ISSUE 5

Pharmacogenomics

MAY 2024

Here's what has happened over the last 6 months and what's to come

Hello!

Within the GMSA there is a major focus on how research and novel genetic technology can be implemented within the NHS, as genomic medicine research is fast-paced and ever-evolving. To meet this challenge the NHSE Genomic Unit developed the idea of Networks of Excellence (NoE) and was launched in 2023.

The NoE aims to provide cutting edge genomic medicine services into the NHS via 8 innovative networks which includes prenatal care, AI, cancer, infectious diseases and pharmacogenomics and medicines optimisation. A full list of the NoE can be found here.

As medicines enter the patient pathway at various timepoints within clinical care, the scope of medicines optimisation can fall within any of these 8 NoE.

However, the biggest focus for pharmacy will be the pharmacogenomics and medicines optimisation NoE. A key project involves the implementation of pharmacogenetics within primary care where testing can support prescribing decisions for statins, serotonin reuptake inhibitors, tricyclic antidepressants, codeine and proton pump inhibitors. A full description of the project can be accessed here.

To be able to start interpreting pharmacogenetic results genomic literacy needs to be improved, and within this issue I have signposted you to some resources to help you get started!

Dharmisha

In this newsletter you can expect:

Mavacamten and *CYP2C19* testing.

September 2023 saw a NICE approval for mavacamten, a first in class selective, allosteric, and reversible cardiac myosin inhibitor, also known as an ATPase inhibitor. It is licensed for the treatment of obstructive hypertrophic cardiomyopathy (oHCM).

oHCM is a disease of the heart muscle in which many of the pathological features are linked to a gene called *MYH7* which encodes for human beta cardiac myosin for ventricular heart muscle and changes within this gene cause oHCM leading to reduced ventricular hypertrophy.

Mavacamten is primarily metabolised by CYP2C19 and to a lesser extent by CYP3A4. Based on pharmacokinetic data patients need to be **genotyped for *CYP2C19*** and patients who have a poor metaboliser **phenotype** will be exposed to more active drug and at risk of more side effects. Therefore, poor metabolisers will require a lower starting dose compared to other metaboliser statuses.

CYP2C19 testing is currently being provided by Bristol-Myers-Squibb for free at two NHS labs based in Manchester and Dundee, and the NHS will provide the testing by early 2025. The CYP2C19 genes which are tested are shown in table 1. Further CPD information can be found within GeNotes here .

Definitions

Allele: a specific version of a gene

Genotype : Two alleles of a gene inherited together

Phenotype : a characteristic determined by genetic variation within your DNA e.g., enzyme expression

Haplotype: DNA changes or variations which are inherited together

Diplotype: A specific combination two haplotypes

GENEOTYPE	PHENOTYPE
*CYP2C19*1*	Normal function
*CYP2C19*2*	No function
*CYP2C19*3*	No function
*CYP2C19*17*	Increased function

Table 1: *CYP2C19* genes tested.

PHENOTYPE	GENOTYPE	Diplotypes	Effect on mavacamten
Poor metabolizer	Two non-functional alleles	***2/*2** ***3/*3** ***2/*3**	Increased risk of systolic dysfunction due to higher mavacamten levels (3x higher)

Table 2: Within pharmacogenetics the phenotype is based on the combination of 2 genes. For a poor metaboliser the patient can inherit one of the three combinations as shown in this table.

CPIC and the role within pharmacogenetics

If you have been to a pharmacogenetic training session, lectures or educational and training webinars, you may have heard the word CPIC being mentioned especially when the speakers get the drug dosing part!

CPIC is acronym for **C**linical **P**harmacogenetic **I**mplementation **C**onsortium, and this consortium consists of volunteers with an expertise in pharmacogenetics and are interested in how pharmacogenetic testing can be implemented into routine clinical care.

One major output is the development of evidence based and peer reviewed drug-genotype clinical guidelines. It should be noted that CPIC does not provide information regarding if or when a pharmacogenetic test should be taken but assumes that pharmacogenetic testing will become common practice. The aim of the guidelines is to provide information on how to interpret a pharmacogenetic result which is in front of you. To date, CPIC have developed 26 guidelines and have formed the bases of UK guidelines for *DPYD*, *TMPT*, *NUDT15* and *MT-RNR1*, all of which are commissioned pharmacogenetic tests within England.

The guidelines CPIC have published are based on Level A evidence which means that the pharmacogenetic information should be used to amend prescribing of the drug in question. Currently there are 26 published level A guidelines which can be found here.

CPIC works closely with two other bodies: the Pharmacogenomics Knowledgebase (PharmGKB) and the Pharmacogenomics Research Network (PGRN). The PharmGKB provide detailed information on pharmacogenetic variants alongside evidence levels and develop curated pharmacokinetic and pharmacodynamic pathways. The PGRN focuses on the discovery and translation of genomic variation influencing therapeutic and adverse drug effects.

When interpreting CPIC guidelines it is important to consider regional/local formulary guidelines and the clinical cohort you are treating. However, they have proven to be an excellent starting point when developing dosing guidelines.

CPIC®
Clinical Pharmacogenetics Implementation Consortium

Pharmacogenetics training – what's out there?

I am completely new to pharmacogenetics where do I start?

For those who are new to pharmacogenetics, there are some great online resources to get you going. CPPE have an online package and recently a new pharmacogenetics specialist programme has been launched by the Medicines Learning Portal.

- Introduction to genomics in pharmacy : CPPE
- Medicines Learning Portal: Pharmacogenomics

I understand the basics and would like to know more without undertaking a formal course.

There's not a lot in terms of a free UK based step up from the resources above, however I have found a resource developed by CPIC which provides case studies and gives you the opportunity to work though questions using pharmacogenetic guidelines. However, it is tailored to USA clinicians, as you need to refer to FDA sites and refers to health insurance. But on having a go myself it is a good free resource to delve into.

- ISCC-PEG Pharmacogenomics Learning Series (genome.gov)

I am interested in pharmacogenetics and in fact I would like to delve deeper into the world of genomics. Plus, it would be good to get a qualification out of it too!

Currently 8 universities are offering a Msc Genomic Medicine course. This course offers a range of modules and if you are an NHS healthcare professional you can apply for funding via Health Education England now called NHS England Education and Training.

If you don't want to do the full masters, you can undertake a couple of modules or complete 4 modules to obtain a certificate or 8 modules for a diploma qualification. For the Msc you will need to complete a research project. The choice is yours. If you have any questions, please feel free to contact me on Dharmisha.Chauhan1@nhs.net

- Master's in Genomic Medicine - Genomics Education Programme (hee.nhs.uk)

Date for your diary!!

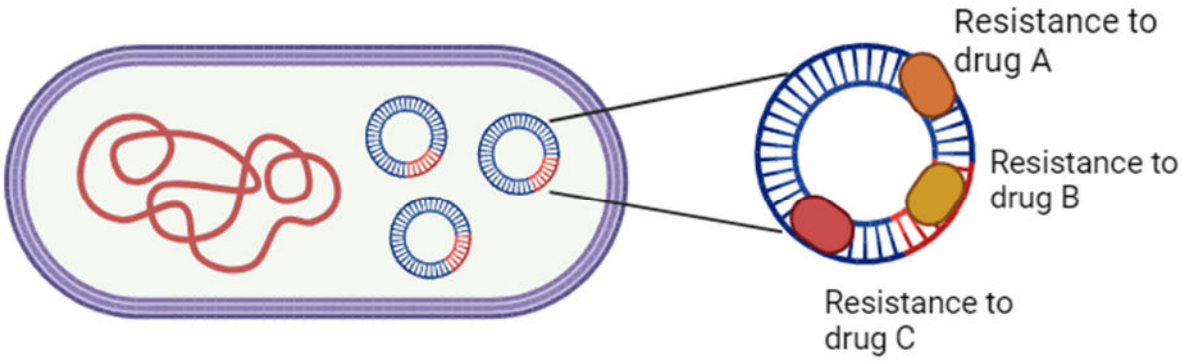
Within North Thames GMSA we are committed in providing education and training and provide key updates on the work we are doing and showcase the amazing work being done within the region!

Our next webinar will be held on **Thursday 23rd May at 2 to 3:30pm**. This will be a **CPD session for the role of *CYP2C19* testing within cardiovascular diseases.**

Our guest speakers will be **Paul Wright**, Consultant Cardiovascular Pharmacist from Bart's NHS Trust and **Paresh Parmar,** Lead Pharmacist Care of Older People and Stroke from Northwick Park Hospital. This will be held as a virtual webinar and a Team's link will be sent out in due course.

In the next issue

- The role of genomics within infectious diseases
- North Thames GMSA updates
- New E&T events
- Role of GeNotes.



If you have any questions, contact me on

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Thank you for reading!