Precision Prescribing with Pharmacogenetics

Dr Danny Meyersfeld | *PhD Molecular Biology*

DNALYSIS

Pharmacogenetics - Definition

Pharmacogenetics is the combination of pharmacology and genetics and is concerned with the inter-individual metabolic and therapeutic responses to a given medication.

- The study of genetic variations which can affect an individual's response to drugs, both in terms of therapeutic effects and adverse effects
- Aims to identify genetic biomarkers affecting drug response and use them to make better drug therapy decisions for everyone.

In simple terms:

Pharmacogenetics is a field of research that studies how a person's genes affect how he or she responds to a medication. The goal is to enable doctors to make better treatment decisions by helping them to select the drugs and dosages best suited for each person.

Precision Prescribing for personalised medicine

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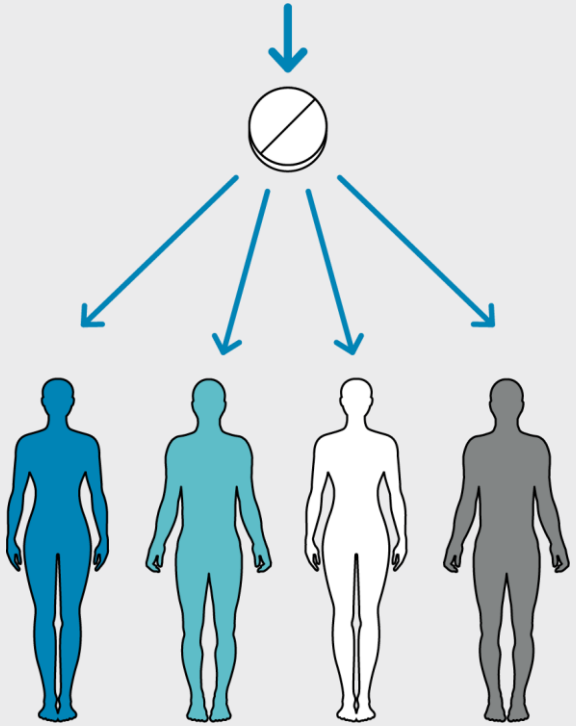
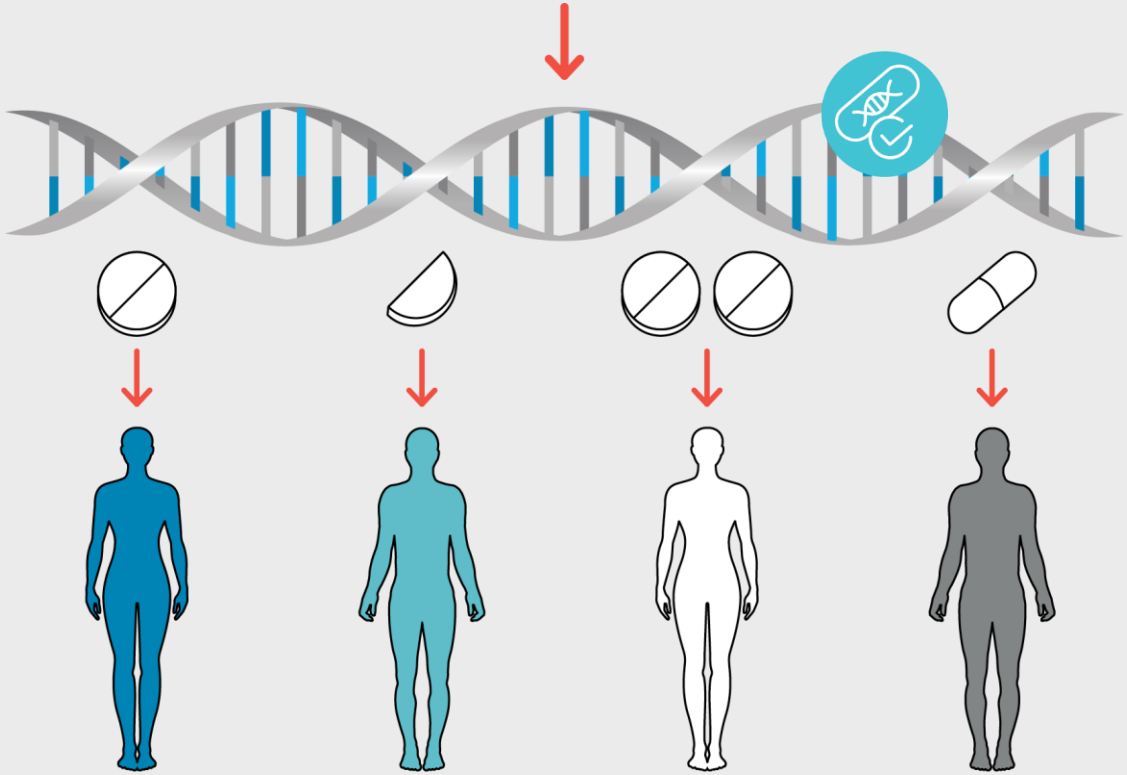
Pharmacogenetics

Blockbuster one-size-fits-all approach to drug development and prescribing



Personalised prescribing enables selection of the **right drug and dose**



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Why is this Important?

The burden of adverse drug reactions (ADRs)

- ADRs are one of the leading causes of morbidity and mortality in health care
- Studies estimate that 6.7% of hospitalized patients have a serious adverse drug reaction with a fatality rate of 0.32%[1].
- More than 2,216,000 serious ADRs in hospitalized patients, causing over 106,000 deaths annually[1].
- This would make ADRs the 4th leading cause of death—ahead of pulmonary disease, diabetes, AIDS, pneumonia, accidents, and automobile deaths[2].

1. Lazarou J, Pomeranz B, Corey PN. Incidence of adverse drug reactions in hospitalized patients: A meta-analysis of prospective studies. JAMA 1998;279:1200–1205
2. Preventable Adverse Drug Reactions: A Focus on Drug Interactions | FDA.

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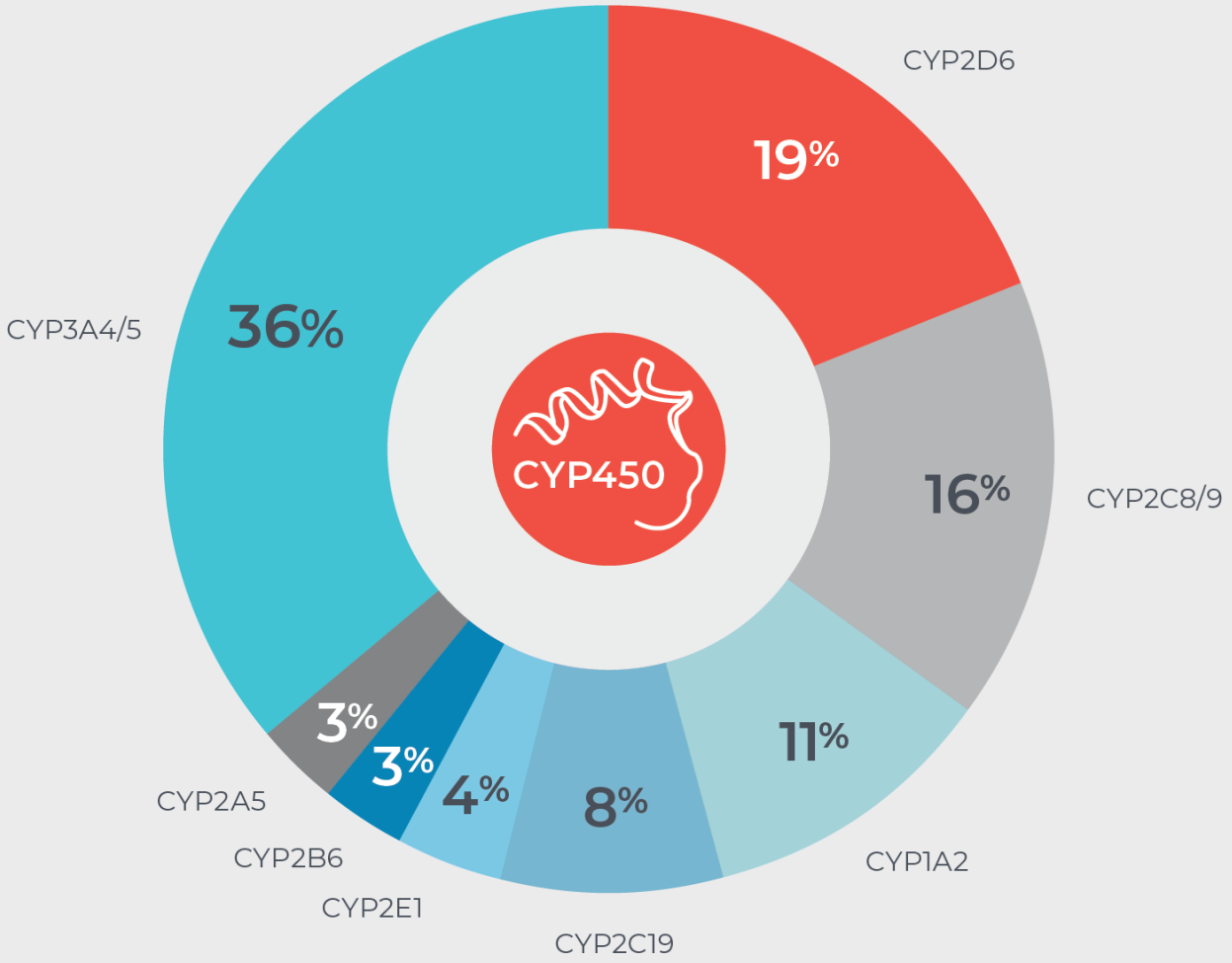
Cytochrome P450 (CYP450) enzymes

- Necessary for the detoxification of foreign chemicals and the metabolism of drugs
- >50 CYP450 enzymes
- Metabolize more than 50% of all drugs in clinical use



Wilkinson GR. Drug metabolism and variability among patients in drug response. N Engl J Med 2005;352:2211-21

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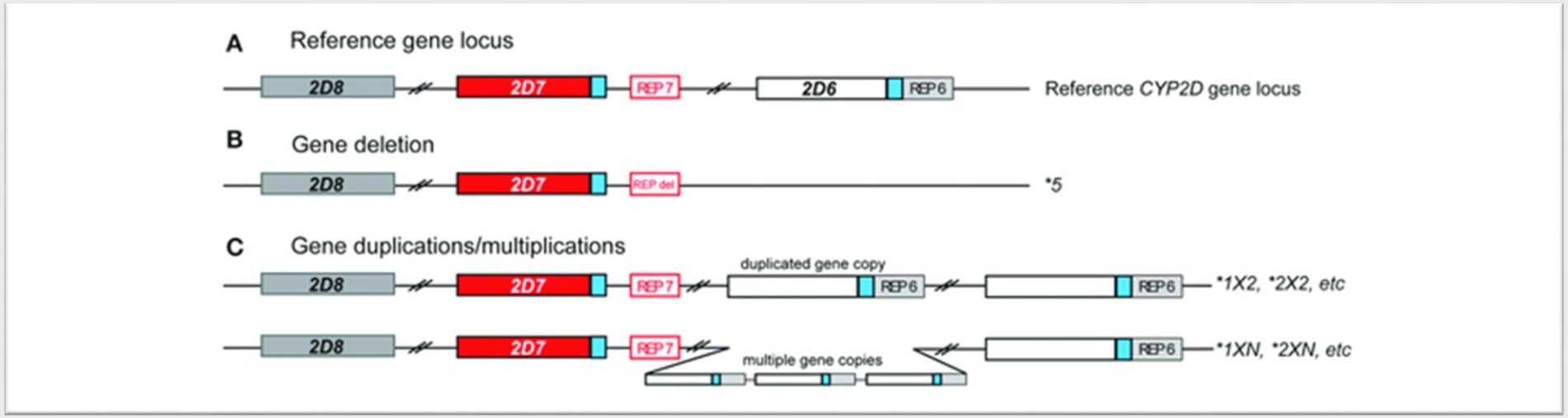
CYP2D6 Structural Variants



- The CYP2D6 enzyme is responsible for the metabolism of many commonly prescribed drugs, including antidepressants, antipsychotics, analgesics, and beta-blockers
- CYP2D6 is one of the most variable of all of the CYP genes; more than 135 distinct variations have been defined in the gene structure
- The combination of these variations determine the haplotype, which can then be converted to a metabolizer status of the individual
- The prevalence of the gene duplications and deletions is critical to the functioning of the enzyme; and why laboratories reporting on CYP2D6 status need to include a copy number assay into their analysis

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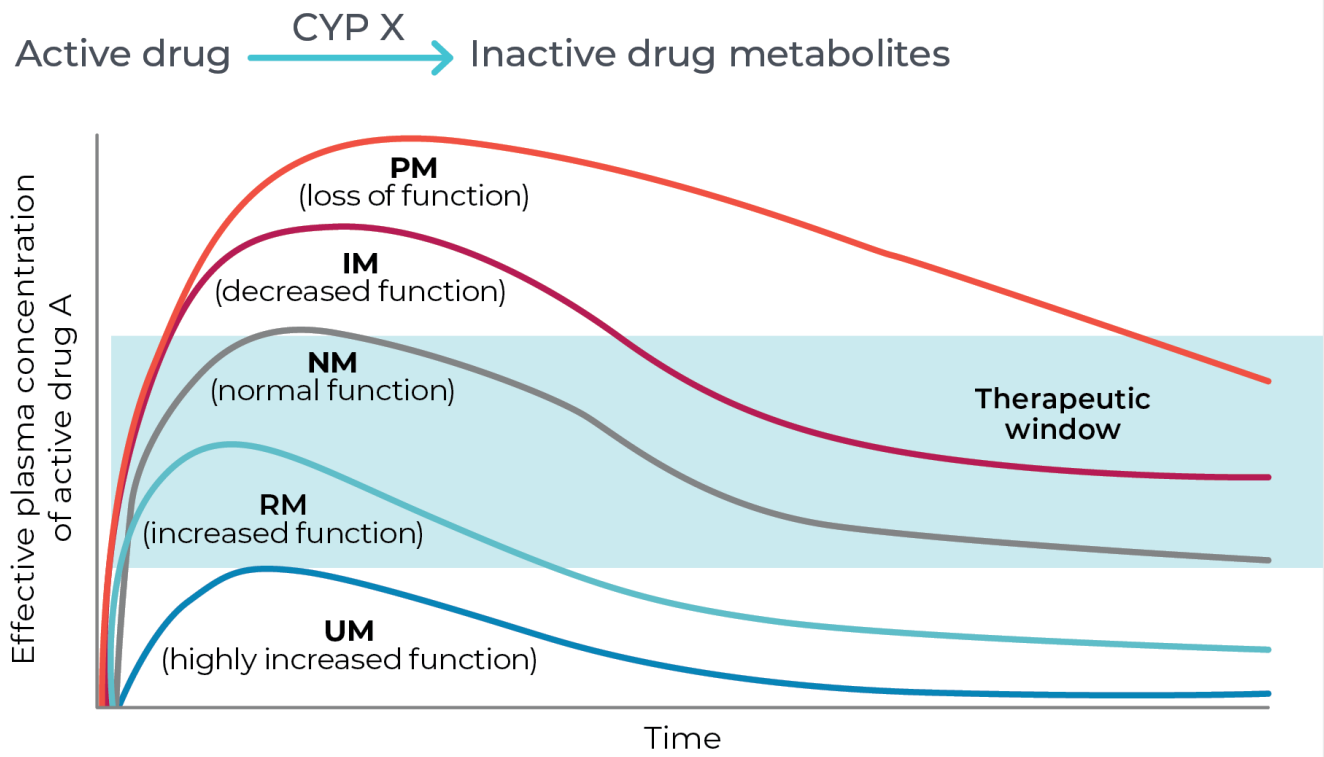
Drug Metabolism

- When an active drug is metabolised by a CYP enzyme, loss of function of the enzyme will increase the effective serum concentration of the active drug; therefore, the patient will be at risk of side effects
- Conversely, increased enzyme function will lead to lower effective serum concentration, potentially contributing to treatment failures

Effect of CYP450 polymorphism on drug metabolism



Decreased / No CYP X function → Greater drug concentration → Higher risk of adverse effect
Increased X function → Lower drug concentration → Higher risk of treatment failure

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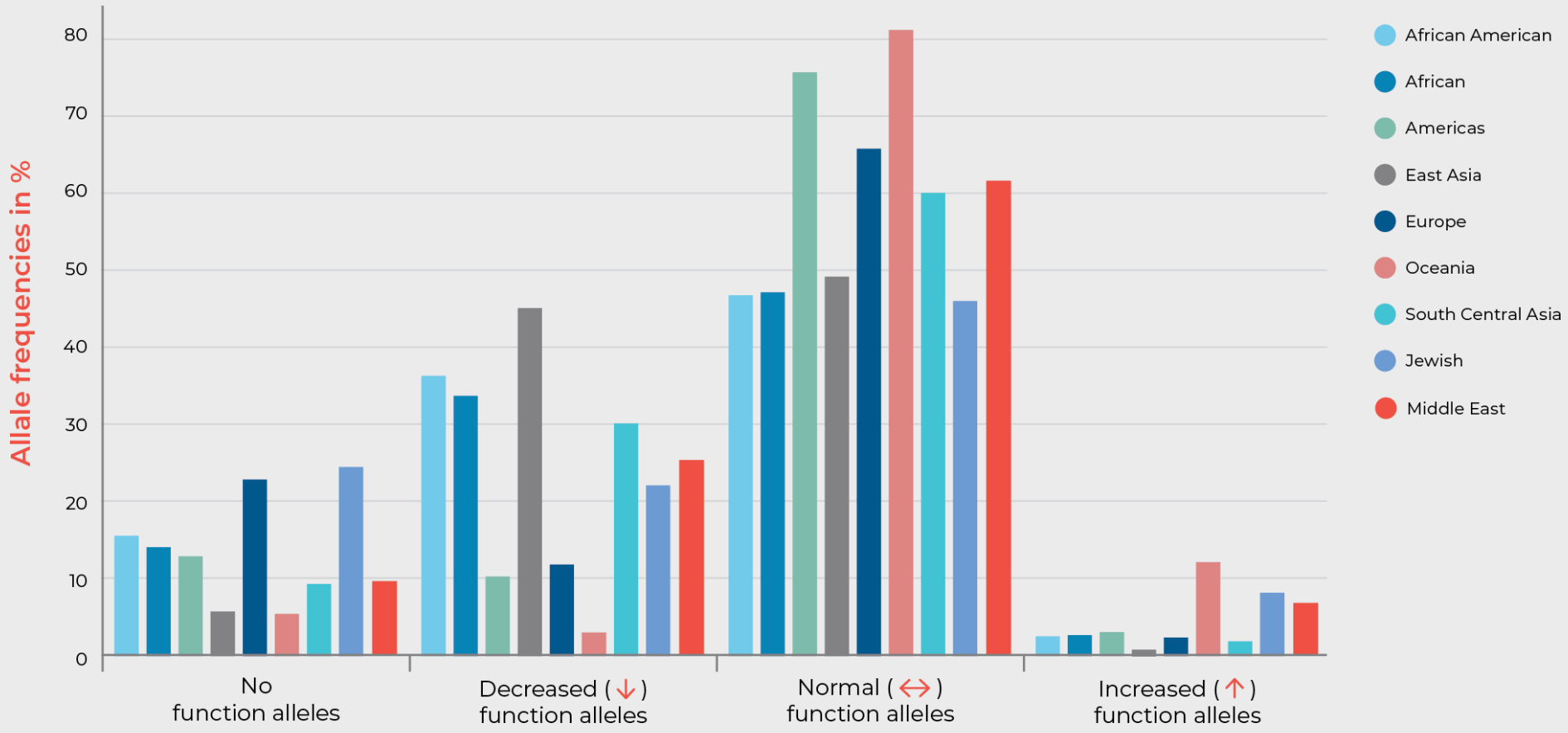
CYP2D6 Phenotype Frequency



Genet Med. 2017 Jan; 19(1): 69–76. Prediction of CYP2D6 phenotype from genotype across world populations.

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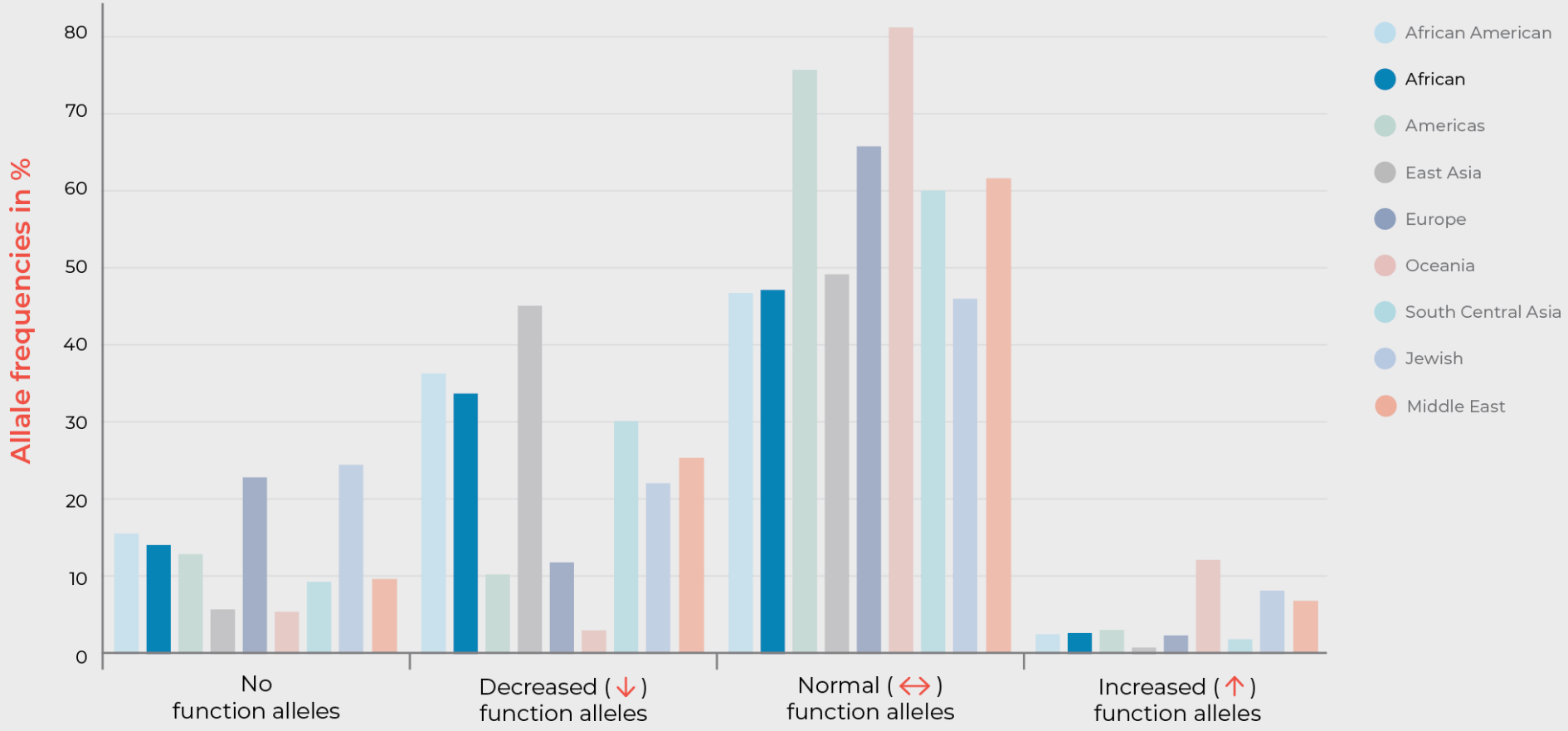
CYP2D6 Phenotype Frequency



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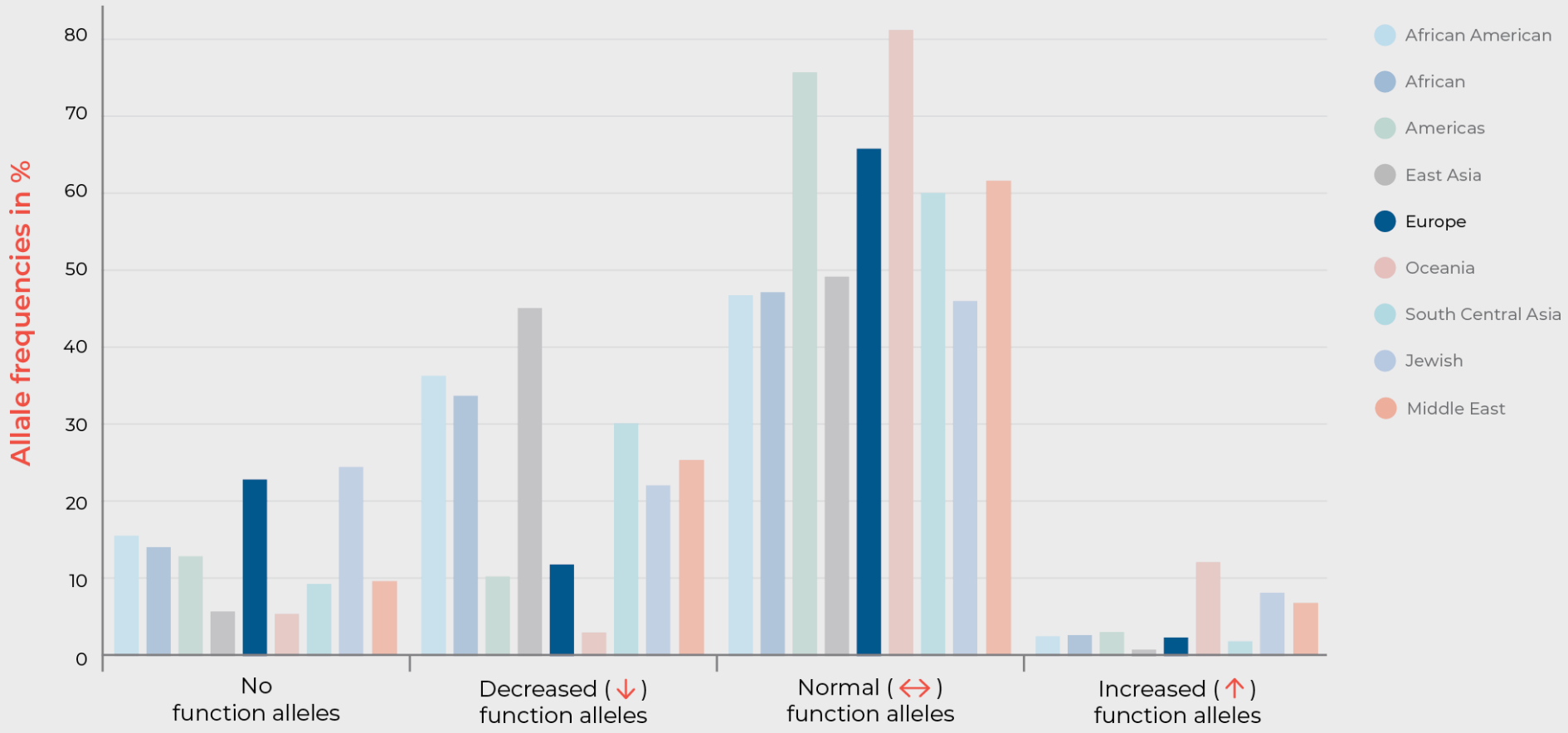

Genet Med. 2017 Jan; 19(1): 69–76. Prediction of CYP2D6 phenotype from genotype across world populations.

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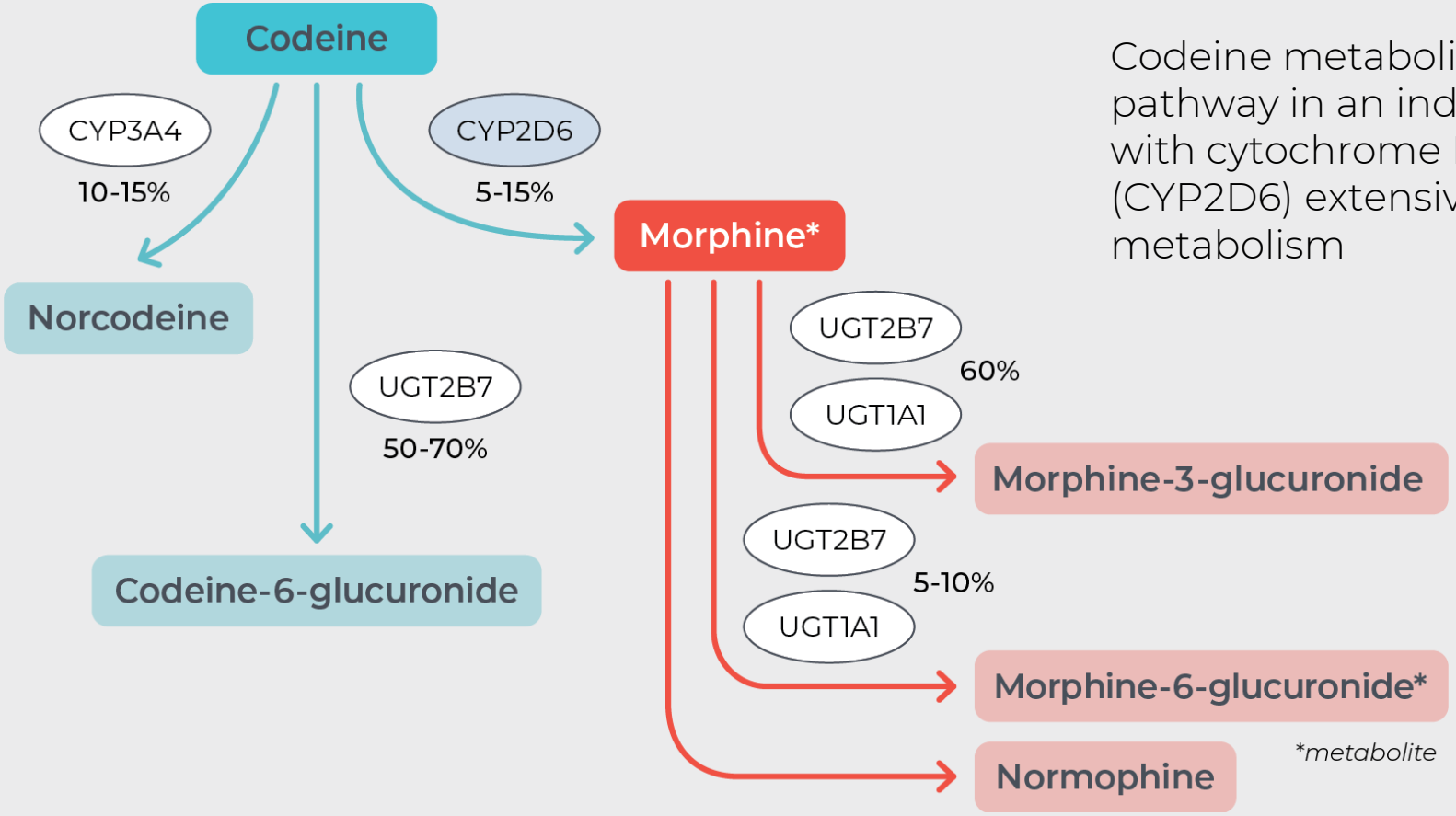
Codeine and CYP2D6

Codeine metabolism pathway in an individual with cytochrome P450 2D6 (CYP2D6) extensive metabolism



Codeine metabolism pathway in an individual with cytochrome P450 2D6 (CYP2D6) extensive metabolism

CPIC Guidelines for Cytochrome P450 2D6 Genotype and Codeine Therapy: 2014 Update. doi:10.1038/clpt.2013.254

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Codeine and CYP2D6

Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother

Gideon Koren, James Cairns, David Chitayat, Andrea Gaedigk, Steven J Leeder

Lancet 2006; 368: 704

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In April, 2005, a full-term healthy male infant, delivered vaginally, showed intermittent periods of difficulty in breastfeeding and lethargy starting on day 7. During a well-baby paediatric visit on day 11, the paediatrician noted that the baby had regained his birthweight. On day 12 however, he had grey skin and his milk intake had fallen He was found dead on day 13. Postmortem analysis showed no anatomical anomalies. Blood concentration of morphine (the active metabolite of codeine) was 70 ng/ml by gas chromatography-mass spectrometry (GC-MS)—neonates breastfed by mothers receiving codeine typically have morphine serum concentrations of 0–2·2 ng/mL. The mother had been prescribed a combination preparation of codeine 30 mg and paracetamol 500 mg after birth for episiotomy pain (initially two tablets every 12 h, reduced to half that dose from day 2 because of somnolence and constipation). She continued the tablets for 2 weeks. Because of poor neonatal feeding, she stored milk on day 10, which was later assayed for morphine by GC-MS. A morphine concentration of 87 ng/mL was found—the typical range of milk concentrations after repeated maternal codeine is 1·9–20·5 ng/mL at doses of 60 mg every 6 h.

Genotype analysis was done for cytochrome P450 2D6 (*CYP2D6*), the enzyme catalysing the O-demethylation of codeine to morphine.[2] The mother was heterozygous for a *CYP2D6*2A* allele with *CYP2D6*2×2* gene duplication, classified as an ultra-rapid metaboliser. This genotype leads to increased formation of morphine from codeine, consistent with the somnolence and constipation she experienced.[3] The maternal grandfather, the father, and the infant had two functional CYP2D6 alleles (*CYP2D6*1/*2* genotypes), classified as extensive metabolisers. The maternal grandmother was an ultra-rapid metaboliser.

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Codeine and CYP2D6

Table 2 Codeine therapy recommendations based on CYP2D6 phenotype

Phenotype	Implications for codeine metabolism	Recommendations for codeine therapy	Classification of recommendation for codeine therapy[a]
Ultrarapid metabolizer	Increased formation of morphine following codeine administration, leading to higher risk of toxicity	Avoid codeine use due to potential for toxicity. Consider alternative analgesics such as morphine or a nonopioid. Consider avoiding tramadol.[b]	Strong
Extensive metabolizer	Normal morphine formation	15–60 mg every 4 h as needed for pain (label recommendation)	Strong
Intermediate metabolizer	Reduced morphine formation	Begin with 15–60 mg every 4 h as needed for pain. If no response, consider alternative analgesics such as morphine or a nonopioid. Monitor tramadol use for response.	Moderate
Poor metabolizer	Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief	Avoid codeine use due to lack of efficacy. Consider alternative analgesics such as morphine or a nonopioid. Consider avoiding tramadol.[b]	Strong

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Codeine Therapy in the Context of Cytochrome P450 2D6 (CYP2D6) Genotype

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Amitriptyline: CYP2C19

Table 3 Dosing recommendations for the tertiary amines amitriptyline, clomipramine, doxepin, imipramine, and trimipramine based on cyp2c19 phenotype

Phenotype	Implication	Therapeutic recommendation[a,b]	Classification of recommendation for amitriptyline[c]	Classification of recommendation for other tertiary amine TCAs[c,d]
CYP2C19 ultrarapid metabolizer and CYP2C19 rapid metabolizer	Increased metabolism of tertiary amines compared to normal metabolizers Greater conversion of tertiary amines to secondary amines may affect response or side effects	Avoid tertiary amine use due to potential for sub-optimal response. Consider alternative drug not metabolized by CYP2C19. TCAs without major CYP2C19 metabolism include the secondary amines nortriptyline and desipramine. If a tertiary amine is warranted, utilize therapeutic drug monitoring to guide dose adjustments.[e]	Optional	Optional
CYP2C19 normal metabolizer	Normal metabolism of tertiary amines	Initiate therapy with recommended starting dose.[f]	Strong	Strong
CYP2C19 intermediate metabolizer	Reduced metabolism of tertiary amines compared to normal metabolizers	Initiate therapy with recommended starting dose.[f]	Strong	Optional
CYP2C19 poor metabolizer	Greatly reduced metabolism of tertiary amines compared to normal metabolizers Decreased conversion of tertiary amines to secondary amines may affect response or side effects	Avoid tertiary amine use due to potential for sub-optimal response. Consider alternative drug not metabolized by CYP2C19. TCAs without major CYP2C19 metabolism include the secondary amines nortriptyline and desipramine. For tertiary amines, consider a 50% reduction of the recommended starting dose.[f] Utilize therapeutic drug monitoring to guide dose adjustments.[e]	Moderate	Optional

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Sertraline: CYP2C19

Table 3b Dosing recommendations for sertraline based on CYP2C19 phenotype

Phenotype	Implication	Therapeutic recommendation	Classification of recommendation[a]
CYP2C19 Ultrarapid metabolizer	Increased metabolism when compared to extensive metabolizers.	Initiate therapy with recommended starting dose. If patient does not respond to recommended maintenance dosing, consider alternative drug not predominantly metabolized by CYP2C19.[b]	Optional
CYP2C19 Extensive metabolizer	Normal metabolism	Initiate therapy with recommended starting dose.	Strong
CYP2C19 Intermediate metabolizer	Reduced metabolism when compared to extensive metabolizers.	Initiate therapy with recommended starting dose.	Strong
CYP2C19 Poor metabolizer	Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	Consider a 50% reduction[d] of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19.[b]	Optional

[a]Rating scheme described in **Supplemental Materials**. [b]Drug-drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when selecting an alternative therapy. [c]Per the FDA warning, citalopram 20 mg/day is the maximum recommended dose in CYP2C19 poor metabolizers due to the risk of QT prolongation. FDA product labeling additionally cautions that citalopram dose should be limited to 20 mg/day in patients with hepatic impairment, those taking a CYP2C19 inhibitor, and patients greater than 60 years of age. [d]Percent dose adjustments corresponding to percent difference in oral clearances have been calculated/estimated by Stingl *et al.* (1).

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PGx and Drug Metabolism

In summary:

- Individual differences in the expression of a protein or enzyme (due to genetic variation) may affect the absorption, distribution, metabolism or excretion of a drug
- These effects could lead to changes in levels of the active drug metabolite, possibly being harmful and warranting the use of a different drug or dose of drug
- *There are approximately 200 drugs with FDA approved pgx-guided dosage information in the package insert*
- There are certain vulnerable patients that are good candidates for pharmacogenetic testing

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Who can benefit?

- Anyone experiencing side effects to specific medications
- Anyone not responding to specific medications
- Anyone requiring doses outside the recommended range
- Anyone planning to start on a new medication
- The aged; often with a high prevalence of polypharmacy

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What are the Challenges?

According to a recent global[1] survey the biggest challenges are

- Insufficient physician knowledge and awareness
- Physician scepticism or perceived lack of evidence
- Unclear test interpretation
- Unclear or lack of guidelines
- Disconnect between clinicians and researchers

- Also.....
- Reporting format
- Potential liability

Abou Diwan E, Zeitoun RI, Abou Haidar L, Cascorbi I, Khoueiry Zgheib N. Implementation and obstacles of pharmacogenetics in clinical practice: An international survey. Br J Clin Pharmacol. 2019 Sep;85(9):2076-2088. doi: 10.1111/bcp.13999. Epub 2019 Jul 7. PMID: 31141189; PMCID: PMC6710530.

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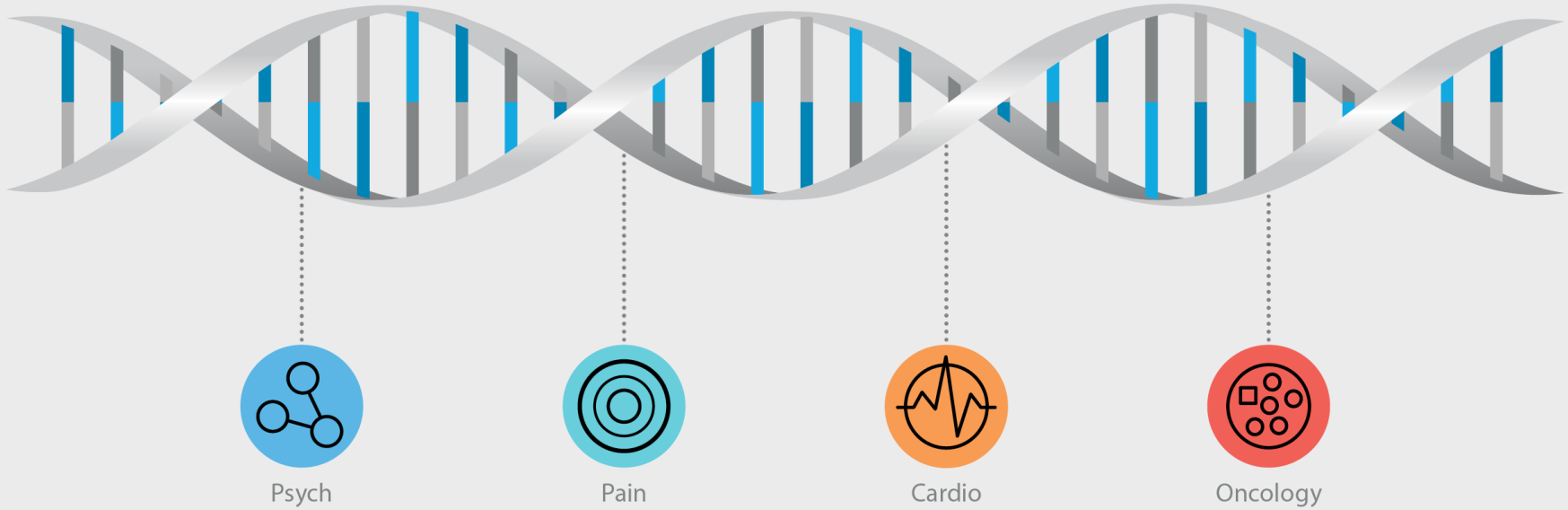

The Solution!

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Medcheck Report

Rigorous gene selection process that has seen only the most scientifically valid and clinically actionable genes included in the test

Current Medications Impacted In This Report

The medications listed below indicate the patient's **Current Medications** impacted in this report.

Atorvastatin	Phenotype	Genetic Test	Results	Evidence Level
Lipitor	Decreased function	SLCO1B1	*1/*5	CPIC A[5];FDA PGx Table[35]

TreatGx
ReviewGx

Implication: SLCO1B1 alleles indicate increased Atorvastatin exposure as compared with normal function

2 For specific CPIC dosing recommendations refer to TreatGx

Current patient medications appear first with any gene-drug interactions highlighted

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Medcheck Report

Medication Summary

1 Mild or no known interaction
2 Moderate gene-drug interaction
3 Serious gene-drug interaction; should be evaluated carefully and alternative medications should be considered

Analgesia

1
Alfentanil
Carisoprodol
Fentanyl
Morphine

2
Acetylsalicylic acid
Celecoxib
Codeine
Flurbiprofen
Hydrocodone
Ibuprofen
Imipramine
Meloxicam
Piroxicam
Tenoxicam
Tramadol

Anesthesia

1

...Autoimmune

1
Cevimeline
Cyclosporine
Mercaptopurine
Tacrolimus
Thioguanine

2
Etanercept

3
Siponimod

Cancer

1
Capecitabine
Fluorouracil

2
Erdafitinib
Tamoxifen

Cardiovascular

1

...Cardiovascular

2
Captopril
Cilazapril
Enalapril
Flecainide
Fluvastatin
Fosinopril
Lisinopril
Lovastatin
Metoprolol
Perindopril
Pitavastatin
Propafenone
Quinapril
Ramipril
Simvastatin
Trandolapril
Warfarin

Endocrinology

3

...Gastroenterology

2
Dronabinol
Lansoprazole
Omeprazole
Pantoprazole

Infection

1
Abacavir
Amikacin
Atazanavir
Efavirenz
Gentamicin
Paromomycin
Plazomicin
Streptomycin
Tobramycin
Voriconazole

2
PEG-interferon alpha

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Medcheck Report

Dosing guidelines

Amitriptyline	Phenotype	Genetic Test	Results	Source/Evidence
Elavil Levate	Intermediate metabolizer	CYP2D6	*3/*10	CPIC A[16];FDA PGx Table[35]
TreatGx ReviewGx	Normal metabolizer	CYP2C19	*1/*1	CPIC A[16]

Implication: CYP2D6 intermediate metabolizer: reduced metabolism of Amitriptyline to less active compounds

Higher plasma concentrations of active drug may increase the risk of adverse drug reactions

2 Consider a reduction of the recommended dose

Nortriptyline	Phenotype	Genetic Test	Results	Source/Evidence
Aventyl Pamelor	Intermediate metabolizer	CYP2D6	*3/*10	CPIC A[16];FDA PGx Table[35]
TreatGx ReviewGx				

Implication: CYP2D6 intermediate metabolizer: reduced metabolism of Nortriptyline to less active compounds

Higher plasma concentrations of active drug may increase the risk of adverse drug reactions

2 Consider a reduction of the recommended dose

GenXys Health Care Systems

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Precision Prescribing
Using medication management software

In collaboration with GenXys Healthcare sytems

GenXys Health Care Systems

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Medication Management Software

- Empowers physicians to use pharmacogenetic testing by automating the report interpretation process and providing all intervention tools in one place; including clear dosing guidelines
- Pharmacogenetics (PGx) recommendations are focused on being clinically actionable and having high levels of evidence
- The opportunity to view PGx guidance alongside other factors usually covered in traditional software: age, renal and hepatic function, drug-drug interactions
- Can be used to identify patients that would benefit from PGx testing

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Medication Management Software

ReviewGx

- A holistic overview of all factors affecting drug response
- Deprescribing opportunities- primarily geared toward safe medication use in older patients / avoiding polypharmacy
- Alerts for certain combinations of medications that have safety issues

TreatGx

- Tailored medication dosing options for the patient
- The ability to view on one screen how several clinically relevant factors will affect medication
- Condition-specific clinical features such as sorting by risk of side effects for antidepressants therapy
- Confidently find the proper medication and the correct dosage

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Medication Management Software

TreatGx- a clinical tool to apply PGx testing in practice

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THANK-YOU

Please visit us at stand A12

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