NHS
North Thames
Genomic Medicine Service

Genomic Medicine in Pharmacy Practice Newsletter

June 2023 Issue 4

Welcome!

It has been a very full but exciting four months since the last update from the North Thames GMSA pharmacy team. **We hosted 3 pharmacogenetic lunch and learn webinars with a total of 140 attendees** for m.1555A>G and TPMT/NUDT15 testing!

We also had an informative and successful **pharmacogenetic mental health workshop** at the Wellcome Café. This brought together mental health care clinicians across **four GMSA** regions to discuss the role of pharmacogenetic testing within mental health care. As progress within pharmacogenomics is steadily increasing, we will continue to provide educational sessions throughout North Thames. **Please have a look at our future events section to find out more.**

In terms of new developments: there has been a positive NICE review for a new technology which can be considered in the **neonatal setting**, and a **draft** NICE consultation for *CYP2C19* testing for clopidogrel for **stroke patients** was released in May. Both of these technologies are **NOT commissioned on the NHS** but a brief overview of the NICE publications are provided within this newsletter.

There has also been a new development with the **MHRA** who are now working with **Genomics England** to create a **yellow card drug safety genetic biobank**, which is the first drug safety regulator in the world to do so at a national level. This project went live on 1st June 2023.

There is a lot happening and it is evident that the role of pharmacy professionals within genomic medicine is vital. Within North Thames we have **over 50 pharmacy champions** and if you would like to join and learn more, please do contact me.

Finally, I want to say a **huge thank you** to both **Veronica Chorro-Mari** (Bart's and now East Kent NHS, antimicrobials) **and Rebecca Burgoyne** (UCLH, haematology). Veronica has been instrumental on the DPYD project and supporting the implementation for the m.1555A>G testing in North Thames, and Rebecca has been a driving force in developing and providing education and training for *TPMT/NUDT15* pharmacogenetic testing in Acute Lymphoblastic Leukemia at a multidisciplinary level.

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Contents


Dharmisha


Veronica


Rebecca

Pharmacogenetics in mental health care

Within mental health care there is an increasing interest to guide treatment decisions based on pharmacogenetic results. This is because up to 50% of patients do not respond to their first antidepressant and 30% of patients will discontinue treatment within the first 6 weeks. There is a body of evidence indicating that multiple genes and genetic variants play a role in determining how individuals respond to antidepressants and the side effects they can experience. Most antidepressant drugs are metabolized by CYP2D6 and CYP2C19, transcribed by the genes *CYP2D6* and *CYP2C19* respectively.

Focus is also moving to widen the scope to antipsychotic medication which is an area currently being researched. For example Professor Elvira Bramon (UCL) is conducting an **NIHR funded study** to understand if pharmacogenetics can help personalise and guide the dosing of all psychotropic drugs. Within this multi-centered study 2000 patients will be recruited and 400 will received pharmacogenetic testing verses standard of care approach (fig 1). In some sites, pharmacists are leading as principle investigators, such as **Yogita Dawda**, consultant pharmacist and mental health lead at Central and North West London NHS Foundation Trust.

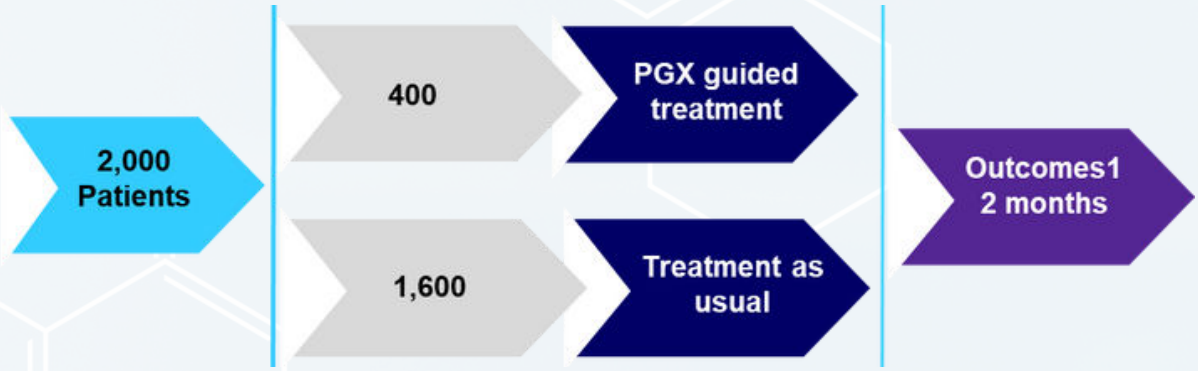

Figure 1: NIHR funded study, schematic for the An academic clinical trial led by Professor Elvira Bramon (UCL, head of mental health neurosciences research department), is investigating the prospective use of pharmacogenetic tools to guide the dosing of psychotropic drugs as its main primary objective.

To support this study within the North Thames GMSA a **mental health specialist interest group** was created in July 2022 (fig 2). This multidisciplinary group with PPIE representation set out to understand what a pharmacogenetic pathway within mental health would look like, and the information we would need to provide to both patients and healthcare professionals.

On 4th May, a **mental health workshop** was hosted at the Wellcome Café to discuss key elements below. This was an **MDT workshop** including mental health clinicians from four GMSA areas (North Thames, South East, Central and South and East GMSA).

- Clinical pathways, with a focus on schizophrenia.
- Challenges, barriers and enablers to pharmacogenetic testing within clinical practice.
- Pharmacogenetic counselling.
- Expected roles and responsibilities of healthcare professionals within mental health care.

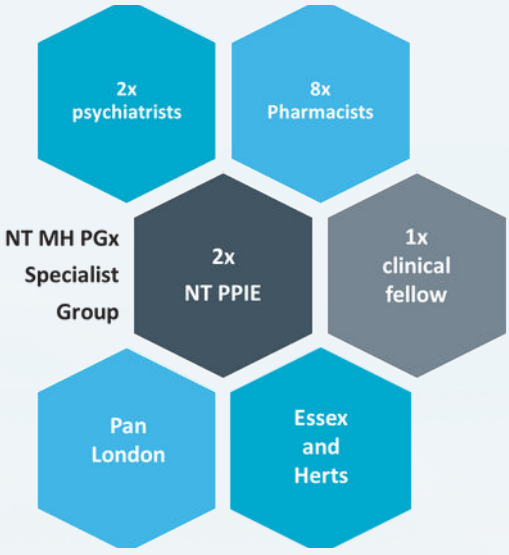

Figure 2: North Thames Mental Health Care Specialist Interest Group. Representation from London, Hertfordshire and Essex.

If you would like to hear more or would like to get involved please contact Dharmisha Chauhan

CYP2C19 and Stroke

By Paresh Parmar, Lead Pharmacist
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Clopidogrel is an antiplatelet drug used to reduce the risk of blood clots in patients after a heart attack or stroke. It is a prodrug that is converted to the active form via CYP2C19. The problem is that in some people, clopidogrel does not work very well as their *CYP2C19* genes are not effective (loss of function). This can then increase the risk of further heart attacks and strokes.

The NICE Diagnostic Assessment Programme is developing a guideline on using clopidogrel genotype testing after an ischaemic stroke or Transient Ischaemic Attack (TIA). The evidence shows that it is cost effective to test people for loss of function of the *CYP2C19* genes and then use alternative antiplatelets in patients identified with the loss of function genes.

This is the beginning of a more personalised treatment approach to preventing further strokes. The Final NICE guideline will be published in October/November 2023.

Note from Dharmisha:

The press release from NICE refers to the **DRAFT** consultation only. Once the final NICE publication is available in October/November 2023, it would not mean that the testing will be automatically commissioned by NHS England. This is because the publication is not a full NICE Technology Appraisal but a diagnostic assessment. We will need to await further information from NHS England.

MT-RNR1 and Aminoglycosides ototoxicity risk

In March 2023 **NICE** published a positive **Early Values Assessment** (https://www.nice.org.uk/guidance/hte6) for a point of care test for the variant **m.1555A>G** found within the mitochondrial gene ***MT-RNR1.***

This genetic change if found can cause ototoxicity when individuals are treated with aminoglycosides within normal therapeutic ranges after one dose. In severe cases it can lead to bilateral hearing loss.

The technology is a point of care test developed by a company called Genedrive which can detect the presence of this variant from buccal swab within 26 mins and was researched within the **neonatal** setting.

The NICE assessment was based on the Pharmacogenetics to Avoid Loss of Hearing (**PALOH**) study and therefore the technology has only been recommended for the neonatal setting. *McDermott, J. H., et al (2021). Pharmacogenetics to Avoid Loss of Hearing (PALOH) trial: a protocol for a prospective observational implementation trial. BMJ open, https://doi.org/10.1136/bmjopen-2020-044457.*

Importantly though the Early Values Assessment was positive this technology is **NOT** commissioned as more data is required, especially on:

- how the test affects time to antibiotics.
- how the test result affects antibiotic prescribing decisions.
- the technical performance and accuracy of the test.

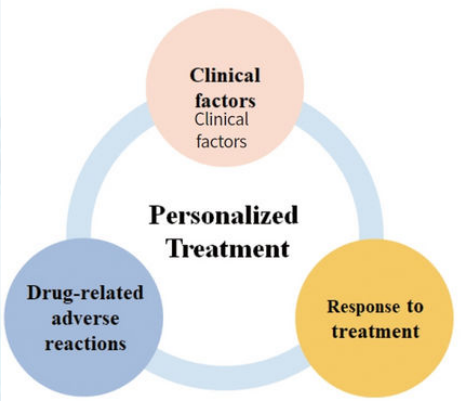
Therefore individual neonatal units may be considering to use the technology at a local level. For all other clinical indications the use of the technology would be within a research setting.

Education and training for this pharmacogenetic test can be found within our North Thames webinar we hosted in May and April: https://www.norththamesglh.nhs.uk/aminoglycosides-pharmacogenetic-testing-webinar/

Please note: To implement this NICE assessment this would be a local decision but if any general governance advice is needed please do contact us North Thames GMSA.

TPMT and *NUDT15* for Acute Lymphoblastic Leukemia only

By Rebecca Burgoyne , Senior Hematology Pharmacist, University College London Hospitals



Thiopurines like 6-mercaptopurine (6-MP) are important cytotoxic agents, but their utility can sometimes be offset by poor patient tolerance and a risk of severe neutropenia. TPMT and NUDT15 are key enzymes in the metabolism of 6-MP; genetic variation in the ***TPMT* and *NUDT15* genes strongly influences the tolerance and safety of 6-MP therapy**. Enzyme activity is regulated by common genetic polymorphisms and reduced activity of these enzymes is one of the factors associated with dose-limiting neutropenia. **Genetic testing of TPMT and NUDT15** allows at risk patients to be identified and dosing of thiopurines to be i**ndividualised** - this means we can reduce the toxicity risk for patients without loss of treatment effectiveness or compromising disease control.

In April 2022 the North Thames Genomic Laboratory Hub now offer *TPMT* and *NUDT15* testing. Dosing guidelines are available for adult patients and can be found here. For paediatric patients the ALL clinical trial protocols should be followed. A pharmacogenetic workshop for dosing in adult patients will be held on 14th June, see below.

MHRA Yellow Card Biobank in partnership with Genomics England

In a new joint venture between the MHRA and Genomics England, they have developed a new biobank to understand how an individual's genetics can have an impact on drug safety. This yellow card biobank will operate alongside the yellow card reporting system and aims to understand which adverse drug reactions are due to genetic changes.

The biobank officially started on 1st June 2023 and will start recruiting patients from 1st September 2023, in which patient samples will be sequenced from Spring 2024. The aim will be to publish findings in 2025.

The first drug to be considered is allopurinol which can cause Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), an adverse rug reaction due to changes within a gene called *HLA*, specially HLA-B*5801.

For more information please use the link below:
MHRA and Genomics England to launch pioneering resource to better understand how genetic makeup influences the safety of medicines - GOV.UK (www.gov.uk)

National Test Directory Update: Olaparib in Breast and Prostate Cancers.

The **national test directory for cancer** was recently updated to include BRCA testing for prostate cancer patients and updated the criteria for breast cancer in the clinical settings where a **PARP inhibitor called olaparib** can be accessed.

Poly-**A**DP **r**ibose **p**olymerase, also known as **PARP**, polices the DNA and repairs any DNA damage. Within normal cells we have more than one DNA repair pathway but many cancer cells only have the PARP system, as seen in breast and prostate cancers. Therefore PARP inhibitors prevent DNA repair causing cell death within cancer cells only. Olaparib is now approved and available for both breast and prostate cancer patients where a pathogenic or clinically significant BRCA variant has been detected.

- **NTD**:https://www.england.nhs.uk/publication/national-genomic-test-directories/
- **NICE TA 886** (Breast - Adjuvant setting)
- **NICE TA 887** (Prostate - previously treated within metastatic setting)

Future Educational Events

Pharmacogenetics Workshop - suitable for all healthcare professionals

- **TPMT/NUDT15 pharmacogenetic training for Acute Lymphoblastic Leukemia**
- **Wednesday 14 June 16:00-17:30**
- **Learning outcomes**: Dosing recommendations for 6-mercaptopurine (6-MP) in adult acute lymphoblastic leukaemia (ALL) patients based on their TPMT and NUDT15 genotypes.
- **To register:** scan the QR code or visit pharmacy-pharmacogenetic-training-session.eventbrite.co.uk

Primary Care Genomic Education Programme

These online workshops will provide an overview of the Genomic Medicine Service and explore its application within primary care.

Across THREE modules, the workshops will cover:

- **Module 1:** An introduction to genomics and the National Genomic Test Directory, familial cancer and risk assessment tools, pharmacogenomics, and direct-to-consumer testing.
- **Module 2:** will explore familial cancer, in particular breast cancer and Lynch syndrome, and provide an introduction to risk assessment tools. 27 June or 12 July 1-2pm.
- **Module 3**: will provide an introduction to pharmacogenomics and advice on how to respond to direct to consumer testing. 13 September, 12 October or 10 November, 1-2pm.

Find out more and register here: www.eventbrite.co.uk/e/think-genomics-primary-care-genomic-education-programme-tickets-546134542117

Lynch syndrome & Colorectal/Endometrial cancer: the role of cancer MDTs

Genetic testing can provide a definitive diagnosis for someone with Lynch syndrome and open up new screening and treatment options. All patients with colorectal and endometrial cancer should now receive genetic testing according to NICE guidelines. Join these workshops to learn from the experts about how you can achieve that for your patients.

These sessions are relevant to anyone who is part of a cancer MDT.

Endometrial:

- 6 June 13:00-14:00 https://www.eventbrite.co.uk/e/638145659847
- 5 September 13:00-14:00 https://www.eventbrite.co.uk/e/638154416037

Colorectal:

- 13 June 13:00-14:00 https://www.eventbrite.co.uk/e/colorectal-cancer-genomics-lynch-syndrome-lunch-learn-more-tickets-637923214507
- 22 September 13:00-14:00 https://www.eventbrite.co.uk/e/638156632667