The Rise of Clinical Pharmacogenomics: A Success Story

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What is pharmacogenomics?

Pharmacogenomics (PGx) is the study of how genetic variants influence a person's response to medications.

Findings from PGx can lead to better future outcomes for both individuals and healthcare providers through improved medication safety and/or efficacy

NHS Tayside and pharmacogenomics

In 2012 we started *ADBR2* genotyping for asthma patients.

The *ADRB2* p.(Gly16Arg) variant is associated with a decline in asthma control for those on beta-agonist drugs (eg. Salbutamol). Asthma patients with this variant may benefit from alternative medications or dosing strategies.

In 2019 our *DPYD* genotyping service began.

Fluoropyrimidine drugs are used as an adjuvant and palliative treatment for colorectal, pancreatic, oesophago-gastric, breast and head/neck cancers.

This treatment is generally well tolerated, but in 5–10% of patients severe adverse drug reactions (ADRs) can occur, which can be fatal in rare cases. A significant proportion of these ADRs are likely to be caused by variants in the *DPYD* gene.

A *CYP2C19* testing pilot was introduced for clopidogrel use in 2022.

Clopidogrel is an antiplatelet medication that is widely prescribed throughout the NHS after a stroke, tranisent ischaemic attack (TIA) or heart attack to reduce the risk of further events.

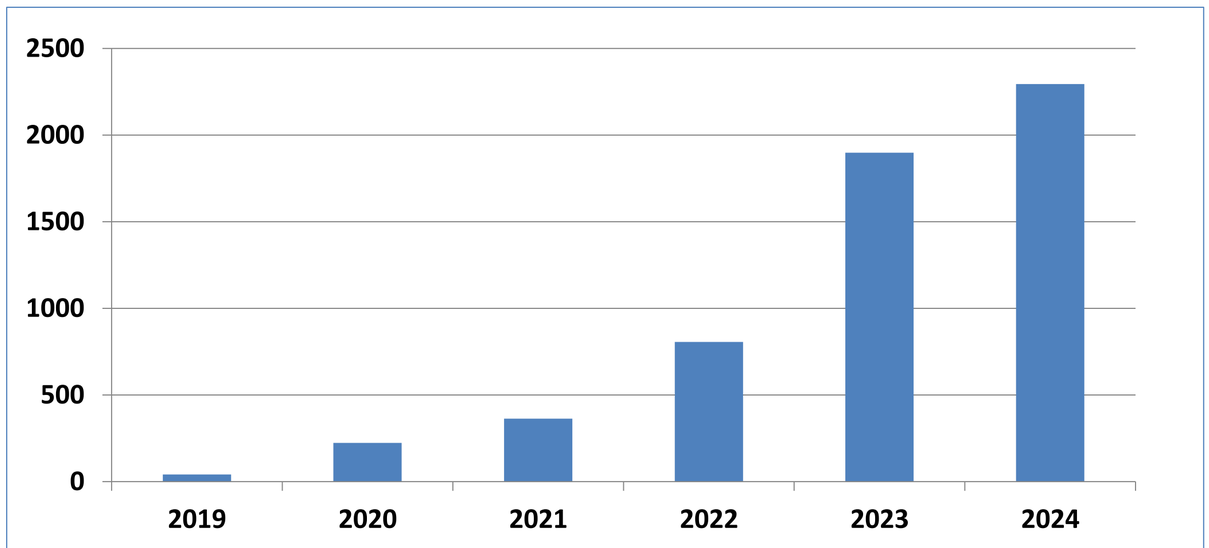
However for around 30% of patients prescribed in Scotland, clopidogrel will not work effectively, due loss of function variants in the *CYP2C19* gene, so further strokes are not prevented.

A *TPMT* genotyping pilot commenced in 2023, now in clinical service.

Thiopurine drugs are used to treat skin disorders, autoimmune diseases, acute lymphoblastic leukaemia and act as immunosuppressants in organ transplant recipients. The metabolism of thiopurines is regulated by the enzyme thiopurine methyltransferase (TPMT).

Approximately 10% of the UK population has reduced TPMT activity, while 0.3% are completely deficient. If treated, these individuals are at risk of accumulating cytotoxic metabolites, leading to bone marrow toxicity and myelosuppression.

Previously, NHS Tayside outsourced blood sample analysis for TPMT enzyme measurement. Now, testing is performed in-house for specific genetic variants in the *TPMT* gene associated with reduced or null enzyme activity, offering a faster and more cost effective approach.



Total number of PGx patient reports issued by NHS Tayside Genotyping during the last 6 years. Over 5600 reports issued in total; 98% of which were for NHS Tayside patients

CYP2C19 testing in NHS Tayside

NHS Tayside was the first board in the NHS to offer a *CYP2C19* testing service, even preceding the eventual NICE approval for this testing to inform clopidogrel prescription in the UK.

We have now genotyped over 3500 NHS Tayside stroke patients. Based on an estimated "number needed to genotype" of 43 to prevent one recurrent stroke, over 80 recurrent strokes have been prevented so far, amounting to over 30 prevented recurrent strokes every year.

As well preventing patient harm, this testing represents a financial saving to NHS Tayside. The average societal cost of stroke per person in the UK is approximately £45,000 for the first year after a stroke. For context, the cost of of genotyping is less than half a standard X-ray.

In 2023 we widened *CYP2C19* genotyping to indicate for voricanazole (an antifungal medication) and in 2024 for mavacamten (a drug treating obstructive hypertrophic cardiomyopathy).

The future of pharmacogenomics

The NHS Tayside P4Me – CYP2C19/ clopidogrel innovation is undergoing approval for rollout to other Scottish healthboards through the ANIA programme. This testing is seen as a pathfinder to broader PGx testing in NHS Scotland.

Proposed PGx testing also includes point of care (POC) testing in NHS Scotland hospital wards (e.g. a neotnatal POC test to identify and remove the risk of permanent hearing loss for babies from gentamicin (antibiotic) induced ototoxicity.)

In the future we will move away from single gene testing to a more cost effective and informative multi-gene panel approach.

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• Dr Judith Strachan (NHS Tayside Blood Sciences) and Dr Craig Mowat (NHS Tayside Gastroenterology)

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