ISSUE 6

Pharmacogenomics

DEC 2024

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

Hello!

In the last issue I focused on a gene called *CYP2C19* which encodes the enzyme CYP2C19 and its importance on mavacamten dosing. In this issue the hot topic is still *CYP2C19*, but for a drug we are more familiar with – clopidogrel.

It has become a hot topic with the pharmacogenomics field due to the positive NICE publication for CYP2C19 genotype testing to guide clopidogrel use after ischaemic stroke or transient ischaemic attack. In anticipation of this publication, with a talented research student Ellie Tavla, we conducted a research project to understand a pharmacist's ability to interpret, review and action *CYP2C19* pharmacogenetic reports and identify the pharmacists views on the report structure. Within this issue Ellie summarizes her results. To build on this work our pharmacy intern, Daniel Murphy has been working on a on-demand tool to guide pharmacists how to navigate, and interpret CYP2C19 report. This step-by-step guide will detail key skills and resources pharmacy professionals at ALL levels will need.

On 26th September we had a brilliant in-person event, our first full day pharmacogenetics education and training day. The day was designed alongside the NHS England » Pharmacy genomics workforce, education and training strategic framework. Filled with great conversations, presentations and a workshop where attendees had a chance to interpret *CYP2C19* pharmacogenetic reports. For those who could not make it, you can view the presentations here.

So what's next for 2025? I have plans to build upon how we engage with our genomic pharmacy network and get more pharmacy professionals thinking about genomics!

Dharmisha Chauhan – Consultant Pharmacist

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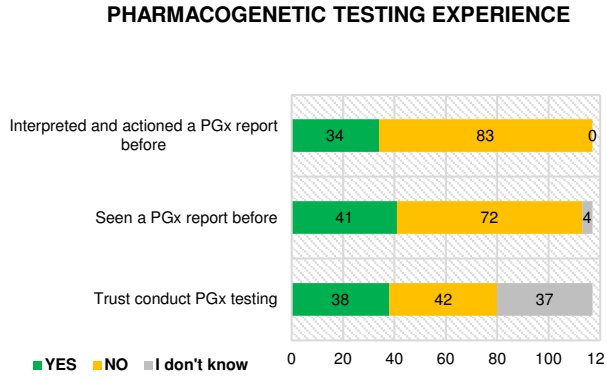
How well can pharmacists interpret a pharmacogenetic report? – *Ellie Tavla, MPharm, CPIPP*

Hello everyone! It is a great honour to be able to discuss and present the results of our research project.

According to background research, positive attitudes in pharmacogenomics have been identified from both doctors and pharmacists, with the latter being more interested in taking on more responsibilities. Knowing that pharmacogenetic testing for *CYP2C19* would soon become part of routine care due to the NICE guidance published in July 2024 for stroke patients, we focussed our research on *CYP2C19* pharmacogenetic test reports for clopidogrel.

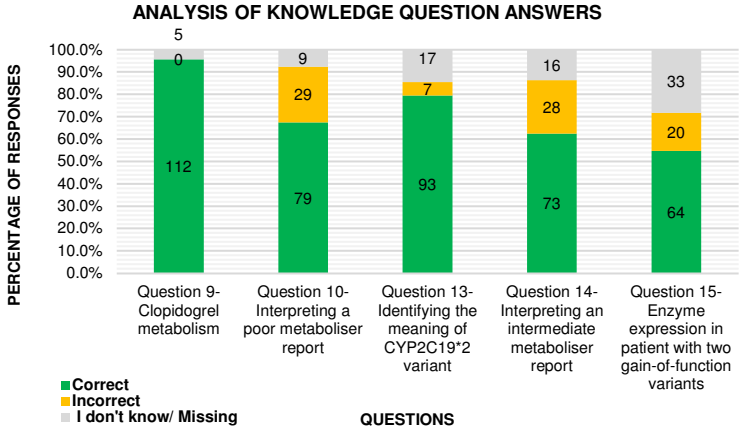
To our knowledge, this was the first study in the UK to look at pharmacists' current abilities in navigating and interpreting such reports.

- 147 pharmacists completed the survey and 117 were included within the analysis. 75.2% from hospital sector.
- 29.1% of participants, stated that they had previously interpreted a pharmacogenetic report, compared to the 32.5% who stated that their place of work conducted pharmacogenetic testing.
- This supports the view that pharmacists are not always involved in report interpretation. When looking at prior knowledge and use of pharmacogenetic resources, 33% of participants were not familiar with any pharmacogenetic resources.



In section 3 of the survey, we focused on providing participants with **two *CYP2C19* case studies**, each with a different pharmacogenetic metaboliser status report. Participants had to answer the questions based on the case study scenario for a poor and intermediate metaboliser.

72% of the knowledge questions were answered correctly. Incorrect answers were observed in the two questions which required good navigation of the pharmacogenetic reports. This indicated that the reporting structure can still be improved. Additionally, the self-reported familiarity to pharmacogenetics and ability to interpret the knowledge questions, contraindicated each other in certain aspects, indicating a lack of awareness in what pharmacogenetics reports include verses a pharmacists' own abilities.



Pharmacists with previous experience with pharmacogenetic reports are shown to be better qualified to interpret them. No statistical significance was observed with more years of experience.

What's next? This study highlighted the lack of education on pharmacogenetic resources and the need of UK wide pharmacogenetic guidelines. To help pharmacists with their responsibilities, pharmacogenetic reports should be standardized. This study will be repeated with greater focus on primary care pharmacy professionals.

How do I navigate and interpret a pharmacogenetic report for clopidogrel? – *Daniel Murphy, North Thames Genomic Medicine Pharmacy Intern*

Hello 😊, for this section I will summarise how I interpret a pharmacogenetic report. I normally start with the fundamental knowledge relating to the drug and gene in question:

Clopidogrel is an antiplatelet drug and prescribed for the prevention of cardio/cerebrovascular events, as well as other indications.

Cytochrome P450 (CYP450) enzymes break down many (~90%) of commonly prescribed drugs in the liver. Variants in the genes which produce CYP450 enzymes may lead to either: increased levels of enzyme with drugs being quickly broken down (rapid/ultrarapid metabolism); decreased levels of enzyme leading to slow breakdown (poor/intermediate metabolism); or a standard level of enzyme breakdown that doesn't need dose adjustment (normal metabolism).

Clopidogrel is a prodrug and requires metabolism by CYP2C19 (one of the CYP450) enzymes to produce the active form (clopidogrel thiol H4). For clopidogrel prescribing in stroke, testing for *CYP2C19* (genetic code for the CYP2C19 enzyme) is beginning to be introduced in practice (this is currently being piloted in a few centres).

For the next step I would then work though the patient's *CYP2C19* report:

Gene test	Diplotype detected	Test result
CYP2C19	*3/*3	Poor metaboliser
		(Decreased enzyme function)

Allelic variants tested for CYP2C19: *2 (c.681G>A), *3 (c.636G>A), *17 (c.-806C>T)

- **Gene test:** The gene tested for is *CYP2C19*
- **Diplotype detected**: The diplotype describes the combination of alleles found in an individual's gene (inherited from both parents). This individual has inherited two '*3' ("star 3") alleles. Pharmacogenomic reports usually use this 'star allele' naming system for simplicity.
- **Test result:** Due to a *3/*3 diplotype, in this example this individual is a poor metaboliser (→)

(→) **Once I have reviewed the metaboliser status, I would then check the available dosing recommendations**:

- ***Regulatory*** (found in drug summary of product characteristics – SmPC)†
  - SmPC: individuals with poor metabolism "form less of the active metabolite"
- **Clinical guidelines** such as those offered by the Clinical Pharmacogenetics Implementation Consortium (CPIC)‡
  - "avoid clopidogrel if possible"
- **For this patient I would prescribe an alternative antiplatelet drug based on CPIC guidelines.**

Working through another report using the same principles:

Gene test	Diplotype detected	Test result
CYP2C19	*1/*1	Normal metaboliser
		(Normal enzyme function)

Allelic variants tested for CYP2C19: *2 (c.681G>A), *3 (c.636G>A), *17 (c.-806C>T)

1. **Gene test:** The gene tested for is *CYP2C19*
2. **Diplotype detected:** This individual has two '*1' (or 'wildtype') alleles
3. **Test result:** Due to a *1/*1 diplotype, this individual is a normal metaboliser
4. **Regulatory information** (SmPC): N/A
5. **CPIC guidelines**: Use standard dose of clopidogrel (75mg/day)
6. **For this patient I would prescribe clopidogrel as per the BNF**

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†SmPCs can be found at www.medicines.org.uk
‡Clinical guidelines can be found at www.pharmgkb.org – *NB prescribing recommendations can differ between guidelines. UK guidelines are in the process of being created but these have not yet been finalized.*

So, what about the other drugs and *CYP2C19*?

As *CYP2C19* testing for clopidogrel is gradually being implemented across England within the first half of 2025, a serious question is being raised: *What about the other drugs which are metabolised by CYP2C19?*

Firstly, not all drugs which are metabolised by CYP2C19 are linked to pharmacogenetic testing but those which have a strong evidence base e.g., level A or level B evidence can be considered to help support prescribing decisions. Drugs which have level A or B evidence *for CYP2C19* testing include serotonin reuptake inhibitors, tricyclic antidepressants, proton pump inhibitors and voriconazole.

Some of the major issues in implementing *CYP2C19* testing relates to increasing awareness on the role of pharmacogenetics especially within primary care sectors, education and training needs and the lack of UK based practice guidelines to support clinical decisions. Within the GMSAs we are aware of these hurdles and are working hard to address the issues both at a regional and national level.

At North Thames GMSA we have developed educational podcasts, face to face pharmacogenetic workshops and we are developing an on-demand tool on how to navigate and interpret a pharmacogenetic report.

At a national level we are working to support the development of UK based pharmacogenetic guidelines with the UK Pharmacogenetics & Stratified Medicine Network. In addition, UKCPA are in the process of creating a pharmacogenetic handbook which has the familiarity and layout of the well-known and used renal drug handbook. This work is being led by Lucy Galloway, consultant pharmacist for South East GMSA, who is also a member of the UKCPA Genomics Group.

Our key aim is to continue working with pharmacists across all GMSA regions to improve pharmacy genomic literacy and in 2025 a new Genomics Knowledge Framework for Pharmacists will be released to further support education and training needs, with a framework for pharmacy technicians to follow soon after.

PGx Podcasts!!

On 26th September 2024, North Thames GMSA released **FIVE pharmacogenetic podcasts**. Each is a **10 to 15 minute bitesize episode** to support pharmacy and healthcare professional's education and training needs.

You can listen to the podcasts on your favourite podcast platform and **search for "Genomics Now"**, which is our North Thames platform to tune in for some quick CPD!

Episode 1: Unlocking the potential of pharmacogenetics in the NHS

Episode 2: Understanding pharmacogenetics, essential concepts for clincians

Episode 3: Advancing pharmacogenetic testing, the role of research and clinical trials

Episode 4: Implementing pharmacogenetics, what's needed in mental health services.

Episode 5: The future of pharmacogenetics, enhancing patient care through genomic counselling.

What's coming next?

In this issue our genomic medicine pharmacy intern explained how he navigates and interprets a pharmacogenetic report.

To support all healthcare professionals, In the New Year we will have a detailed 15 minute video walking you through a *CYP2C19* pharmacogenetic report. This will be set up as an **on-demand training tool**. This tool can be used alongside the pharmacogenetic podcast **episode 2**. In addition, our *CYP2C19* pharmacogenetic case studies and workshop materials from our face to face event can be found using the link below **and you can have a go in interpreting a pharmacogenetic report**! Pharmacogenomics Study Day (September 2024) - North Thames GMS : North Thames GMS

In the next issue

- The role of genomics within infectious diseases
- North Thames GMSA updates
- New education and training sessions
- North Thames GMSA workforce, education and training strategy and how you can get involved!!

Wishing everyone a Merry Christmas and a Happy New Year!