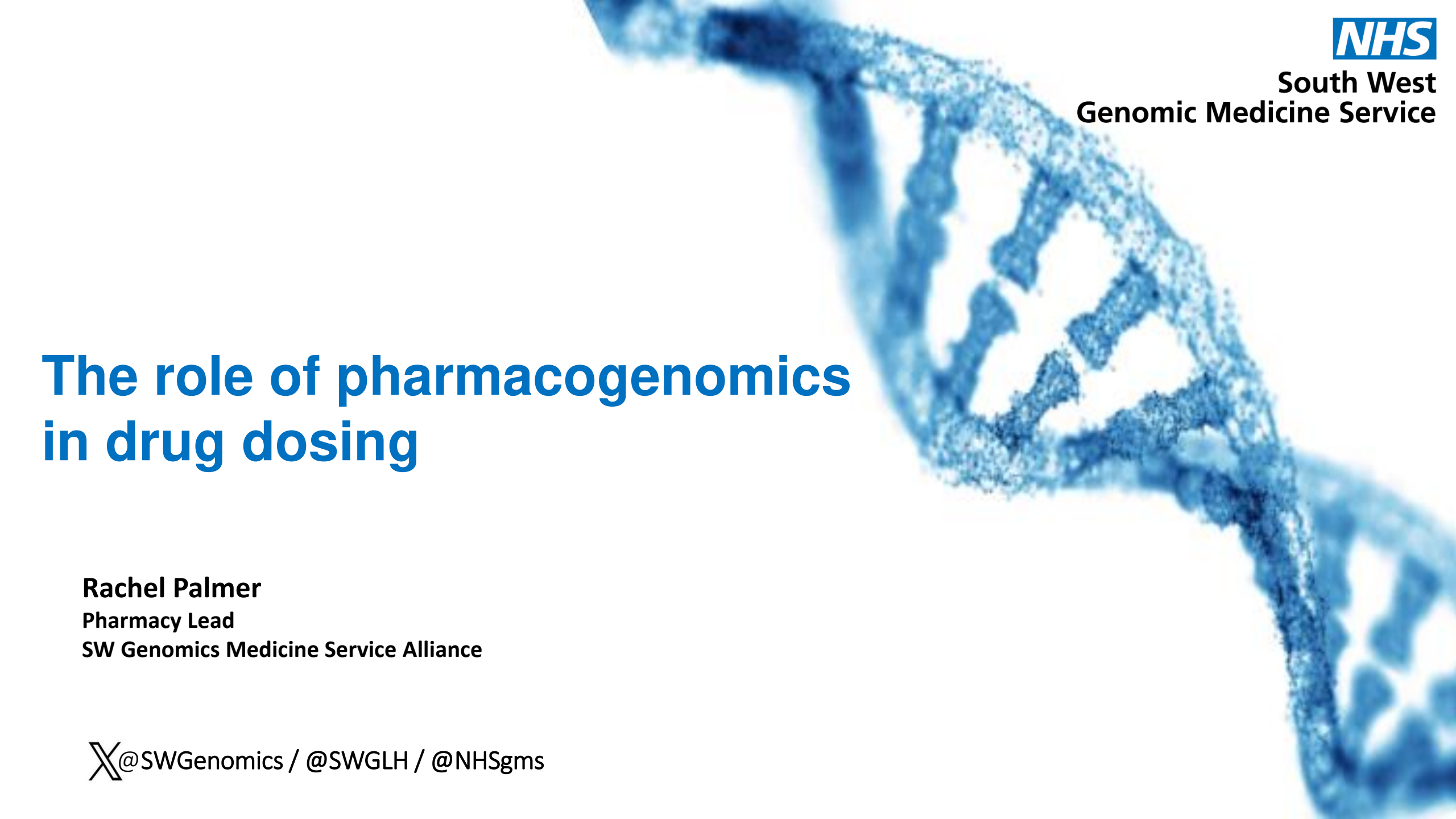

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The role of pharmacogenomics in drug dosing

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SW Genomics Medicine Service Alliance

@SWGenomics / @SWGLH / @NHSgms

Pharmacogenomics (PGx)

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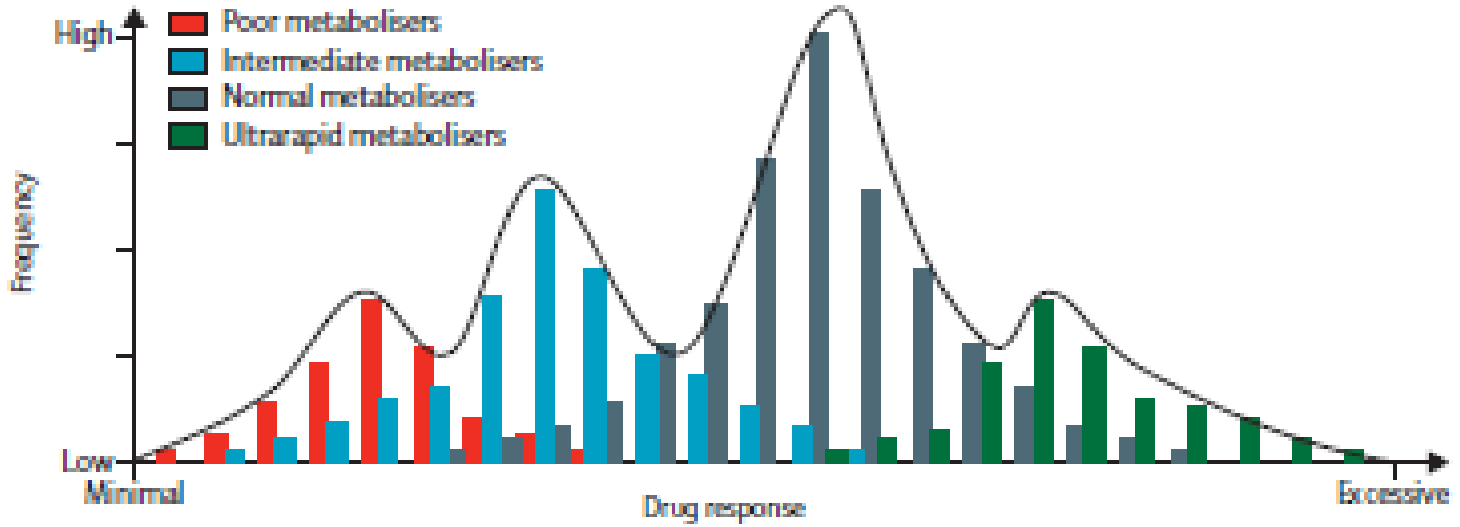
Pharmacogenomic variants affect an individual's response to a drug

Pharmacology + **Genomics** = **Safe, effective medicines tailored to variations in a person's genes**



Roden et al (2019)

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Metaboliser status *CYP2C19*

GENOTYPE	PHENOTYPE
*CYP2C19*1*	Normal function
*CYP2C19*2*	Loss of function
*CYP2C19*3*	Loss of function
*CYP2C19*17*	Gain of function

Phenotype	Diplotype
Ultrarapid metabolisers	2x gain of functional alleles
Normal metaboliser	2x normal functional alleles
Intermediate metabolisers	1x normal function allele and 1x loss of function allele OR 1x gain of function allele and 1x loss of function allele
Poor metabolisers	2x loss of functional alleles

Slide credit; NT GMSA

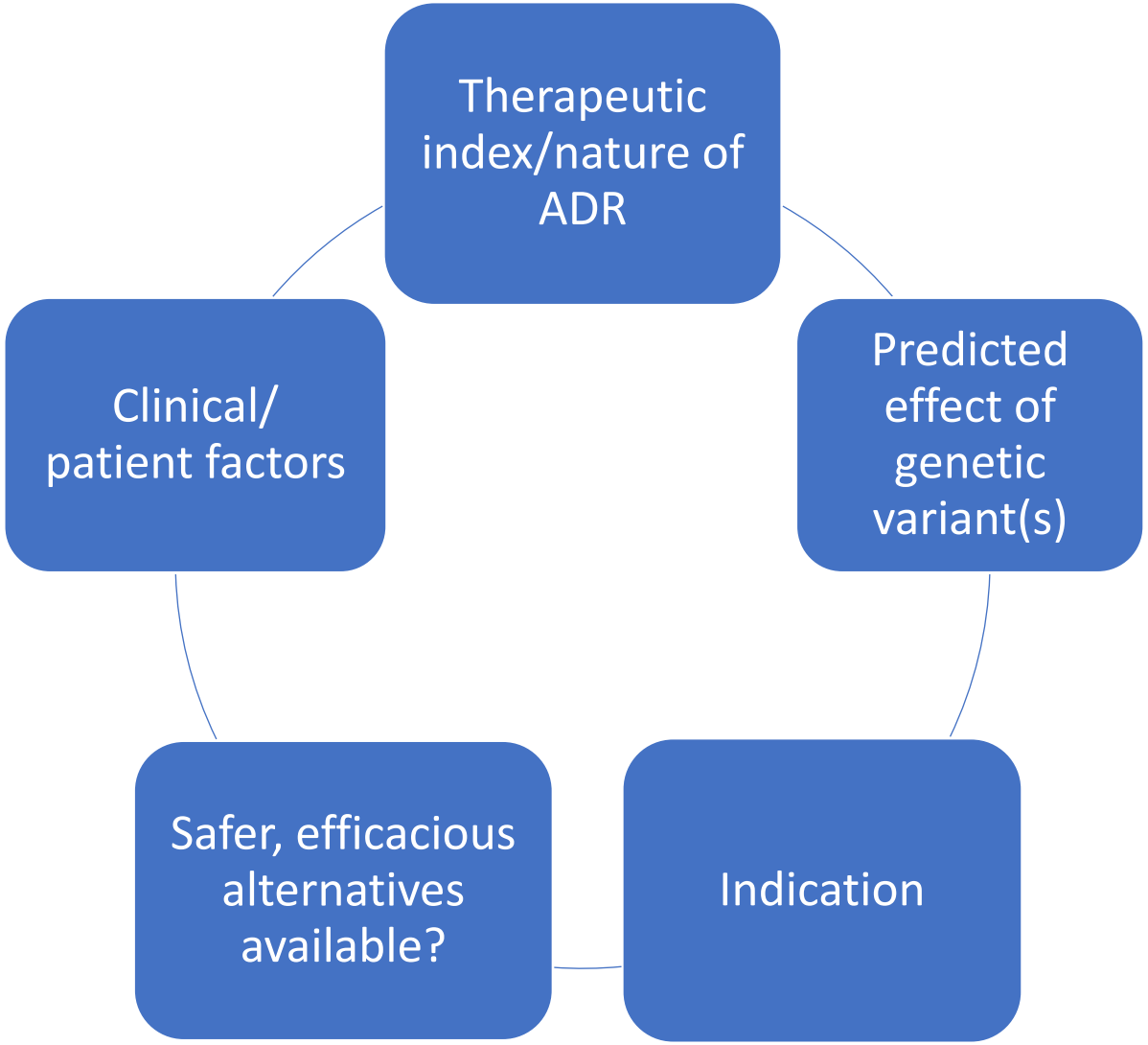
Why is there variation in drug response between individuals?

Pharmacogenomics **will not replace** our clinical judgement; it is an **additional tool** within our medicines optimisation toolbox, still need to consider:

- Renal and liver function
- Drug-drug interactions
- Co-morbidities etc.

Slide credit Genomics Education

Drug avoidance versus dose reduction



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How are dose reductions calculated?

‘In silico’ functional studies

Pharmacokinetic data

Clinical trial & real-world data

Monitor closely & consider other clinical factors. Dose titration may be required

Information on PGx dose adjustment

- SmPC
- BNF
- UK-specific pharmacogenomics dosing guidance (*DPYD, TPMT/NUDT15*)
- International dosing guidance
  - CPIC
  - DPWG
  - PharmGKB/DNA-driven Rx
  - May not reflect UK drug availability or commissioning

Pharmacogenomics in Practice: *DPYD* Testing

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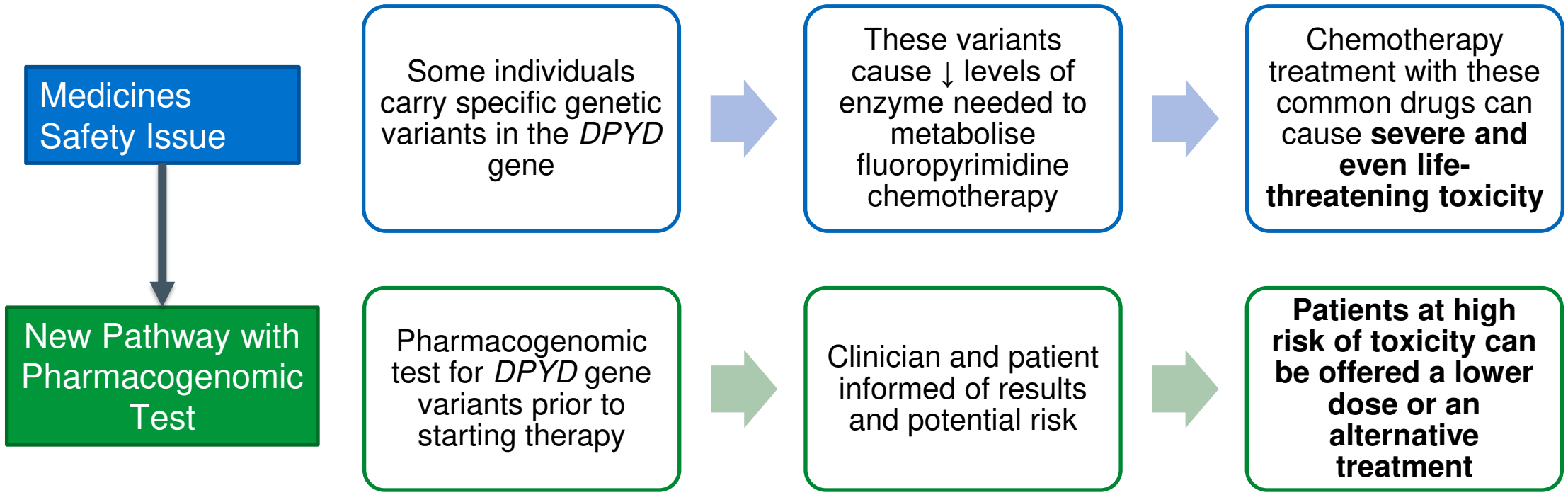
- *DPYD* pharmacogenomic test offered to all patients prior to starting fluoropyrimidine chemotherapy (5-fluorouracil, capecitabine)



- Anticipated to ↓ severe toxicity (≥ grade 3), ↓ hospitalisation, ↓ deaths, ↓ use of rescue drug

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DPYD dosing guidance

UKONS Oncology Nursing Society · The Royal College of Pathologists · Clinical Oncology, The Royal College of Radiologists
bopa · acp Association of Cancer Physicians · Royal College of Physicians

UK Chemotherapy Board

Personalised Medicine Approach For Fluoropyrimidine-based Therapies

Table 1. *DPYD* heterozygous genotype and recommended dose reduction

allele	% DPD activity associated with a heterozygous genotype	Recommended dose adjustment for a heterozygous genotype
c.1905+ 1G>A (IVS14+1G>A)	50	50% dose reduction or alternative therapy*. If tolerant after the first cycle, dose increment to a dose of 75% of the target dose over subsequent cycles.
c.1679T>G (p.I560S)	50	50% dose reduction or alternative therapy*. If tolerant after the first cycle, dose increment to a dose of 75% of the target dose over subsequent cycles.

Mavacamten

- Indicated in hypertrophic obstructive cardiomyopathy
- Mandatory requirement for *CYP2C19* genotyping as part of product licence

‘Patients with CYP2C19 poor metaboliser phenotype may have increased mavacamten exposures (up to 3 times) that can lead to increased risk of systolic dysfunction compared to normal metabolisers’

Mavacamten

CAMZYOS™▼ (mavacamten) Interactive Dosing Guide

CAMZYOS is indicated for the treatment of symptomatic (NYHA class II, III) obstructive HCM in adult patients.[1]

Treatment monitoring and warnings for use

This is not an exhaustive list; please refer to the SmPC before prescribing.

CYP2C19 poor metabolisers may have up to three times increased CAMZYOS exposure vs normal metabolisers. If CYP2C19 phenotype is unknown then follow the poor metabolisers dosing guidance.

Certain CYP450 inhibitors and inducers are contraindicated in patients taking CAMZYOS because of increased heart failure risk. More information can be found here.

CAMZYOS can cause heart failure due to systolic dysfunction; therefore, patients should be regularly monitored for obstructive HCM symptoms, LVOT gradient with Valsalva manoeuvre, and LVEF using echocardiogram.

In patients with an intercurrent illness, such as serious infection or arrhythmia (including AF or other uncontrolled tachyarrhythmia) that may impair systolic function, LVEF assessment is recommended, and dose increases are not recommended until the intercurrent illness is resolved.

Statins & SLCO1B1

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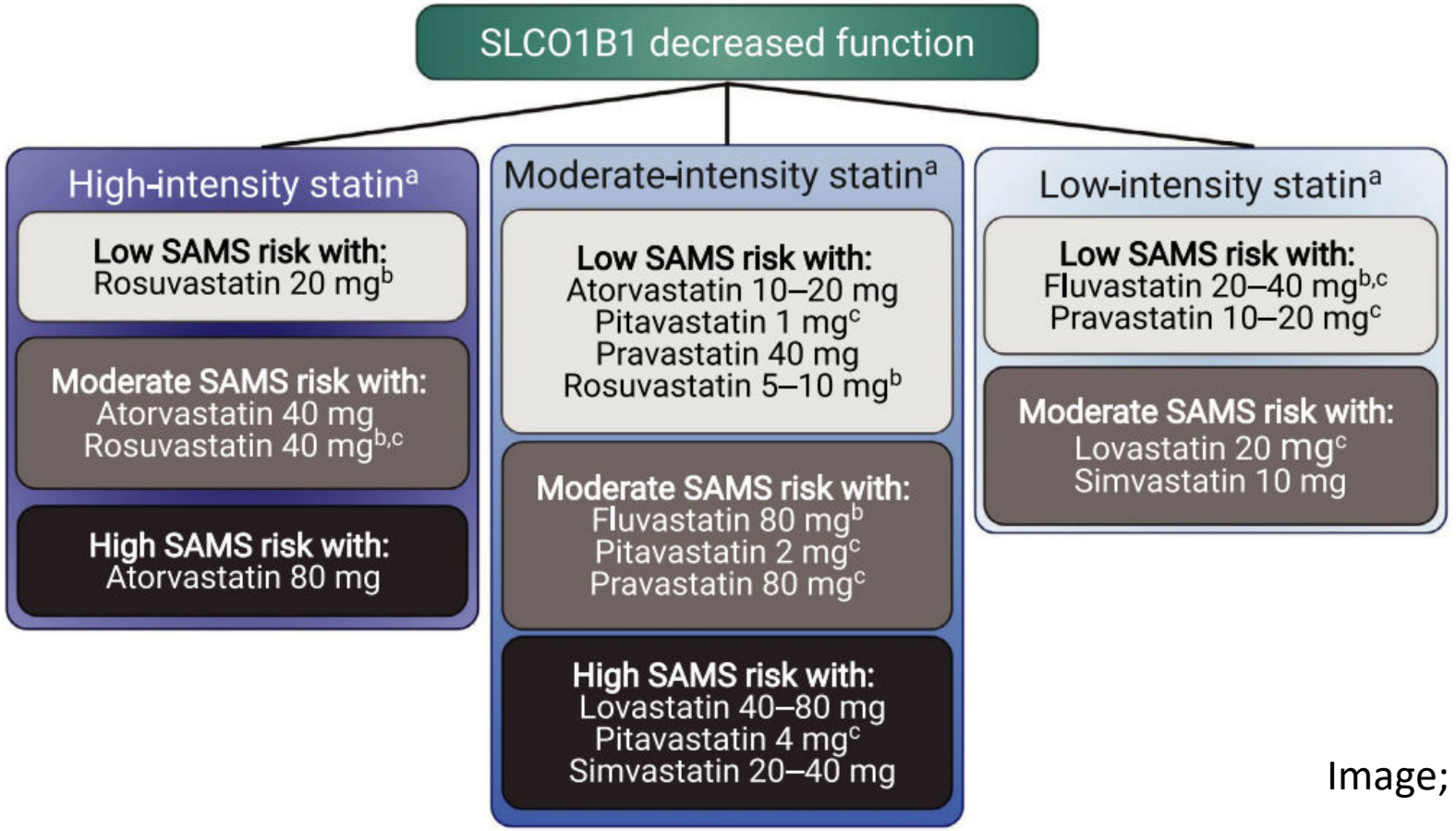
- SLCO1B1 facilitates hepatic uptake of statins
- Decreased function can markedly increase exposure to statins



Image; CPIC guidance 2022

Omeprazole & CYP2C19

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CPIC GUIDELIN

Check for updates

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2C19* and Proton Pump Inhibitor Dosing

emc

Losec Capsules 10mg

Active Ingredient: omeprazole

Company: Neon Healthcare Ltd

- Rapid metaboliser; Standard starting dose. Consider increasing by 50–100% for the treatment of H. pylori and erosive esophagitis
- Poor metaboliser; For chronic therapy & efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy

- Poor metabolisers; metabolism of omeprazole is probably mainly catalysed by CYP3A4. ….the mean AUC was 5 to 10 times higher in poor metabolisers ….. **These findings have no implications for the posology of omeprazole**

Information sources – SPCs; 4.2 Posology & administration

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Citalopram

For known poor CYP2C19 metabolisers, initial dose 10mg

Metoprolol

PM [CYP2D6] poor metabolisers may require lower than normal doses

Amitriptyline

Known poor metabolisers of CYP2D6 or CYP2C19 may have higher plasma concentrations of amitriptyline and its active metabolite nortriptyline. Consider a 50% reduction of the recommended starting dose

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Thank you!