

# Pharmacogenomics (PGx) in Clinical Practice

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(Stroke & TIA)



# Objectives



**Brief introduction  
to PGx**



**Specific clinical  
examples in  
practice**



**Healthcare  
Landscape**



**Resources**



## Genomics

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- The study of an organism's complete set of genetic information.
- The genome includes both genes (coding) and non-coding DNA.
- 'Genome': the complete genetic information of an organism.

VS



## Genetics

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- The study of heredity
- The study of the function and composition of single genes.
- 'Gene': specific sequence of DNA that codes for a functional molecule.

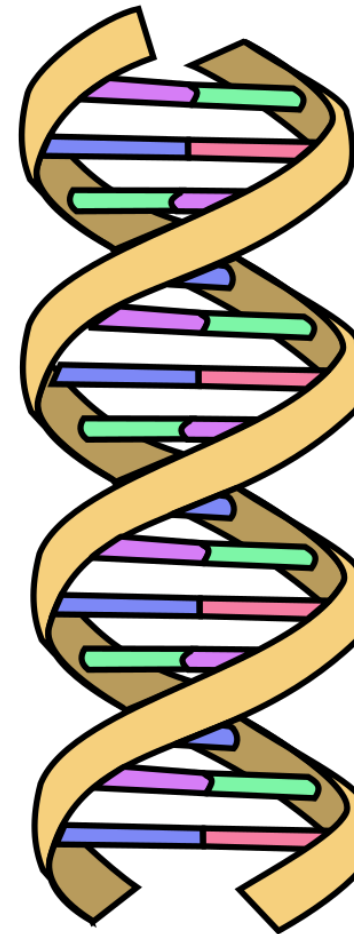
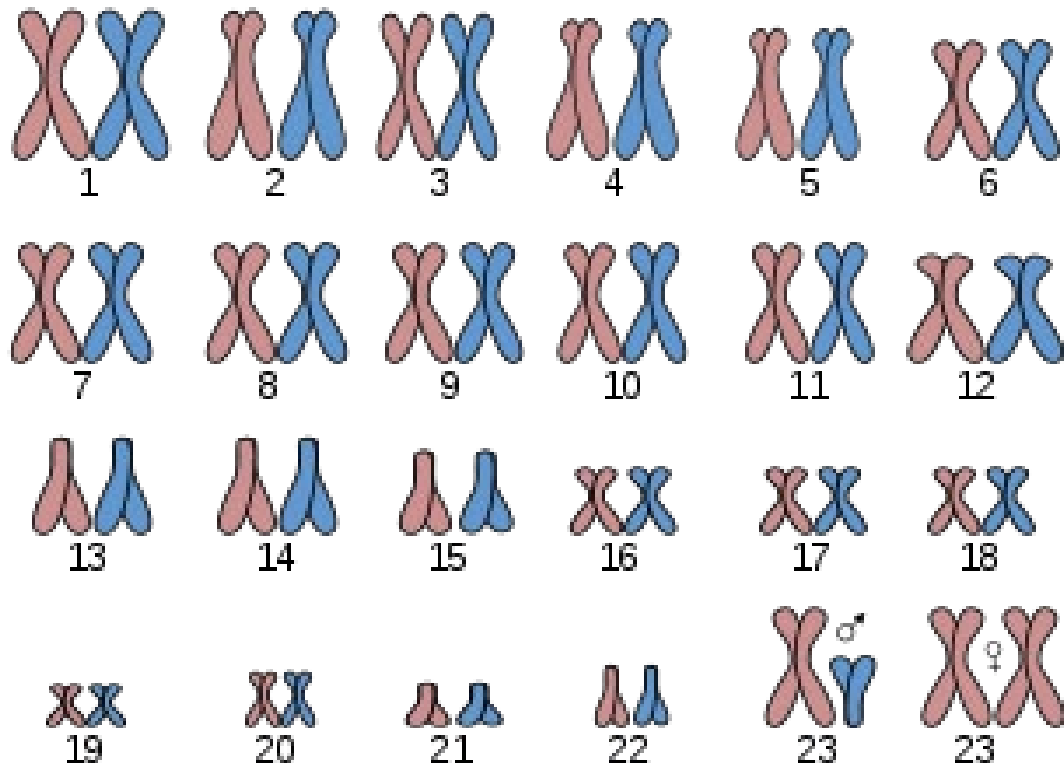
# **(Pharmaco)genomics – what is it?**

## **Genomic medicine:**

Utilisation of genomic data to guide diagnosis, predict disease (and prognosis) and inform therapeutics

## **Pharmacogenomics:**

Influence of an individual's genes on their response to a medicine



-  = Adenine
-  = Thymine
-  = Cytosine
-  = Guanine
-  = Phosphate backbone

DNA

If you spoke  
one 'letter' of DNA  
per second

T, A, A, C, G, T, A, C, C, A, T, C

24 hours a day,

it would take about

100 years to recite the entire  
human genome





TGCC TA

UNMUTATED DNA

TGAC TA

SUBSTITUTION

TGCCC TA

INSERTION

TGCTA

DELETION

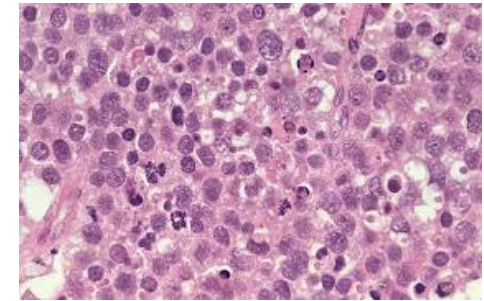
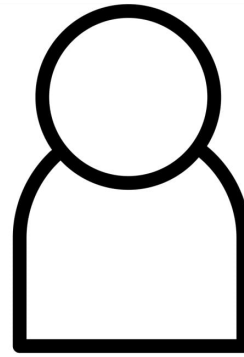
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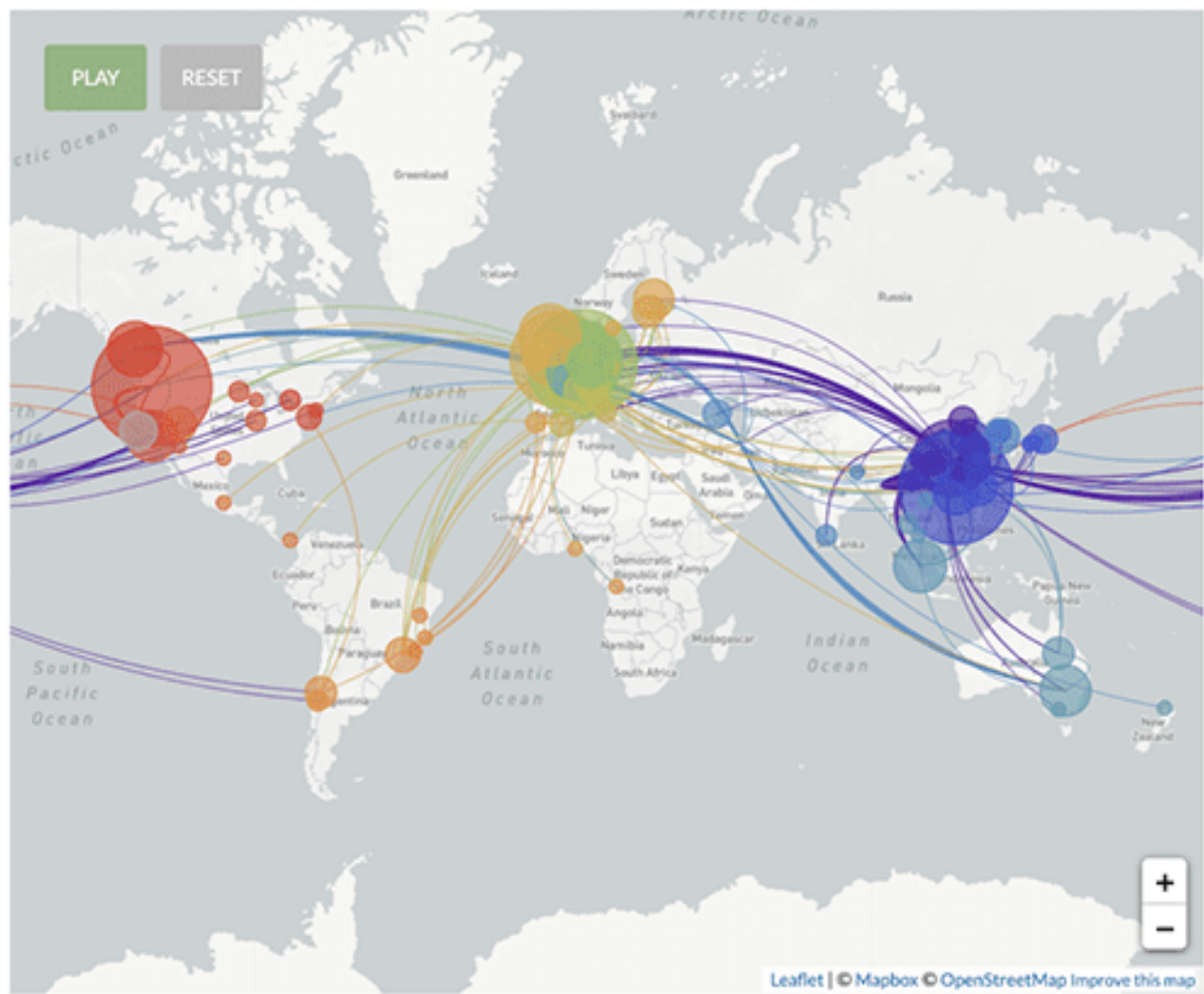
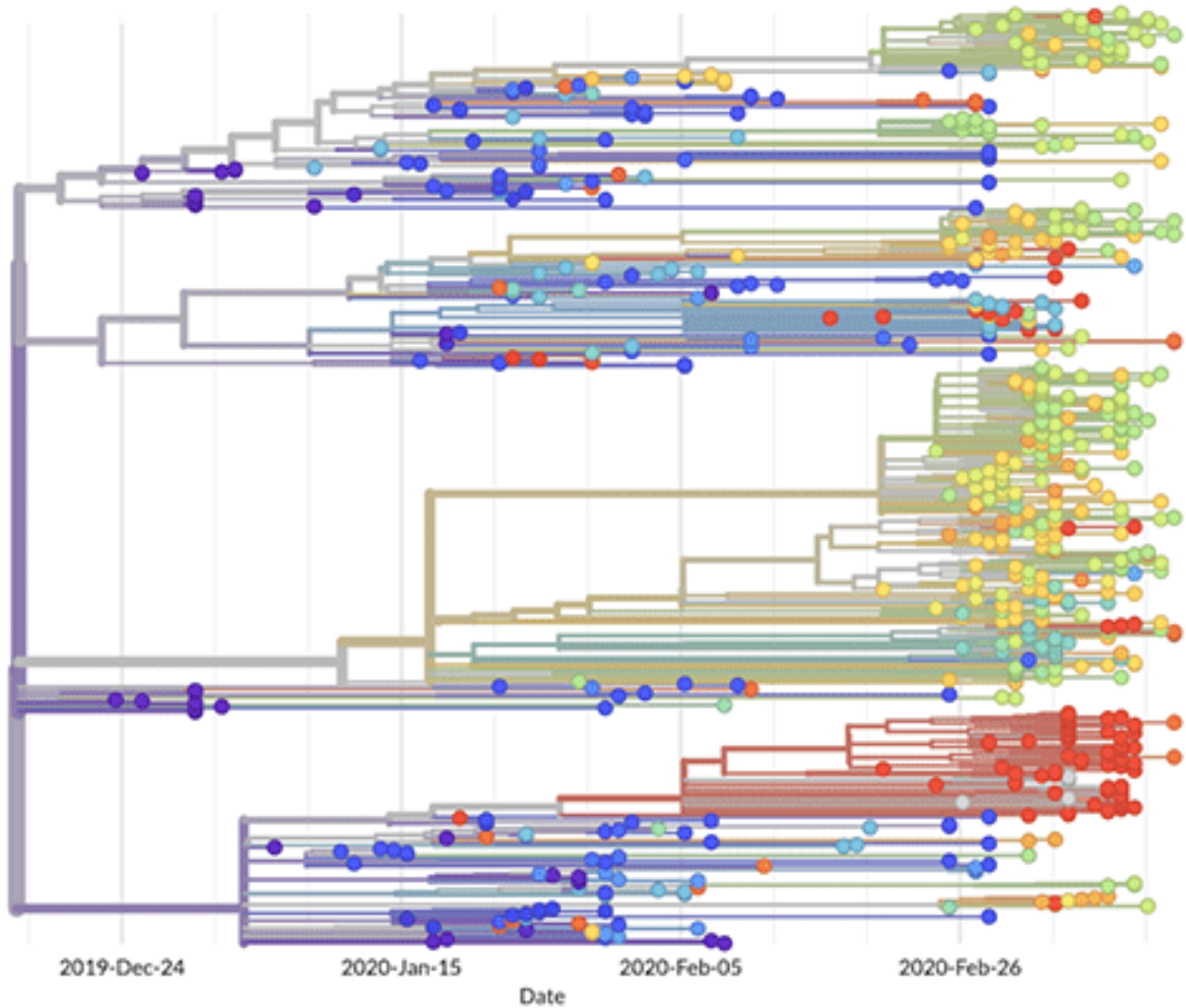
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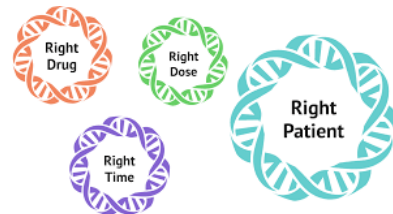
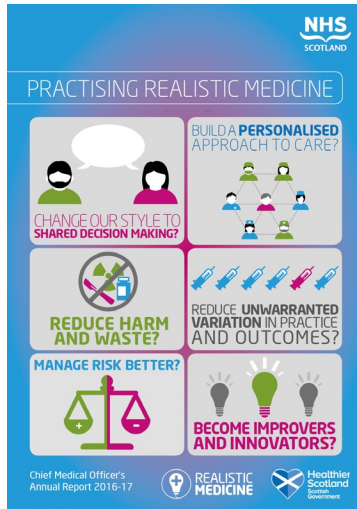
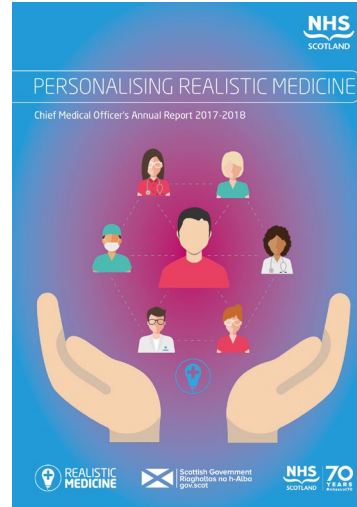
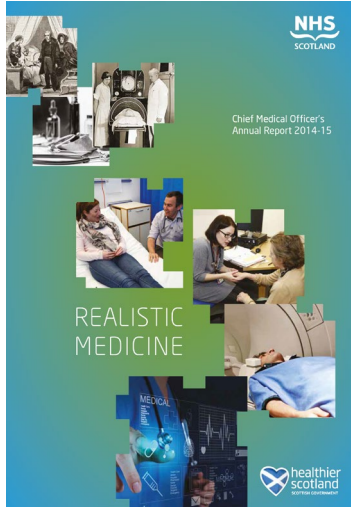
# Genomics and Healthcare

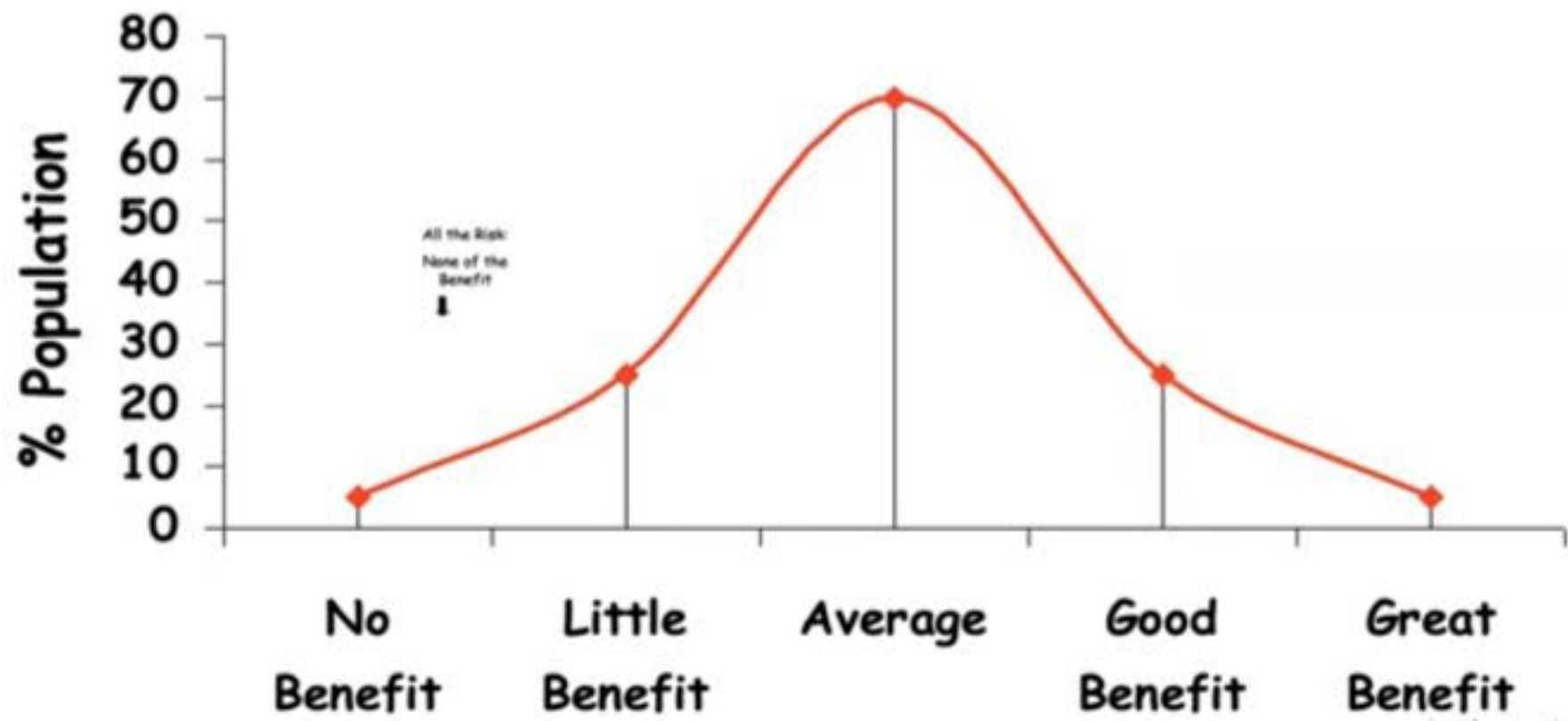


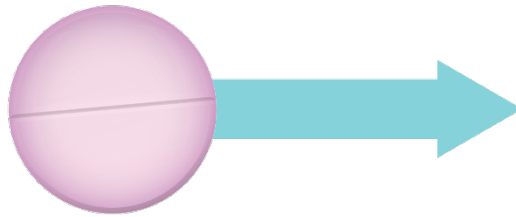
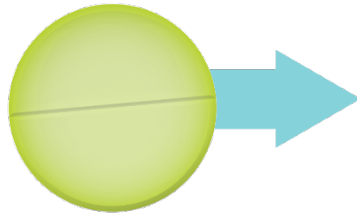
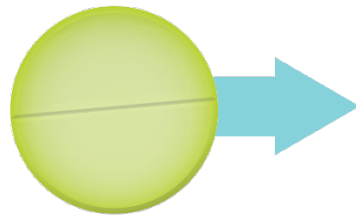


# Pharmacogenomics – so what?









# Clinical examples

- HIV – abacavir (HLA-B\*5701)
- Oncology – fluroquinolones (DPYD)
- Cardiovascular – antiplatelet therapy (CYP2C19)
- Mental health – antidepressants (CYP2C9)
- Pain – codeine (CYP2D6)
- Antimicrobials – gentamicin (MT-RNR1)
- Gastroenterology/Rheumatology – azathioprine (TPMT)

# Abacavir

- Nucleoside reverse transcriptase inhibitor
- Combination therapy as treatment of HIV infection
- Risk of HSR
  - Can have multi-organ involvement and life threatening
  - 5-8% of individuals within first 6/52 of therapy
  - Cannot re-initiate
  - Challenges with anti-retroviral therapy
  - Highest in those who test positive for HLA-B\*5701 allele
  - **Status MUST be documented prior to commencing therapy**
  - **Example of pharmacogenetic test to prevent significant toxicity**



[Home](#) > [Drug Safety Update](#)

## **5-fluorouracil (intravenous), capecitabine, tegafur: DPD testing recommended before initiation to identify patients at increased risk of severe and fatal toxicity**

Patients with complete or partial dihydropyrimidine dehydrogenase (DPD) deficiency are at increased risk of severe and fatal toxicity during treatment with these medicines. All patients should be tested for DPD deficiency before initiation to minimise the risk of these reactions.

# Summary of Product Characteristics

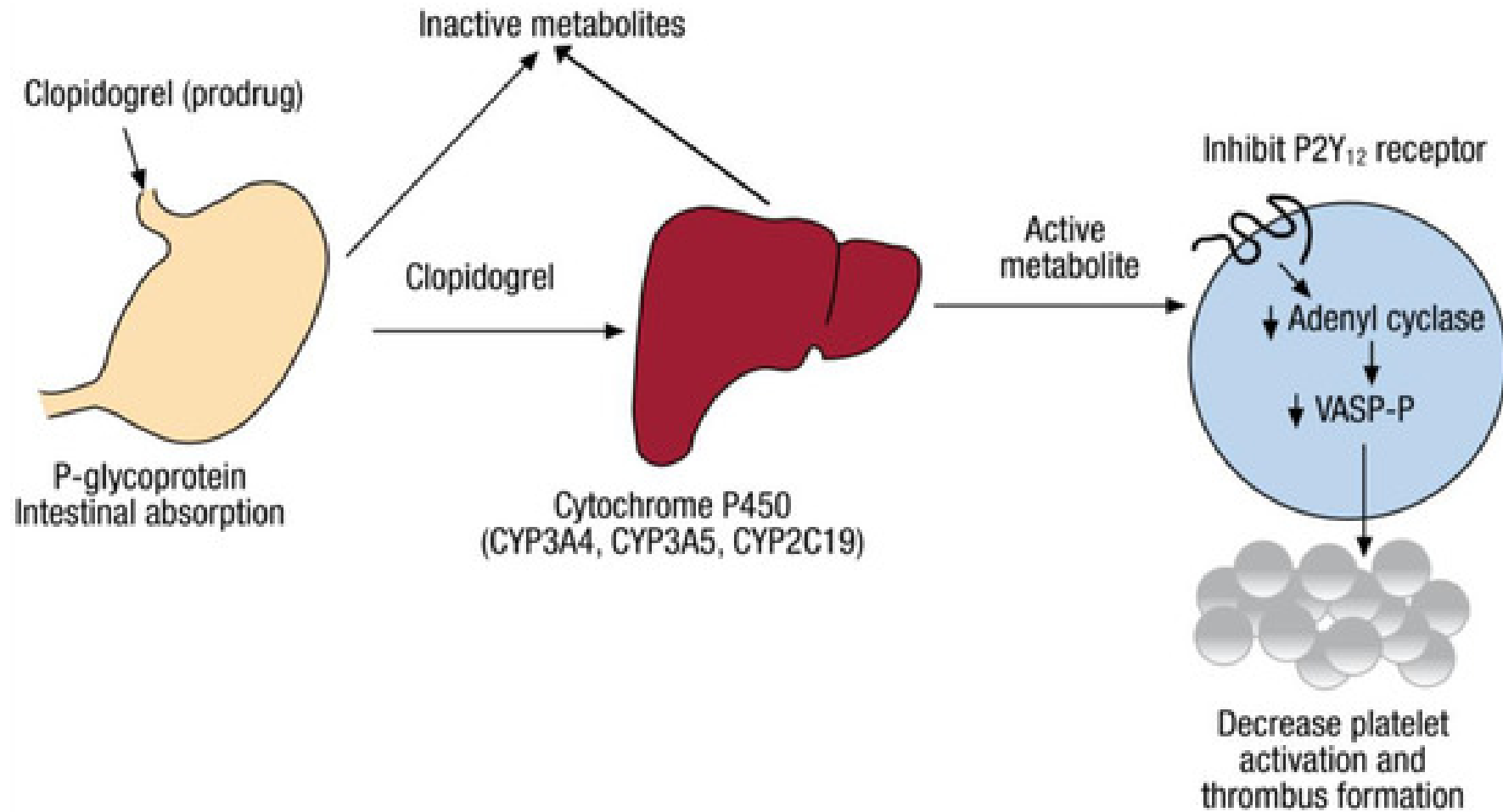
- *Cytochrome P450 2C19 (CYP2C19)*
- Pharmacogenetics: In patients who are poor CYP2C19 metabolisers, **clopidogrel** at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Tests are available to identify a patient's CYP2C19 genotype.
- CYP2D6 metabolism
- **Codeine** is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate therapeutic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.
- *Known poor metabolisers of CYP2D6 or CYP2C19*
- These patients may have higher plasma concentrations of **amitriptyline** and its active metabolite nortriptyline. Consider a 50% reduction of the recommended starting dose.



**ANIA | Pharmacogenetics Programme**



**Pharmacogenetic testing to guide use of clopidogrel following ischaemic stroke or transient ischaemic attack (TIA) in adults**



Ref: *J. Pers. Med.* 2018, 8(1), 8; <https://doi.org/10.3390/jpm8010008>



Guidance

Standards and  
indicators

Clinical Knowledge  
Summaries (CKS)

British National  
Formulary (BNF)

British National  
Formulary for  
Children (BNFC)

Life  
sciences

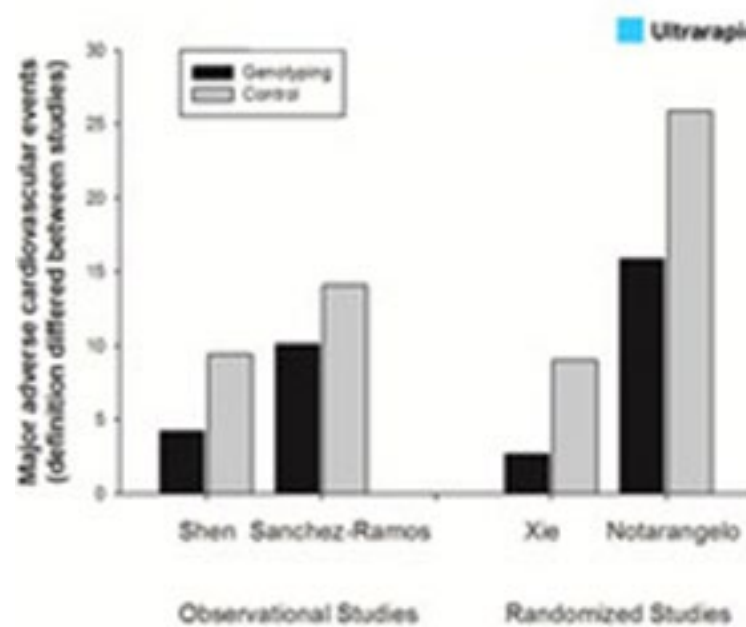
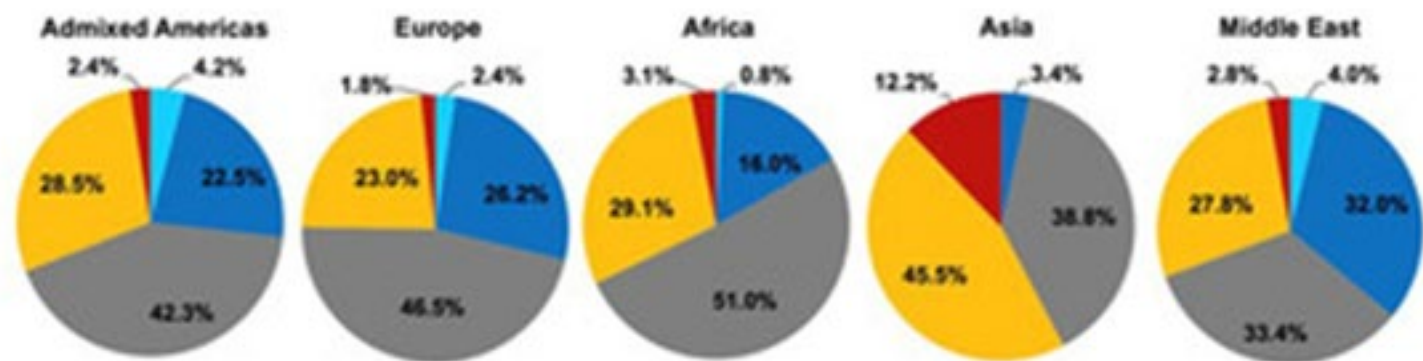
More from  
NICE

[Home](#) > [NICE Guidance](#) > [Conditions and diseases](#) > [Cardiovascular conditions](#) > [Stroke and transient ischaemic attack](#)

# CYP2C19 genotype testing to guide clopidogrel use after ischaemic stroke or transient ischaemic attack

Diagnostics guidance | DG59 | Published: 31 July 2024

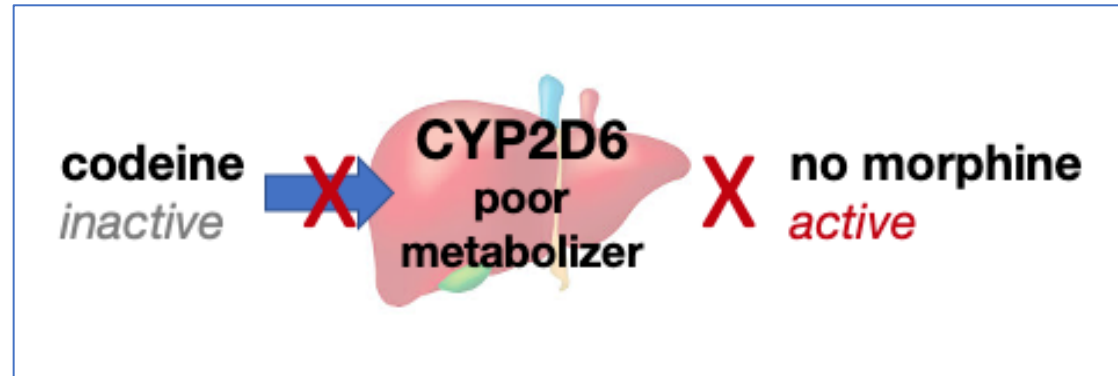
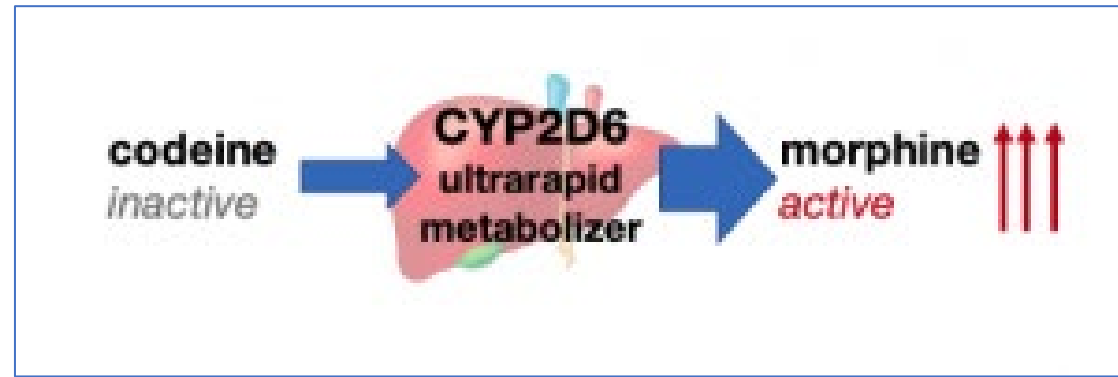
# Genotyping for clopidogrel responsiveness

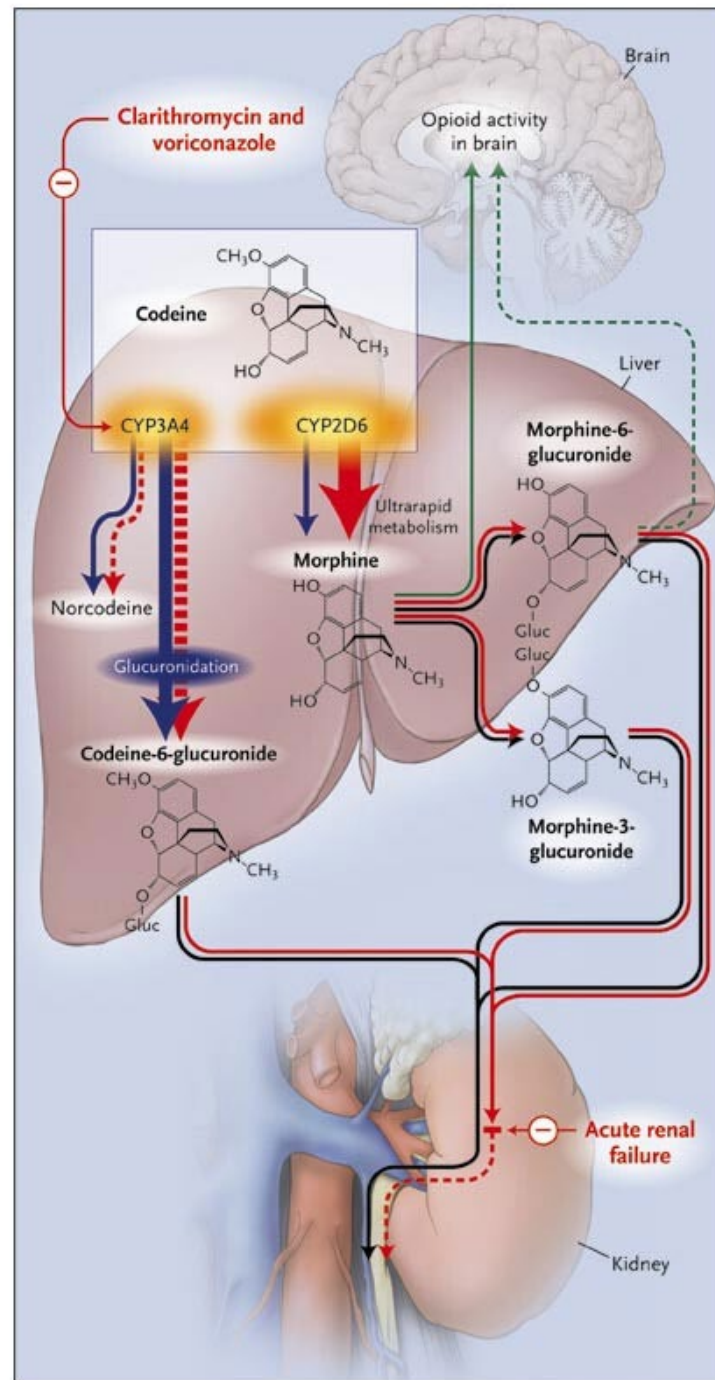


■ Ultrarapid 
 ■ Rapid 
 ■ Normal 
 ■ Intermediate 
 ■ Poor

Metabolizer phenotype	Genotype	U.S. population	Response to clopidogrel
Ultra-rapid (UM)	2 increased function alleles (*17/*17)	1-5%	Normal or increased antiplatelet response to clopidogrel
Rapid (RM)	1 increased function and 1 normal function allele (*1/*17)	20-30%	Normal or increased antiplatelet response to clopidogrel
Normal (NM)	Absence of any tested increased function or LOF alleles (*1/*1)	35-50%	Normal antiplatelet response to clopidogrel
Intermediate (IM)	1 LOF allele (*1/*2, *1/3, *2/17, *3/*17)	20-30%	Reduced antiplatelet response to clopidogrel
Poor (PM)	2 LOF alleles (*2/*2, *2/3, *3/*3)	1-5%	Significantly reduced antiplatelet response to clopidogrel

# Codeine & CYP2D6





Ref: *N Engl J Med* 2004;351:2827-2831  
 DOI: 10.1056/NEJMoa041888

# Healthcare Landscape

- **England**

- [NHS England » NHS Genomic Medicine Service](#)
- 7 Genomic Medicine Service Alliances

- **Scotland**

- [Home - Scottish Strategic Network for Genomic Medicine](#)
- [Genomic medicine strategy 2024 to 2029 - gov.scot](#)

- **Wales**

- [AWMGS - Genomics Strategy for Wales](#)

# Challenges

## Data platform

- Recorded as 'allergy'
- Visibility/accessibility of the data

Equity to service

Educating workforce

Real world data

Patient  
perception/education

# Genomics Education Programme



- <https://www.genomicseducation.hee.nhs.uk/>
- Free to access
- Delivered by HEEs Genomics Education Programme
- Bitesize (10min) resources, online modules
- Master's in Genomic Medicine (funding for NHS-E staff only)

# Genomics Education Programme - GeNotes

## Oncology

Short, useful summaries to support your clinical decisions when considering genomic testing

Coming soon

## Cardiology

Step-by-step guides on how to access genomic testing and what to do when results come back

Coming soon

## Endocrinology

Key information for clinicians accessing genomic testing for their patients

Coming soon

## Fetal and Women's Health

Clinical presentations from pre-pregnancy to antenatal care

Coming soon

## Paediatrics

Built around patient scenarios, these articles outline key information about testing and results

Coming soon

## Pharmacogenomics

When and why genomic testing is of relevance when prescribing and dispensing

**Questions?**

