che le aziende farmaceutiche sono chiamate a mettere in atto per essere proattive nell'identificare i rischi non ancora noti associati ai farmaci.

Documenti Correlati

THE ITALIAN PHARMACOVIGILANCE NETWORK



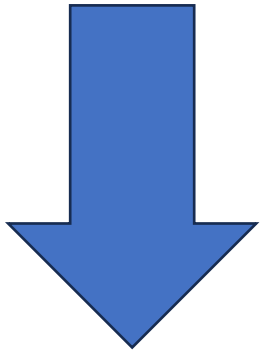
PHARMACOGENETIC TESTs

The most studied genes in order to:

- Predict the therapeutic response or the risk of adverse drug reactions (**pre**-treatment test)
- Interpret the observed adverse reaction (**post**-treatment test)

These genes are:

- metabolism enzymes (CYP, UGT, DPYD, TPMT)
- Cellular transporters useful for drug absorption and elimination (SLC and ABC)



To promote the dissemination of pharmacogenetic tests and their clinical applicability, the **FDA and the Clinical Pharmacogenetics Implementation Consortium (CPIC) have published drug-specific guidelines to indicate which drug to use or at what dose based on pharmacogenetic biomarkers associated with modified responses**.

PHARMACOGENETIC TESTs

Predictive test: before defining therapy, in order to choose the most appropriate drug and dosage in a personalized way, based on the genetic profile.

Reactive test: after the start of therapy, in case of adverse reactions or poor response to the treatment

The predictive test can be particularly useful in selected groups of patients, with certain risk factors or fragile categories such as children, the elderly, pregnant women and subjects with polytherapy.

Tests already in daily clinical practice

Interpreting the tests is complex: it requires knowledge of external confounding factors (tobacco use, alcohol, etc.), specific patient information (age, etc.), ethnicity, genetic profile, etc.

The test result must always be interpreted in a probabilistic way and never in a dichotomous way (all or nothing)

Tabella 12.4 Esempi di test farmacogenetici in uso nella pratica clinica.

Farmaco	Biomarker genetici	Implicazioni cliniche
Abacavir	HLA-B*5701	Aumento del rischio di reazione di ipersensibilità da farmaco
Antidepressivi SSRI e triciclici	CYP2C19*2, *3, *17	Variabilità nella risposta farmacologica in termini sia di efficacia sia di tossicità
	CYP2D6*3, *4, *5, *6, *9, *10, *17, *29, *41, xN	
Atazanavir	UGT1A1*28	Aumento del rischio di iperbilirubinemia nei soggetti omozigoti *28/*28
Carbamazepina e Oxcarbazepina	HLA-B*1502, HLA-A*3101	Aumento del rischio di sindrome di Stevens-Johnson e necrolisi epidermica tossica (SJS/TEN)
Clopidogrel	CYP2C19*2, *3, *17	Ridotta conversione del farmaco in metaboliti attivi (ridotta attività antipiastrinica)
Codeina	CYP2D6*3, *4, *5, *6, *9, *10, *17, *29, *41, xN	Aumento del rischio di tossicità da morfina nei soggetti metabolizzatori ultrarapidi
Fluoropirimidine	DPYD*2A, c.1129-5923C>G, DPYD*13, c.2846A>T, DPYD*6	Aumentato rischio di tossicità ematologica e gastrointestinale (ridotto metabolismo)
Irinotecan	UGT1A1*28	Aumentato rischio di tossicità ematologica nei soggetti omozigoti *28/*28
Statine	SLCO1B1 c.521T>C (rs4149056)	Aumento del rischio di miopatie
	CYP2C9*2, *3	
	ABCG2 c.421C>A (rs2231142)	
Tamoxifene	CYP2D6*3, *4, *5, *6, *9, *10, *17, *29, *41, xN	Ridotta conversione del farmaco in metaboliti attivi (ridotta risposta terapeutica)
Tiopurine	TPMT*2, *3B, *3C, *4	Aumentato rischio di mielosoppressione
	NUDT15 c.415C>T (rs116855232)	
Warfarin	CYP2C9*2, *3	Variabilità nella risposta farmacologica sia in termini di efficacia sia di tossicità
	VKORC1 c.-1639G>A (rs9934438	

Abbreviazione: SSRI, inibitori selettivi della ricaptazione della serotonina.

VORICONAZOLE

- For fungal infections
- Metabolized by CP2C19
- CP2C19 genotyping is recommended to optimize therapy
- Ultra-rapid metabolizers: failure
- Slow metabolizers: toxicity

FLUOROPYRIMIDINES

DPYD gene encodes dihydropyrimidine dehydrogenase (DPD), for catabolism of fluoropyrimidines

- Reduced activity for non-functional variants: DPYD*24, *13, rs67376798, HapB3
- Genotyping
- Guidelines suggest a 50% reduction in the initial dose in subjects with one non-functional allele or an alternative drug for individuals with two non-functional alleles

TAMOXIFEN

- Metabolized by CYP2D6 to more potent metabolites
- Variants cause significant reductions in concentrations: therapeutic failure
- Guidelines: alternative drug in patients with one or two non-functional variants, or a dosage increase associated with monitoring of the main metabolite endoxifen

STATINS

- SLCO1B1 gene encodes the OATP1B1 transport protein for statin uptake.
- Variants reduce the functionality and plasma clearance of simvastatin, with increased myopathy
- Not observed for other statins
- Guidelines: simvastatin dose reduction or use of other statins for which the association with the SLCO1B1 genotype is not evidenced

PLoS Med . 2025 Mar 27;22(3):e1004565. doi: 10.1371/journal.pmed.1004565

PLOS MEDICINE

RESEARCH ARTICLE

Pharmacogenetics and adverse drug reports: Insights from a United Kingdom national pharmacovigilance database

Emma F. Magavern[1*‡], Maia Megase[1‡], Jack Thompson[2], Gabriel Marengo[1], Julius Jacobsen[1], Damian Smedley[1], Mark J. Caulfield[1]

1 William Harvey Research Institute, Queen Mary University of London, London, United Kingdom
2 Department of Clinical Toxicology and General Medicine, St Thomas' Hospital, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

‡ These authors are joint first authors on this work.
* e.magavern@qmul.ac.uk

Abstract

Abstract

Background

Adverse drug reactions (ADRs) harm patients and are costly for healthcare systems. Genetic variation contributes to variability in medication response and prospective knowledge of these variants can decrease risk of ADRs, as shown in the PREPARE trial. Reduction in ADRs would affect only those reactions to drugs contained in well-validated pharmacogene–drug pairs. The scope of ADRs represented by these drugs on a population scale is unclear. The objective of this study was to characterize the pharmacogene–drug-associated ADR reporting landscape from a national regulatory pharmacovigilance dataset to elucidate the scale of potential ADR mitigation by pharmacogenomics (PGx) implementation.

There were 1,345,712 ADR reports, attributed to 2,499 different substances. 115,789 adverse drug reports (9%) were associated with drugs for which ADR risk can be modified based on pharmacogenomic prescribing guidance. Seventy-five percent of these (*n* = 87,339) were due to medicines which interact with only three pharmacokinetic pharmacogenes (*CYP2C19*, *CYP2D6*, *SLCO1B1*). Forty-seven percent of all the PGx mitigatable ADRs identified were attributed to psychiatric medications (*n* = 54,846), followed by 24% attributed to cardiovascular medications (*n* = 28,279). Those experiencing PGx mitigatable ADRs, as compared with non-PGx mitigatable ADRs, were older and the ADRs more often consisted of severe non-fatal reactions. Many PGx-associated psychiatric drug ADRs were overrepresented as compared with prescribing prevalence, but fatal cardiac arrhythmias were uncommon consequences, comprising only 0.4% of these ADRs (*n* = 172 of *n* = 48,315 total ADRs).

Limitations of this data source include under reporting of ADRs and reporting bias. These findings are based on analysis of the Yellow Card dataset described and may not represent all ADRs from a generalised patient population.

l.pmed.1004565 March 27, 2025 1 / 15

Conclusions

Nine percent of all reported ADRs are associated with drugs where a genetic variant can cause heightened risk of an ADR and inform prescribing. A panel of only three pharmacogenes could potentially mitigate three in every four PGx modifiable ADRs. Based on our findings, Psychiatry may be the single highest impact specialty to pilot PGx to reduce ADRs and associated morbidity, mortality and costs.

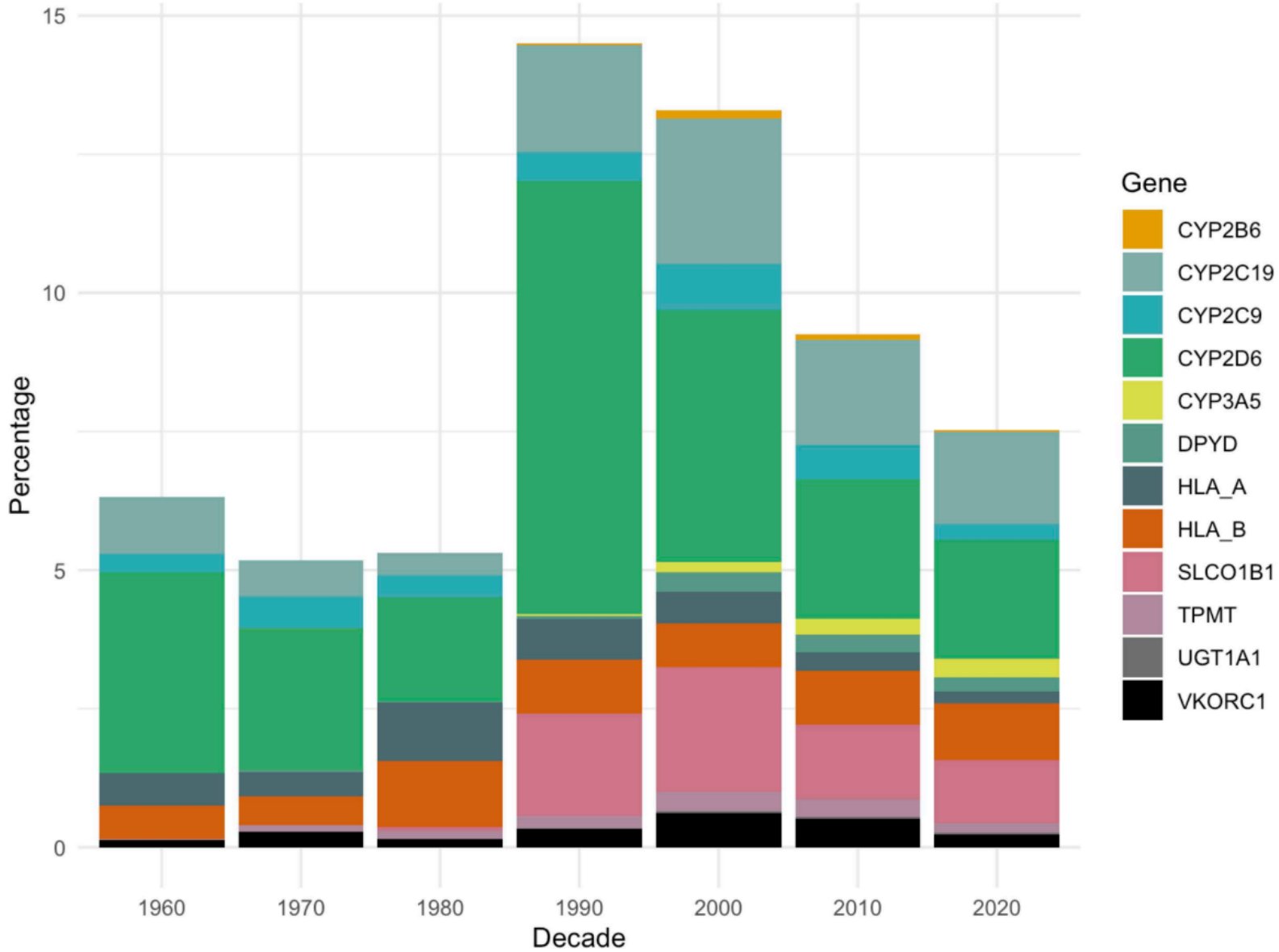
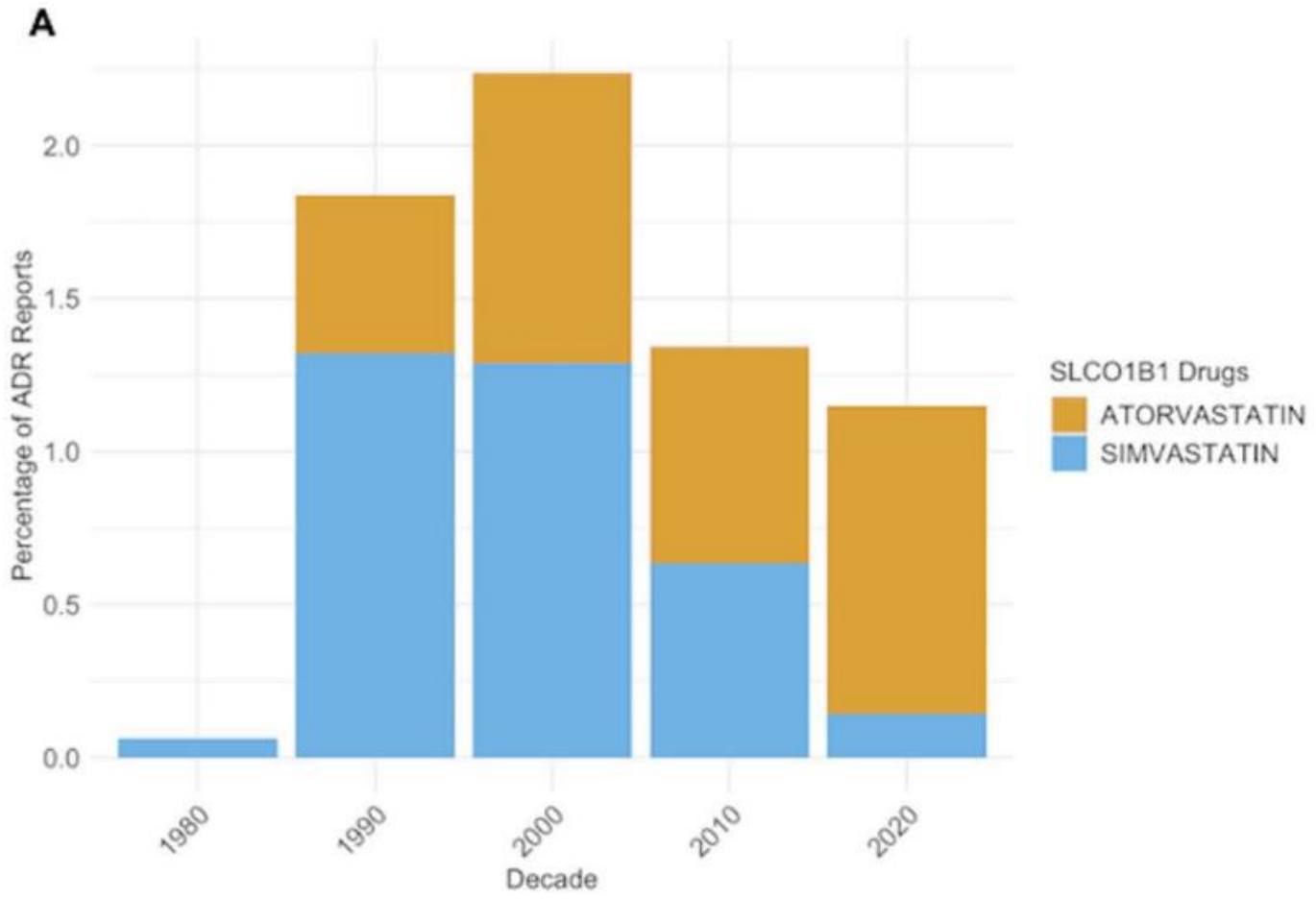


Fig 1. Percentage of ADR reports for PGx drugs and associated genes by decade. The *x*-axis shows decade of ADR report to reflect changes in prescribing trends over time. The total number of ADRs reported in each decade are as follows: 1960 = 21,341, 1970 = 65,318, 1980 = 132,500, 1990 = 181,754, 2000 = 229,721, 2010 = 396,779 and 2020 = 318,299. ADR, adverse drug reaction; PGx, pharmacogenomics.

SLCO1B1 is associated with the use of statins, so trends were clearly interpretable over time, but there has been a **shift from simvastatin to atorvastatin**-related ADRs over time.

***SLCO1B1* gene variants**, particularly **c.521T>C (rs4149056)**, are strongly **associated with an increased risk of statin-induced myopathy** (muscle pain/weakness) by reducing hepatic uptake of the drug, leading to higher blood levels.

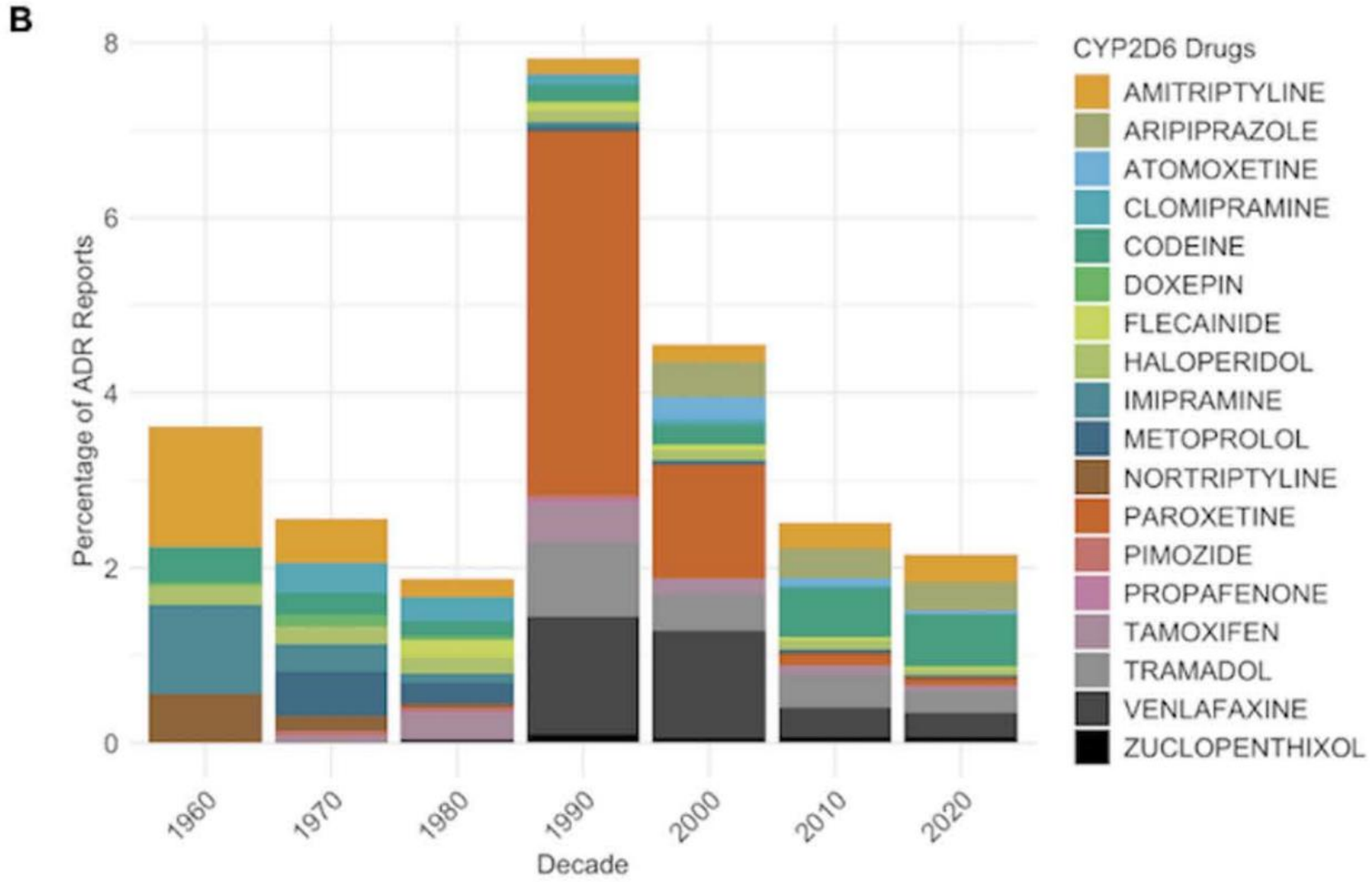
Testing for these variants allows for personalized **statin dosing** (especially for simvastatin) to improve safety, with recommendations for reduced doses or alternative agents for carriers.



CYP2D6 and CYP2C19 metabolised medications (many of which are antidepressants, antipsychotics or analgesics) by decade are shown.

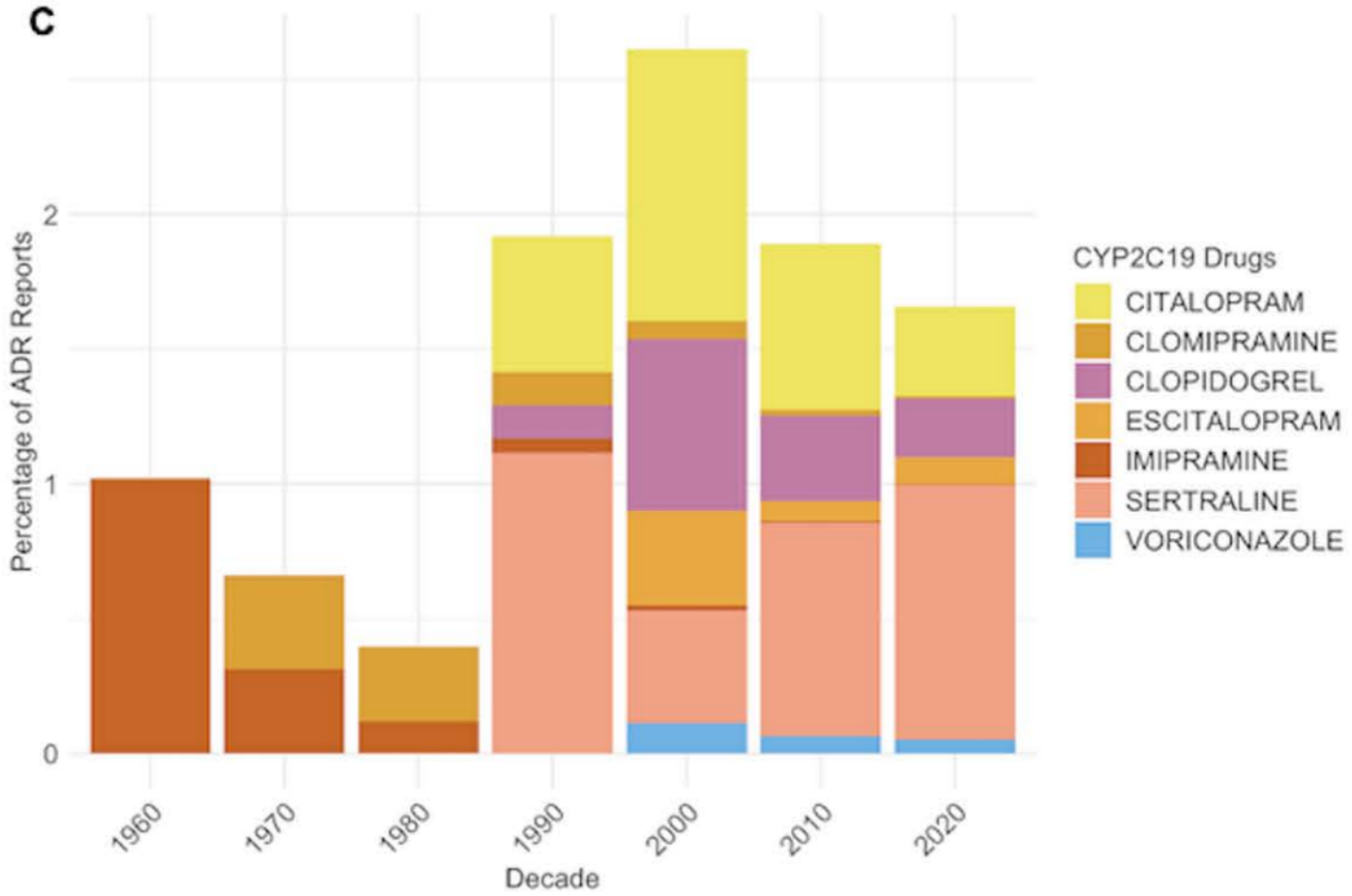
CYP2D6 gene variants significantly impact the metabolism of many antidepressants and anxiety medications, with **poor metabolizers (PMs)** facing a higher risk of adverse drug reactions (ADRs) and **ultra-rapid metabolizers (UMs)** risking therapeutic failure.

This revealed, for example, that the peak in the 1990s in CYP2D6 drug-related reporting was due to paroxetine.



With regards to **CYP2C19**, tricyclic antidepressant-associated reporting has decreased over time, but serotonin reuptake inhibitors- (SSRIs) associated ADR reports have increased, as prescribing practice has shifted to SSRIs (as seen by progressively lower reports of imipramine and clomipramine ADRs and the emergence of sertraline ADRs after licensing in 1990).

Variations in this gene can lead to altered enzyme activity, causing **poor, intermediate, or rapid metabolism**, which significantly affects drug concentration in the body and increases the risk of Adverse Drug Reactions (ADRs)



The following table shows patient demographics, ADR severity and reporter details for the PGx mitigatable and non PGx mitigatable ADRs.

Table 1. ADR report numbers and patient demographics stratified by drug PGx status. Sex, age and severity comparison between pharmacogene actionable medicines and non pharmacogene actionable medicines.

	Total ADRs	**PGx drug ADRs**	**Other ADRs**
	(*N* = 1,345,712)	**(*N* = 115,789)**	**(*N* = 1,229,923)**
Male (%)	38% (*n* = 512,241)	40% (*n* = 45,876)	38% (*n* = 466,365)
Female (%)	57% (*n* = 769,852)	56% (*n* = 64,903)	57% (*n* = 704,949)
(Missing data %)	5% (*n* = 63,619)	4% (*n* = 5,010)	5% (*n* = 58,609)
Age (mean ± SD)	46.9 (±21.1 years)	47.1 (±20.5 years)	46.9 (±21.1 years)
(Missing data %)	22% (*n* = 289,118)	16% (*n* = 18,192)	22% (*n* = 270,926)
Severity			
Nonserious (%)	30% (*n* = 409,188)	27% (*n* = 30,678)	31% (*n* = 378,510)
Serious (%)	65% (*n* = 874,564)	69% (*n* = 80,062)	64% (*n* = 794,502)
Fatal (%)	5% (*n* = 61,944)	4% (*n* = 5,049)	5% (*n* = 56,895)
(Missing data %)	0% (*n* = 16)	0% (*n* = 0)	0% (*n* = 16)
HCP reporter (%)	80% (*n* = 1,082,961)	80% (*n* = 93,082)	80% (*n* = 989,879)
Patient/Carer (%)	16% (*n* = 213,597)	17% (*n* = 19,247)	16% (*n* = 194,350)
Both %	4% (*n* = 49,154)	3% (3,460)	4% (*n* = 45,694)
Direct reports (%)	67% (*n* = 903,325)	75% (*n* = 86,665)	66.4% (*n* = 816,660)
Indirect reports (%)	33% (*n* = 442,387)	25% (*n* = 29,124)	33.6% (*n* = 413,263)
(Missing data %)	0% (*n* = 0)	0% (*n* = 0)	0% (*n* = 0)

ADR, adverse drug reaction; PGx, Pharmacogenomic; SD, Standard deviation; HCP, Healthcare professional. Indirect reports come from industry as compared with direct reports to the MHRA. There were no counts of missing data from Direct vs Indirect reporter category.

They are overall more common in females

There was a higher percentage of males with PGx mitigatable ADRs than non-PGx mitigatable ADRs

Patients who experienced PGx mitigatable ADRs were older and had more severe but non-fatal reactions as compared with patient who experienced a non-PGx mitigatable ADR

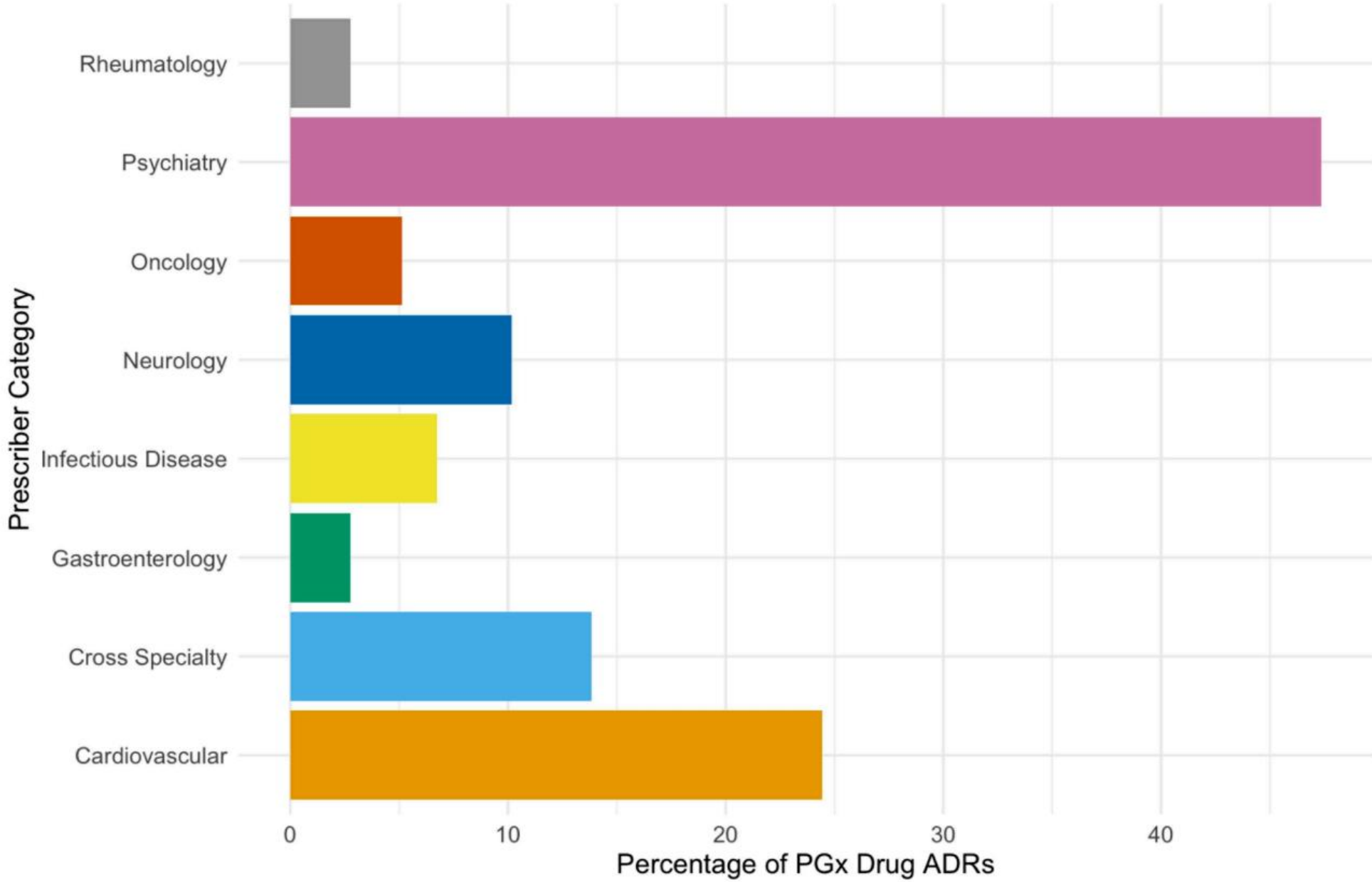


Fig 3. Percentage of PGx mitigatable ADRs by prescriber specialty. The breakdown of prescribing indication by specialty can be

Rheumatology medications: azathioprine, mercaptopurine.

Psychiatry medications: citalopram, escitalopram, paroxetine, sertraline, venlafaxine, amitriptyline, clomipramine, doxepin, imipramine, nortriptyline, carbamazepine, aripiprazole, haloperidol, pimozide, zuclopenthixol, atomoxetine.

Oncology medications: capecitabine, 5-fluorouracil, irinotecan, tamoxifen, tegafur, thioguanine, mercaptopurine.

Neurology medications: phenytoin, carbamazepine, azathioprine, mercaptopurine.

Infectious Disease medications: efavirenz, flucloxacillin, voriconazole.

Gastroenterology medications: azathioprine, mercaptopurine.

*Cross Speciality medications: codeine, tramadol, tacrolimus, azathioprine, mercaptopurine.

Cardiovascular medications: flecainide, propafenone, metoprolol, atorvastatin, simvastatin, acenocoumarol, clopidogrel, warfarin.

*Cross Specialty medications include analgesics and immunosuppressants prescribed by multiple different specialties for multiple different organ indications. ADR, adverse drug reaction; PGx, pharmacogenomics.

A comparison of prescribing prevalence data with proportion of mitigatable ADRs associated with PGx drugs is shown. It is notable that **the majority of the PGx drugs with disproportionately high Yellow Card ADR reporting as compared with prescribing prevalence are psychiatric drugs**.

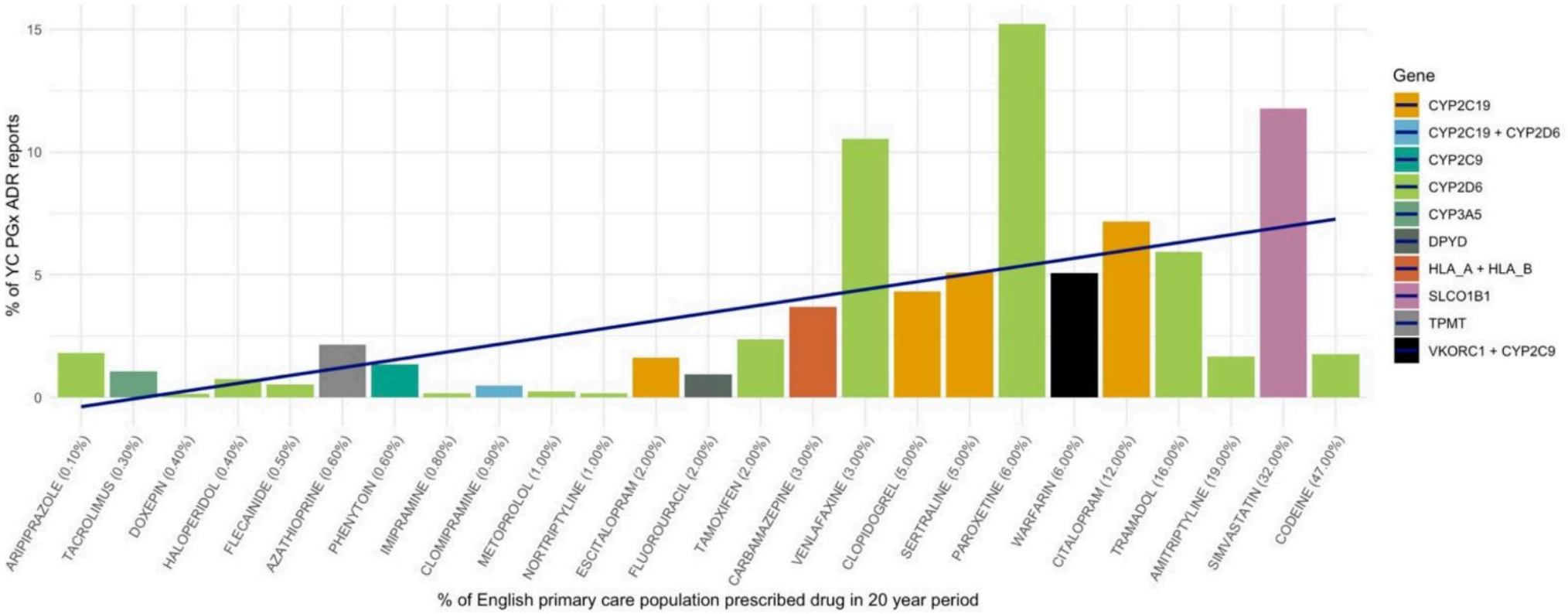
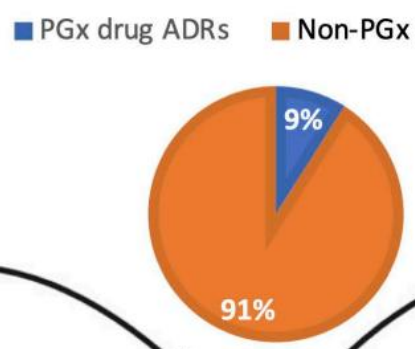


Fig 4. Proportion of ADRs per drug compared with prescribing prevalence. The *x*-axis denotes prescribing prevalence (% of the population prescribed the drug in a 20-year period (1993–2012) based on the published CPRD data from Kimpton and colleagues [16]). The *y*-axis shows the percentage of all PGx mitigatable ADRs represented by each drug during the same 20-year period. Those medicines which extend over the blue line are overrepresented in Yellow Card ADR volume as compared with prescribing prevalence. ADR, adverse drug reaction.

>1 MILLION ADRS

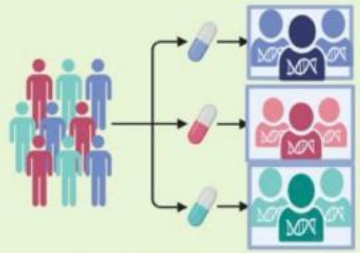


Report characteristics

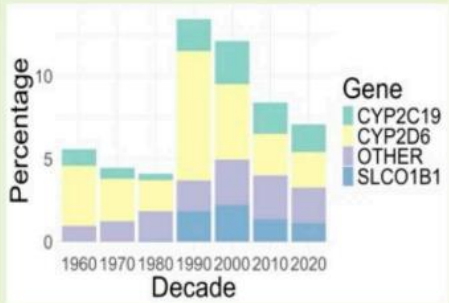
Programmatic ADR data extraction

- Years: 1963 - March 2024
- 1,345,712 ADR reports
- 2,499 substances

Drugs linked with gene



3 In every 4 PGx drug ADRs associated with 3 genes: *CYP2D6, CYP2C19, SLCO1B1*



PGx drug ADRs: patient demographics

- Age
- Male
- Severe reaction
- Reported by patient/carer

PGx drug ADRs by Specialty

47% of PGx mitigable ADRs Psychiatry drugs

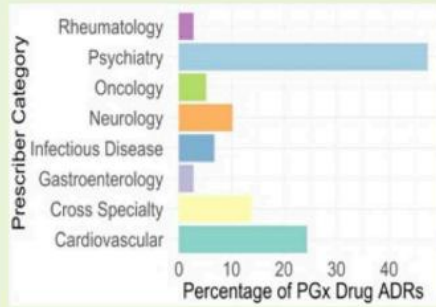


Table 2. A typical metaboliser prevalence for CYP2D6 and CYP2C19 across diverse ancestry groups. These are genetically predicted based on data published by PharmGKB and CPIC. We have defined atypical metabolisers as the following: poor (activity score 0 for 2D6), intermediate (activity score <1 for 2D6), and ultrarapid metabolisers (activity score >2 for 2D6).

Biogeographical groups	CYP2D6 atypical metabolisers	CYP2C19 atypical metabolisers
African American/Afro-Caribbean	22%	40%
American	10%	24%
Central/South Asian	15%	52%
East Asian	34%	59%
European	19%	33%
Latino	14%	23%
Near Eastern	28%	29%
Oceanian	22%	94%
Sub-Saharan African	25%	37%

https://doi.org/10.1371/journal.pmed.1004565.t002

THE GUIDELINES

AIM: to furnish precise information and indication about how translate the genetic information into clinical practices in managing the therapy, about how to adjust the dosage or choose alternative drugs.

Tabella 12.1 Siti utili in farmacogenetica.

Sito	Indirizzo Internet
Pharmacogenomics Knowledgebase (PharmGKB)	www.pharmgkb.org/
Clinical Pharmacogenetics Implementation Consortium (CPIC)	https://cpicpgx.org/
Pharmacogene Variation Consortium (PharmVar)	www.pharmvar.org/
US Food and Drug Administration (FDA) *Table of Pharmacogenomic Biomarkers in Drug Labeling*	www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling
FDA Table of Pharmacogenetic Associations	www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations
European Medicines Agency (EMA) SmPC (*Summary of product characteristics*)	www.ema.europa.eu/
The Genetic Testing Reference Materials Coordination Program (GeT-RM)	www.cdc.gov/labquality/get-rm/inherited-genetic-diseases-pharmacogenetics/pharmacogenetics.html
Drug Interactions Flockhart Table	https:// drug-interactions.medicine.iu.edu/MainTable.aspx
Association for Molecular Pathology Clinical Practice Committee's Pharmacogenomics (PGx) *Working Group*	www.amp.org/clinical-practice/practice-guidelines/
Dutch Pharmacogenetics Working Group	www.pharmgkb.org/page/dpwg

ClinPGx is now the home of CPIC - welcome, CPIC users!

ClinPGx

PharmDOG GSI CPIC Data Focus Help

Search ClinPGx

The evolution of PharmGKB + CPIC

ClinPGx is a comprehensive clinical pharmacogenomic (PGx) resource created to support and expand PGx knowledge, implementation and education. It integrates the PharmGKB, CPIC and PharmCAT projects, with additional features and content to come. Our goals are to make clinical PGx accessible and facilitate its integration with genomic medicine. ClinPGx is an affiliate grant of the Clinical Genome Resource (ClinGen).

What is ClinPGx? What is Pharmacogenomics? ClinPGx Blog

CPIC

The Clinical Pharmacogenetics Implementation Consortium creates evidence-based gene/drug clinical practice guidelines enabling clinicians to use PGx in patient care.

What is CPIC?

The **Clinical Pharmacogenetics Implementation Consortium (CPIC®)** is an international consortium of individual volunteers and a small dedicated staff who are interested in facilitating use of pharmacogenetic tests for patient care.

One barrier to implementation of pharmacogenetic testing in the clinic is the difficulty in translating genetic laboratory test results into actionable prescribing decisions for affected drugs.

CPIC's goal is to address this barrier to clinical implementation of pharmacogenetic tests by creating, curating, and posting freely available, peer-reviewed, evidence-based, updatable, and detailed gene/drug clinical practice guidelines (see all CPIC publications). CPIC guidelines follow standardized formats, include systematic grading of evidence and clinical recommendations, use standardized terminology, are peer-reviewed, and are published in a leading journal (in partnership with Clinical Pharmacology and Therapeutics) with simultaneous posting on this site, where they are regularly updated. CPIC's Informatics Working Group supports the adoption of CPIC guidelines by identifying and addressing technical barriers to their implementation in electronic health records.

PharmCAT

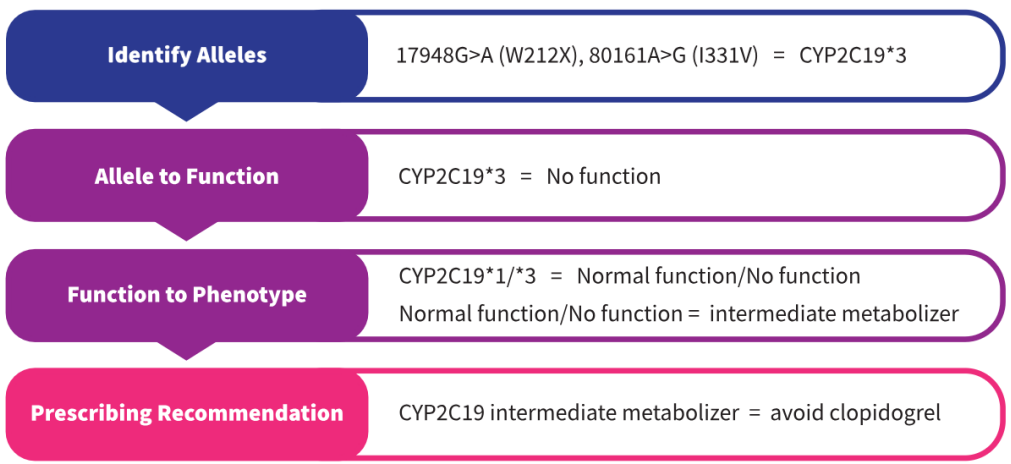
The Pharmacogenomics Clinical Annotation Tool

Download v3.2.0 | View on GitHub | View on DockerHub

PharmCAT (Pharmacogenomics Clinical Annotation Tool) is a bioinformatics tool that analyzes genetic variants to predict drug response and tailor medical treatment to an individual patient's genetic profile. It does this in two phases:

1. Processes VCF files from next generation sequencing (NGS) or genotyping methods and identifies pharmacogenomic (PGx) genotypes and infers haplotypes, typically called star alleles.
2. Uses the pharmacogene diplotypes (combination of maternal and paternal star alleles) to predict PGx phenotypes and reports the corresponding drug-prescribing recommendations from CPIC guidelines, ClinPGx-annotated DPWG guidelines and ClinPGx-annotated FDA-approved drug labels.

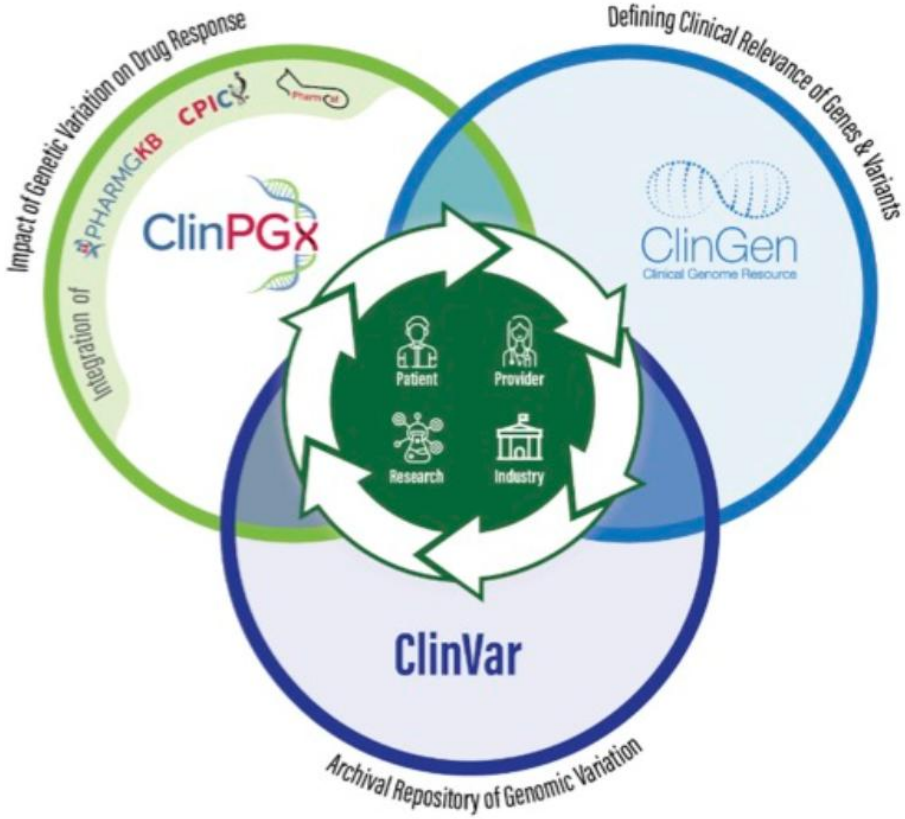
This is a very high-level example of this process:



About ClinPGx

ClinPGx is a comprehensive pharmacogenomics (PGx) resource designed **to provide clinicians, laboratories, researchers and patients access to PGx information**. Its goals are to:

1. **catalog, curate, annotate, integrate, generate and disseminate PGx knowledge** through expert manual curation, AI/automated processes, and community-based curation
2. **advance PGx clinical implementation** through expert, peer-reviewed, clinical CPIC guidelines, and assignment of gene-drug validity and actionability and PGx variant classification
3. **facilitate PGx integration with genomic medicine** through alignment with ClinGen curation frameworks and ClinGen/ClinVar submissions
4. **promote PGx education** through collaborations with the PGx education community and creation of educational materials.



Medical Genetics Summaries [Internet].

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Search this book

Abacavir Therapy and *HLA-B*57:01* Genotype

Laura Dean, MD and Megan Kane, PhD.

Author Information and Affiliations

Created: September 1, 2015; Last Update: March 31, 2026.

Estimated reading time: 26 minutes

Introduction

Go to:

Abacavir (brand name Ziagen) is used in the treatment of human immunodeficiency virus (HIV) infection. Abacavir is a nucleoside (and nucleotide) reverse transcriptase inhibitor (NRTI), and is used in combination with other medications as part of antiretroviral therapy (ART) (1).

Hypersensitivity reactions associated with abacavir can be severe and potentially fatal. Symptoms include fever, rash, vomiting, and shortness of breath. They typically appear within the first 42 days of treatment (9 days median onset). (1) *HLA-B*57:01* significantly increases the risk of hypersensitivity reactions when abacavir is administered.

Screening for the *HLA-B*57:01* allele before starting abacavir therapy is recommended for all individuals according to the FDA drug label for abacavir (Table 1) (1). Abacavir is contraindicated in *HLA-B*57:01*-positive individuals, and in individuals with a prior hypersensitivity reaction to abacavir. Even if previously tolerated, screening should happen before restarting abacavir therapy if *HLA-B*57:01* status is unknown. Abacavir therapy should be permanently discontinued if hypersensitivity is suspected. (1)

Guidelines from the professional societies Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) also recommend that *HLA-B*57:01* screening should be performed before initiation of abacavir therapy and an alternate drug be administered for individuals with the allele (Table 2, Table 3)(2, 3, 4).

Globally, there is wide variability in the frequency of this allele in the human leukocyte antigen B (*HLA-B*) gene, with estimates ranging from less than 1% to more than 10% (5). The *HLA-B* gene plays an important role in how the immune system recognizes and responds to pathogens and mediates hypersensitivity reactions. *HLA-B*57:01* has been found to be associated with abacavir hypersensitivity across different ethnicities, including Caucasians, Hispanics, and individuals of African origin (3, 6).

abacavir

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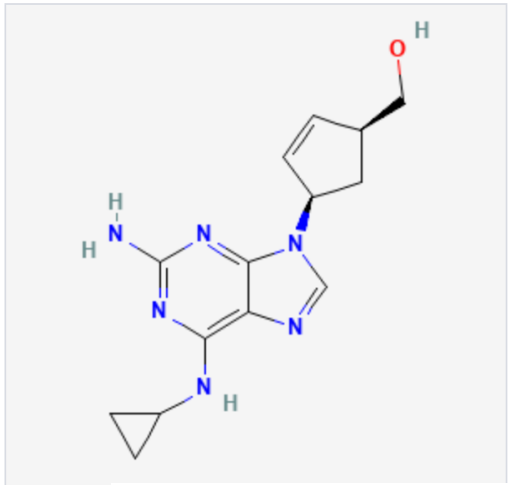
Pediatric

Structure



large version
3D version
source: PubChem

Indication

ZIAGEN, a nucleoside analogue human immunodeficiency virus reverse transcriptase inhibitor, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection(FDA label)

Classifications

Search

Drug
Antiinfectives For Systemic Use

Drug
Antivirals For Systemic Use

Drug
Antivirals for treatment of HIV infections, combinations

Drug
direct acting antivirals

Drug
Nucleoside and nucleotide reverse transcriptase inhibitors

Mixtures

The following mixtures contain abacavir.

- dolutegravir / abacavir / lamivudine
- lamivudine / abacavir
- zidovudine / lamivudine / abacavir

Metabolites

abacavir metabolizes into the following:

- abacavir 5'-monophosphate
- abacavir carboxylate
- abacavir glucuronide
- carbovir 5'-diphosphate
- carbovir 5'-monophosphate
- carbovir 5'-triphosphate

(source: ClinPGx)

Molecular Properties

SMILES

```
C1CC1NC2=NC(=NC3=C2N=CN3[C@@H]4C[C@@H](C=C4)CO)N
```

(source: PubChem)

Synonyms

- ABC
- abacavir
- Epzicom
- Ziagen
- Kivexa (Abacavir Sulfate + Lamivudine)
- Trizivir (Abacavir Sulfate + Lamivudine + Zidovudine)

Annotation of CPIC Guideline for abacavir and HLA-B

Alternate Drug | Pediatric

Summary

The CPIC dosing guideline does not recommend abacavir for individuals with the HLA-B*57:01 variant allele, and it should be considered only under exceptional circumstances.

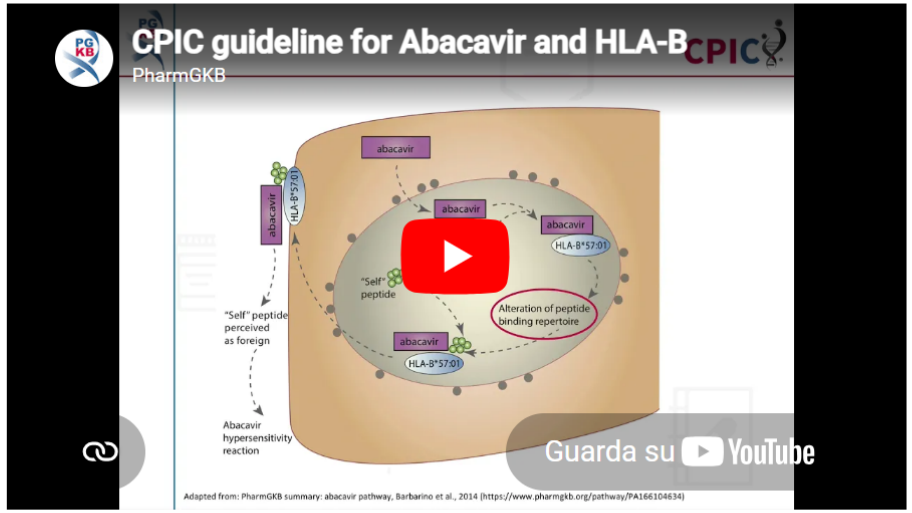
Specify a genotype or phenotype for specific annotations

HLA-B -- --

Find Results

⚠ **Verify all entered information and recommendations that are retrieved before implementing in a healthcare setting**

Annotation



May 2014 Update

abacavir

Annotation of CPIC Guideline for abacavir and HLA-B

Alternate Drug | Pediatric

Summary

The CPIC dosing guideline does not recommend abacavir for individuals with the HLA-B*57:01 variant allele, and it should be considered only under exceptional circumstances.

Genotype-specific results

Alternate Drug

Submitted Genotype

HLA-B: *57:01/*57:01

Implications

HLA-B: Significantly increased risk of abacavir hypersensitivity

Recommendation

Abacavir is not recommended

Annotation of CPIC Guideline for abacavir and HLA-B

Alternate Drug | Pediatric

Summary

The CPIC dosing guideline does not recommend abacavir for individuals with the HLA-B*57:01 variant allele, and it should be considered only under exceptional circumstances.

Genotype-specific results

Submitted Genotype

HLA-B: *58:01/*58:01

Recommendation

This genotype/phenotype has no recommendation.

Change Genotype

May 2014 Update

Accepted article preview online 21 February 2014; Advance online publication 12 March 2014

The 2014 update of CPIC guidelines regarding abacavir has been published in *Clinical Pharmacology and Therapeutics*. Literature published between April 2011-November 2013 was reviewed and there is **no new evidence that would change the original guidelines. Therefore, the dosing recommendations in the original publication remain clinically current**.

- These guidelines are applicable to:
  - HIV Patients
  - "Although much of the evidence linking HLA- B*57:01 to abacavir hypersensitivity was conducted in adults, there is no reason to suspect that children positive for HLA- B*57:01 would be at less risk for abacavir hypersensitivity reactions than adults positive for HLA-B*57:01. Furthermore, the Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection; http://aidsinfo.nih.gov/con-tentfiles/lvguidelines/pediatricguidelines.pdf) recommends against the use of abacavir in children who test positive for HLA-B*57:01."
- Download and read:
  - Clinical Pharmacogenetics Implementation Consortium Guidelines for *HLA-B* Genotype and Abacavir Dosing: 2014 Update
  - 2014 supplement
  - HLA Gene-Specific Information Tables
  - Abacavir Drug Resource Mappings
  - Abacavir Pre and Post Tests Alerts
  - Abacavir Clinical Decision Support Flow Chart

Drug Label Annotations

ClinPGx annotates regulatory agency-approved drug labels containing PGx information. Read more about ClinPGx drug label annotations, the drug label sources, PGx Levels and the "tags" found in the table below. FDA, EMA and HCSC labels are annotated when found on the FDA Table of Pharmacogenomic Biomarkers in Drug Labels. Labels from other regulatory agencies were annotated as collaborations and are not routinely updated.

Sort and filter the table using the column headers and selection boxes. Download the entire table using the button at the top right of the table.

8 annotations

Legend Download

	PGX LEVEL	SOURCE	TITLE	GENES
	All	All		
Details	Testing Required	EMA	Annotation of EMA Label for abacavir and HLA-B Alternate Drug Prescribing Info	HLA-B
Details	Testing Required	FDA	Annotation of FDA Label for abacavir and HLA-B Alternate Drug Prescribing Info FDA Biomarker	HLA-B
Details	Testing Required	HCSC	Annotation of HCSC Label for abacavir and HLA-B Alternate Drug Prescribing Info	HLA-B

Details	Testing Required	Swissmedic	Annotation of Swissmedic Label for abacavir and HLA-B Alternate Drug Prescribing Info	HLA-B
Details	Testing Required	Swissmedic	Annotation of Swissmedic Label for lamivudine / abacavir and HLA-B Prescribing Info	HLA-B
Details	Testing Required	Swissmedic	Annotation of Swissmedic Label for zidovudine / lamivudine / abacavir and HLA-B Prescribing Info	HLA-B
Details	Testing Required	Swissmedic	Annotation of Swissmedic Label for dolutegravir / abacavir / lamivudine and HLA-B Prescribing Info	HLA-B
Details	Informative PGx	PMDA	Annotation of PMDA Label for abacavir and HLA-B	HLA-B

Annotation of EMA Label for abacavir and HLA-B

Testing Required | Alternate Drug | Prescribing Info

The EMA European Public Assessment Report (EPAR) for abacavir (Ziagen) states that screening for the HLA-B*5701 allele should be performed in any HIV-infected patient, and that the drug should not be used in patient's with the HLA-B*57:01 allele.

Prescribing Information

"Before initiating treatment with abacavir, screening for carriage of the HLA-B*5701 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*5701 allele."

Excerpts from the abacavir (Ziagen) EPAR:

> Before initiating treatment with abacavir, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin(see section 4.4). Abacavir should not be used in patients known to carry the HLA-B*5701 allele

> The risk for abacavir HSR to occur is high for patients who test positive for the HLA-B*5701 allele. However, abacavir HSRs have been reported at a lower frequency in patients who do not carry this allele.

> HLA-B*5701 is the only identified pharmacogenetic marker that is consistently associated with clinical diagnosis of an ABC HSR reaction. However, some patients with a suspected ABC hypersensitivity reaction may not have the HLA-B*5701 allele.

For the complete EPAR text with sections containing pharmacogenetic information highlighted, see the abacavir EPAR PDF

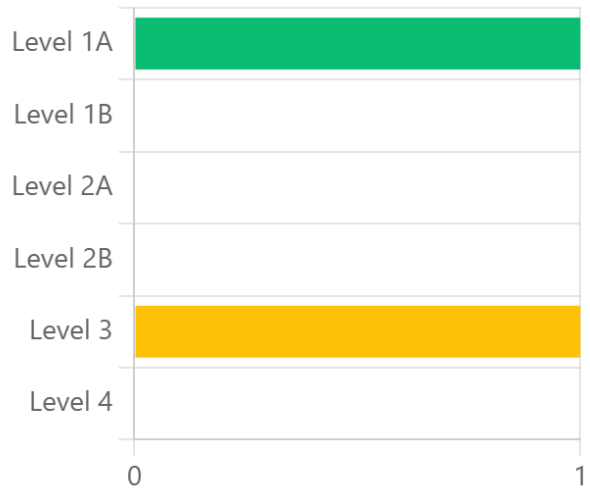
abacavir

Summary Annotations

Focus on Pediatrics OFF

Summary annotations (formerly "clinical annotations") provide information about variant-drug pairs based primarily on variant annotations and incorporating variant-specific prescribing guidance from clinical guidelines and FDA-approved drug labels, when available. Curators manually review annotations and create genotype-based summaries describing the phenotypic impact of the variant. Each summary annotation is assigned a Level of Evidence, which is generally informed by the summary annotation's score.

Note: Alleles in ClinPGx are mapped to the positive chromosomal strand. Therefore, variants in genes on the "minus" strand (eg. *VKORC1*) are complemented in ClinPGx annotations.



Annotations by level

Read more about Summary Annotations

Read more about Variant Annotations

Annotations by level

Read more about Summary Annotations | Read more about Variant Annotations

2 summary annotations

Fullscreen | Edit Columns | Show Filters | Download

	LEVEL	VARIANT	GENE	DRUGS	PHENOTYPE CATEGORIES	PHENOTYPE	PEDIATRIC
Details	Level 1A	HLA-B*57:01	HLA-B	abacavir	Toxicity	Drug Hypersensitivity, HIV infectious disease	
Details	Level 3	rs3093726	LST1, LTA, LTB	abacavir	Toxicity	Drug Hypersensitivity	

Summary annotation for HLA-B*57:01; abacavir; Drug Hypersensitivity and HIV Infections (level 1A Toxicity)

Level of Evidence

Level 1A

Phenotype Category

Toxicity

Genes

HLA-B

Variant

ALLELE	PHENOTYPE
*57:01 Presence	Patients with one or two copies of the HLA-B*57:01 allele have an increased risk of hypersensitivity to abacavir as compared to patients with no HLA-B*57:01 alleles or negative for the HLA-B*57:01 test. Other genetic and clinical factors may also influence the risk of abacavir-induced adverse reactions.

The level of evidence on this clinical annotation reflects the strength of the evidence base at the level of the gene and not at the level of individual alleles.

Summary annotation for rs3093726 (LST1, LTA, LTB); abacavir; Drug Hypersensitivity (level 3 Toxicity)

Level of Evidence

Level 3

Phenotype Category

Toxicity

Genes

LST1, LTA, LTB

Variant

rs3093726

Haplotypes

Drugs

abacavir

ALLELE	PHENOTYPE
CC	Patients with the CC genotype may have Increased risk of hypersensitivity when treated with abacavir as compared to patients with the TT genotypes. This variant is a tagging SNP for HLA-B*5701, for which there is greater evidence of association with abacavir-induced hypersensitivity. Other genetic and clinical factors may also influence a patient's risk for adverse events.
CT	Patients with the CT genotype may have increased risk of hypersensitivity when treated with abacavir as compared to patients with the TT genotype. This variant is a tagging SNP for HLA-B*5701, for which there is greater evidence of association with abacavir-induced hypersensitivity. Other genetic and clinical factors may also influence a patient's risk for adverse events.
TT	Patients with the TT genotype may have decreased but not absent risk of hypersensitivity when treated with abacavir as compared to patients with the CC genotype. This variant is a tagging SNP for HLA-B*5701, for which there is greater evidence of association with abacavir-induced hypersensitivity. Other genetic and clinical factors may also influence a patient's risk for adverse events.

abacavir

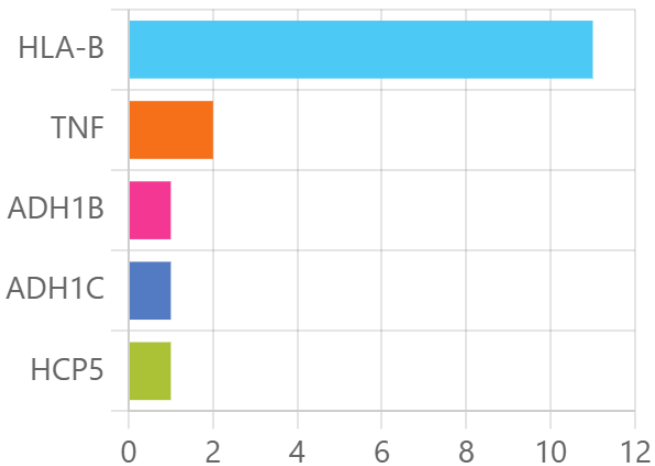
Variant Annotations

Variant annotations report the association between a variant and a drug phenotype from a publication. Annotations are created manually by Scientific Curators who curate key information and provide a structured, one-sentence summary of each association. More information about the association may be reported as free text in the "More Details" column of the table.

Note: Alleles in ClinPGx are mapped to the positive chromosomal strand. Therefore, variants in genes on the "minus" strand (eg. *VKORC1*) are complemented in ClinPGx annotations.

Read more about variant annotations

Focus on Pediatrics OFF



Annotations by gene (top 5)

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Links

19 annotations

Fullscreen | Edit Columns | Download

	VARIANT	LITERATURE	GENES	ASSOCIATION	SIGNIFICA
					(unfiltered
Details	rs1229984	PMCID:PMC7266722	ADH1B	Allele T is not associated with severity of Drug Hypersensitivity due to abacavir as compared to allele C.	no
Details	HLA-B*57:01	PMID:18184080	HLA-B	HLA-B *57:01 is associated with increased risk of Drug Hypersensitivity when treated with abacavir in people with HIV Infections.	yes
Details	HLA-B*57:01	PMID:22197535	HLA-B	HLA-B *57:01 is associated with increased risk of Drug Hypersensitivity when treated with abacavir in people with HIV Infections.	yes
Details	HLA-B*57:01	PMID:18256392	HLA-B	HLA-B *57:01 is associated with increased risk of Drug Hypersensitivity when treated with abacavir in people with HIV Infections.	yes

Note: Alleles in ClinPGx are mapped to the positive chromosomal strand. Therefore, variants in genes on the "minus" strand (eg. *VKORC1*) are complemented in ClinPGx annotations.

19 annotations

Fullscreen | Edit Columns | Download

	VARIANT	MORE DETAILS	DRUGS
Details	rs1229984	There was no significant difference in genotype frequencies between patients with abacavir hypersensitivity syndrome and abacavir-tolerant patients. All patients in the study carried the HLA-B*57:01 allele. Please note that alleles have been complemented to the positive strand.	abacavir
Details	HLA-B*57:01	The HLA-B*57:01 allele was present in 42.3% of cases of abacavir hypersensitivity, as compared to 3.7% of abacavir-tolerant controls.	abacavir
Details	HLA-B*57:01	As compared to those without the HLA-B*57:01:01 allele (referred to as *57:01 in the paper).	abacavir
Details	HLA-B*57:01	This study demonstrated that prospective screening was highly	abacavir

abacavir

Literature

The publications shown below are associated with this chemical based on (1) literature annotations, (2) variant annotations, or (3) pathways.

Search

Filter by PGx Paper Types

All

Sort by

Publication Date - Descending

114 items

Literature

Comparison of different methods for the detection of HLA-B* 57:01 allele in people living with HIV in Eastern Uttar Pradesh, India.

BMC infectious diseases. 2025. Rai Tulika Kumari, Chakravarty Jaya, Priyanka Kumari, Gautam Abhilasha and Srivastva Shweta.

PGx Paper Type: Methods

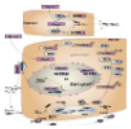
abacavir

Pathways

Pathway

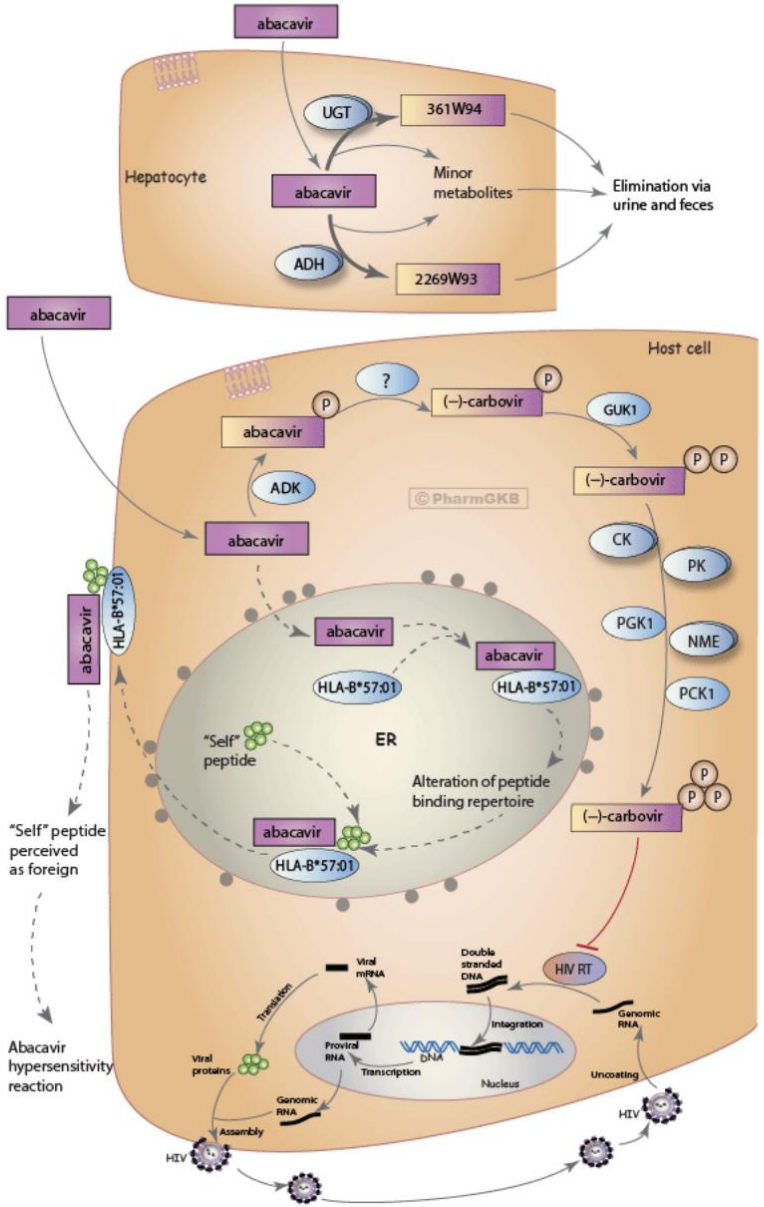
[Abacavir Pathway, Pharmacokinetics/Pharmacodynamics]

Schematic representation of abacavir metabolism and mechanism of action. The potential mechanism of an abacavir hypersensitivity reaction is also shown.



Summary

Schematic representation of abacavir metabolism and mechanism of action. The potential mechanism of an abacavir hypersensitivity reaction is also shown.



PGx Level

Testing Required The label states or implies that some sort of gene, protein or chromosomal testing, including genetic testing, functional protein assays, cytogenetic studies, etc., should be conducted on the gene or gene product mentioned in the annotation before using this drug. This requirement may only be for a particular subset of patients. If the label states a test "should be" performed, this is interpreted as testing required.

Testing Recommended The label states or implies that some sort of gene, protein or chromosomal testing, including genetic testing, functional protein assays, cytogenetic studies, etc., is recommended to be carried out on the gene or gene product mentioned in the annotation before using this drug. This recommendation may only be for a particular subset of patients. ClinPGx considers labels that say testing "should be considered" or "consider genotyping or phenotyping" to be recommending testing.

Actionable PGx The label discusses a dose adjustment, contraindication or alternate drug recommendation, or other guidance for patients with a particular genotype or metabolizer phenotype, if known. However, the label does not require or recommend genotype or phenotype testing before using the drug.

The criteria for Actionable PGx were updated in August 2024: FDA, EMA and HCSC labels which were previously assigned as Actionable PGx but did not have Prescribing Info were reassigned to Informative PGx. This update was not applied to Swiss and Japanese label annotations.

Informative PGx The label contains information regarding a particular gene/protein/variant/phenotype which may affect drug metabolism or concentration, rate of side effects (e.g. carvedilol), or general risk to the patient (e.g. avatrombopag), with no further guidance as to what to do in this situation. A clinician may find this information actionable (e.g. by avoiding the drug in that patient population) but no action is provided on the drug label.

The criteria for Informative PGx were updated in August 2024: FDA, EMA and HCSC labels which were previously assigned as Actionable PGx but did not have Prescribing Info were reassigned to Informative PGx. FDA, EMA and HCSC labels which previously were assigned as Informative PGx were transitioned to "No Clinical PGx". This update was not applied to Swiss and Japanese label annotations.

No Clinical PGx The label contains information stating that particular genes/proteins/variants or metabolizer phenotypes do not affect a drug’s efficacy, dosage, metabolism or toxicity. Or, the label states that particular variants or phenotypes affect a drug’s efficacy, dosage, metabolism or toxicity, but this effect is not “clinically significant".

Drug Label Annotation Tags

Prescribing Info ClinPGx Drug Label Annotations will include prescribing guidance in the "Prescribing" section of the annotation if the label discusses a dose adjustment, alternate drug recommendation or other guidance for patients with a particular genotype or metabolizer phenotype.

Dosing Info The label provides a dose adjustment based on gene/protein/chromosomal variants or phenotypes (e.g. "poor metabolizers"). The label may also state that a dose adjustment is "required" or "should be given".

Alternate Drug The label says that a drug is contraindicated, or has other language such as the drug "should not be used" or that a different drug "should be considered" or is "recommended", for a particular set of patients based on gene/protein variants or phenotypes (e.g. "poor metabolizers").

Other Guidance The label provides any guidance other than a dose adjustment or alternate drug recommendation for patients with a particular genotype or metabolizer phenotype, or any guidance for patients with a particular genotype or metabolizer phenotype in the context of drug-drug interactions. Examples of such guidance are if a drug “should be used with caution", or if clinicians should "monitor" these patients for adverse events/reactions.

Indication The gene or variant is an Indication for the drug, or the drug is for use in a specific population defined by the gene or variant(s), according to the label.

Cancer Genome The label discusses a gene or variant present in a tumor/cancer cell.

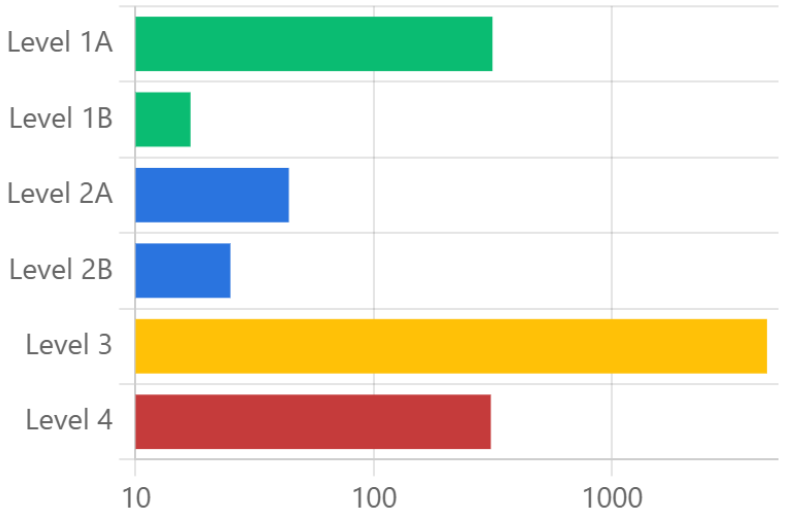
FDA Biomarker and Ex-FDA Biomarker The label is, or used to be but no longer is, found on the FDA's Table of Pharmacogenomic Biomarkers in Drug Labels, respectively.

Summary Annotations

ClinPGx summary annotations (also known as clinical annotations) provide information about variant-drug relationships based on variant annotations from peer-reviewed, published literature, and include variant-specific prescribing guidance from annotated clinical guidelines and FDA-approved drug labels when available. ClinPGx scientists manually review variant annotations and create summaries describing the phenotypic impact of the variant. The summary annotation is given a score, based on the scores of the supporting annotations, which is used by ClinPGx scientists to assign a Level of Evidence. Levels range from 1-4, with level 1 meeting the highest criteria.

Each row in the table below contains information from a single annotation. The full summary and supporting evidence, including publication PMIDs, can be found by following the "Read Now" link.

To view summary annotations for specific associations, please use the search box at the top of this page to search for genes, variants or drugs of interest. Once on the gene, variant or drug page, click on the "Clinical Annotations" tab in the left-hand menu.



Summary annotation counts by level

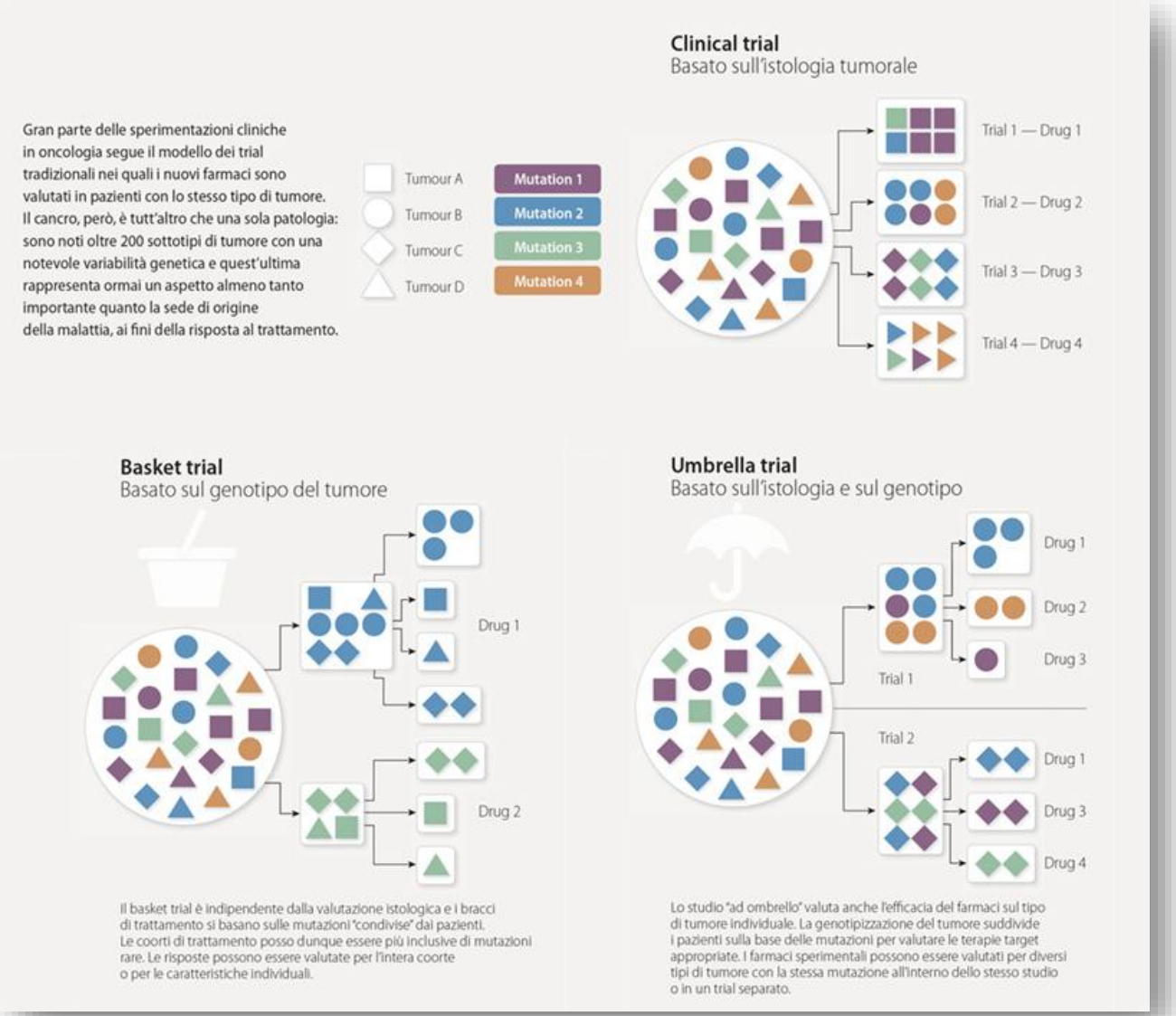
HOW TO PREPARE THE 10-15min PRESENTATION:

1. TO CHOOSE A PGx DRUG

2. TO EXPLAIN THE THERAPEUTIC ACTION AND THE MECHANISM OF ACTION

3. TO EXPLAIN THE PGx CONCERN

4. TO CHECK ALL THE INFO IN ClinPGX



Differentiation of neoplastic diseases based on mutations and use of information derived from genetic heritage to develop **targeted therapies**.

BASKET TRIAL: the same treatment is studied for different pathologies that present the same molecular alterations

UMBRELLA TRIAL: many targeted therapies are tested on a single disease stratified into multiple subgroups divided by genetic alterations.