CYP2C19 genetic testing and prescribing'

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Section 1: Introduction

These recommendations are relevant to medicines optimisation, to all prescribers and roles involved in medicines review including stroke teams, primary care prescribers, pharmacists, clinical pharmacologists and prescribers in medical and care of the elderly settings.

The National Institute for Health and Care Excellence (NICE) guidance recommends use of *CYP2C19* testing to guide new prescription of clopidogrel in acute ischaemic stroke or transient ischaemic attack and the Medicines and Healthcare products Regulatory Agency (MHRA) requires *CYP2C19* genotype for mavacamten use in the treatment of hypertrophic obstructive cardiomyopathy. Clinical teams requesting *CYP2C19* testing have a responsibility to communicate prescribing actions to the patient and to communicate relevant data across the healthcare system.

- Diagnostics Guidance [DG59]: CYP2C19 testing to guide clopidogrel use after ischaemic stroke or transient ischaemic attack (TIA) (July 2024).
- Technology appraisal guidance [TA913]: Mavacamten for treating symptomatic hypertrophic obstructive cardiomyopathy (December 2023)

Section 2 Recommendations

Recommendation 1:

Structured data capturing *CYP2C19* metaboliser status should be included in the patient record and related communications. The following SNOMED-CT codes should be utilised:

- Cytochrome P450 family 2 subfamily C member 19 poor metaboliser (finding) SCTID: 738786005
- Cytochrome P450 family 2 subfamily C member 19 intermediate metaboliser (finding) SCTID: 738787001
- Cytochrome P450 family 2 subfamily C member 19 normal metaboliser (finding) SCTID: 738788006
- Cytochrome P450 family 2 subfamily C member 19 rapid metaboliser (finding) SCTID: 787193001
- Cytochrome P450 family 2 subfamily C member 19 ultra-rapid metaboliser (finding) SCTID: 738790007

Use of *CYP2C19* metaboliser status to guide prescription of other medications, changes to pre-existing clopidogrel prescription and clopidogrel prescription for other indications is not addressed in current UK guidance and is outside the scope of current routine NHS practice.

Recommendation 2:

With the exception of prescription initiation in the context of acute ischaemic stroke, transient ischaemic, or Obstructive Hypertrophic Cardiomyopathy (Mavacamten) prescribers should not be expected to utilise *CYP2C19* metaboliser status to guide prescribing practice until the following are implemented within NHS infrastructure:

- UK-based guidance which supports genomics-informed medicines optimisation
- Clinical Decision Support Systems which present *CYP2C19* metaboliser status and integrate with UK-based guidance to provide evidence-based actionable recommendations at point-of-prescription
- Competency frameworks and educational resources supporting core knowledge and skills for prescribers

Prescribers with additional expertise in Genomics-informed Medicines optimisation may wish to utilise CYP2C19 metaboliser status to guide prescribing decisions pending the publication of UK guidance.

Recommendation 3:

Prescribers should:

- always act within the limits of their knowledge and competency to ensure they provide 'reasonable care', and seek advice from expert sources if needed
- act in the context of shared decision-making with the patient.
- reference and take into account trusted UK sources such as MHRA Drug Safety alerts, Summary of Product Characteristics (SmPC), the BNF, local and national guidance
- Follow appropriate local procedures for non-formulary, off-label, or unlicensed medication use

Section 2: Background

2.1 Pharmacogenomics

Pharmacogenomics refers to the use of genomic information to predict effectiveness or the risk of an adverse drug reaction (ADR) to a particular medication: genomics-informed medicines optimisation describes its use to guide prescribing decisions. It has the potential to significantly improve patient outcomes to certain medications and has been implemented for specific drug-gene pairs. Its use is predicted to increase significantly over coming years as evidence of utility increases and processes to support its use are developed.

Testing for variants in the *CYP2C19* gene can help predict the response to several medicines metabolised by the *CYP2C19* liver enzyme encoded by this gene. The genotype directly affects the level of enzyme function, referred to as 'metaboliser status' of which there are 5 types listed in Table 1.

1. **Poor Metabolisers (PM)**: These individuals are predicted to have reduced enzyme function.
2. **Intermediate Metabolisers (IM)**: These individuals are predicted to have a moderate level of enzyme function.

3. **Extensive or Normal Metabolisers (EM)**: These individuals are predicted to metabolise drugs at a normal rate, which is considered the standard or typical response.
4. **Rapid Metabolisers (RM)**: These individuals are predicted to metabolise drugs at an increased rate.
5. **Ultra-rapid Metabolisers (UM):** These individuals are predicted to metabolise drugs rapidly.

An individual's genotype result is just one factor which influences response to medicines, in combination with other factors such as age, renal function, comorbidities and other medicines. As such, an individual's pharmacogenetic results should always be considered holistically.

2.2 Data and Informatics considerations

NICE have issued two sets of guidance regarding *CYP2C19* "*genotype-guided"* prescribing in the UK, which will result in the generation of CYP2C19 metaboliser status within Inherited Cardiac Conditions and Acute Stroke healthcare settings respectively:

- Technology appraisal guidance [TA913]: *Mavacamten for treating symptomatic hypertrophic obstructive cardiomyopathy* (December 2023). Overview | Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy | Guidance | NICE
- Diagnostics Guidance [DG59]: *CYP2C19 genotype testing to guide clopidogrel use after ischaemic stroke or transient ischaemic attac*k (TIA) (July 2024). Overview | CYP2C19 genotype testing to guide clopidogrel use after ischaemic stroke or transient ischaemic attack | Guidance | NICE

The **Professional Record Standards Body (PRSB) '*Guidance for using pharmacogenomic information in clinical practice*'** includes recommendations that genetic data should be: recorded in standardised terminology and formats in electronic health records (EHRs), integrated with clinical decision support in the form of evidence-based actionable recommendations at the point of prescribing, available for patients and interoperable to allow sharing of information across the healthcare system.

- Pharmacogenomics-Report_V1.0.pdf

Accurate recording and availability of *CYP2C19* metaboliser status within the health record is crucial to ensure that the rationale for *CYP2C19*-guided prescription of Clopidogrel for an individual patient is clear and not reversed during subsequent healthcare contacts and medication reviews. NHSE-convened Pharmacogenomics Digital Group has recommended recording of structured data in the form of SNOMED-CT codes for *CYP2C19* metaboliser status. This also supports patient access and availability for future prescribing decisions in line with developing UK guidance.

- SNOMED CT - NHS England Digital

2.3 *CYP2C19* metaboliser status additional implications

CYP2C19 metaboliser status is relevant to prescription of clopidogrel for additional indications; individuals who are poor or intermediate metabolisers are predicted to derive less benefit from clopidogrel when prescribed in the context of ischaemic heart disease and peripheral vascular disease. CYP2C19 metaboliser status is also relevant to prescription of other medications including

Selective Serotonin Re-uptake Inhibitors (SSRIs) and Proton Pump Inhibitors (PPIs), with implications for risk of adverse events and likely medication effectiveness.

Individuals who are CYP2C19 poor metabolisers are at increased risk of side-effects from SSRIs, most notably prolonged QT-interval with citalopram. In the UK for citalopram the SmPC states that " *An initial dose of 10 mg daily during the first two weeks of treatment is recommended for patients who are known to be poor metabolisers with respect to CYP2C19. The dose may be increased to a maximum of 20 mg daily.*"

- MHRA Products | Search results

2.4 Prescriber responsibilities and legal issues. Guidance and Resources:

The RCGP Curriculum states "it is essential to follow the law and GMC guidance and to take account of licensing and local prescribing guidance as well as other relevant regulations. This includes clinical guidelines published by":

- NICE (England) Homepage | NICE
- SIGN (Scotland) Home
- Scottish Medicines Consortium and Health Improvement Scotland (Scotland) SMC | Scottish Medicines Consortium
- Department for Health, Social Services and Public Safety (Northern Ireland) Home | Department of Health
- All-Wales Medicines Strategy Group (Wales) All Wales Medicines Strategy Group | GOV.WALES
- Medical Royal Colleges and other authoritative sources Home - AOMRC
- The British National Formulary (BNF) BNF (British National Formulary) | NICE
- BNF for Children BNFC (British National Formulary for Children) | NICE

As of January 2025 there is no other peer-reviewed UK guidance (outside that listed in section 2.4 or standards for clinical practice relevant to *CYP2C19* testing or metaboliser status.

International clinical guidelines developed by the Clinical Pharmacogenetics Implementation Consortium (CPIC) summarise the evidence base and prescribing recommendations for genomics-informed medicines optimisation of medications impacted by CYP2C19 metaboliser status and of Clopidogrel for alternative indications.

- (Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C19 Genotype and Clopidogrel Therapy: 2022 Update - PubMed).

3.0 Conclusions

Patients within England will be eligible for *CYP2C19* testing for specified indications: new Clopidogrel prescription for acute stroke and TIA, and Mavacemten for Hypertrophic Cardiomyopathy. This will result in a scenario where CYP2C19 metaboliser status will be generated in the absence of implemented informatics solutions and data standards to support sharing of the data across care settings, the absence of UK clinical guidance for use outside of these indications and the absence of a

clinical decision support system which integrates with evidence-based actionable prescribing recommendations.

Several national programmes and workstreams are working to generate evidence and consensus to address these gaps in implementation including NHS England and the national PROGRESS pilot study (Spotlight: PROGRESS project :: North West Genomics Medicine Service Alliance) This position statement provides interim support and recommendations for prescribers until these implementation gaps are addressed.

4.0 Genomics-informed medicines optimisation: The Future

Several national programmes are underway to support prescribers in implementing pharmacogenomics over the medium to long term, including:

- NHSE collaboration with the BNF
- PROGRESS / Clinical Decision Support Systems (CDSS)
- Workforce development and educational initiatives, including a competency framework (NHSE Genomics Education Programme) and 'just in time' resources (GeNotes https://www.genomicseducation.hee.nhs.uk/news/genotes-pharmacogenomics-launches-today/)
- Centre for Excellence in Regulatory Science and Innovation in Pharmacogenomics

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5.0 References and Supporting resources

Includes here table of metaboliser statuses and frequencies for different ethnicities

Clopidogrel — Knowledge Hub Includes metaboliser statuses

Ethnicity and Clopidrogel https://doi.org/10.1136/openhrt-2023-002436

Academy of Medical Sciences. 24207767 https://acmedsci.ac.uk/

Spotlight: PROGRESS project :: North West Genomics Medicine Service Alliance

NHS England » National genomic test directory

The Professional Record Standards Body - PRSB

Clinical Pharmacogenetics Implementation Consortium CPIC

Patient Information

- Patient information: More than 2,000 patients tested in UK's first routine genotyping project for clopidogrel prescribing - The Pharmaceutical Journal Note ethnic differences in metabolizer status
- Patient leaflets (https://www.nw-gmsa.nhs.uk/patients/patient-information-and-resources)

6.0 Authorship

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