ISSUE 9

Pharmacogenomics

North Thames
Genomic Medicine Service

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Two years ago, I set out to complete a **National Genomic Test Directory application** for *UGT1A1* testing in relation to irinotecan, a chemotherapy agent routinely used in oncology. As one of the older cytotoxic agents, irinotecan is frequently prescribed alongside fluoropyrimidines. I kept coming back to a simple question: we routinely test for *DPYD*, but what about *UGT1A1*?

Through the British Oncology Pharmacy Association Genomic Cancer Advisory Group, we established a task-and-finish group and drawing on the expertise of colleagues across the profession, we successfully secured **clinical approval** for the application. While we are still awaiting confirmation of central commissioning arrangements, this represents a significant step in the right direction.

In the meantime, we must ensure that clinicians are equipped to implement pharmacogenetic testing effectively once it becomes available. Most importantly, they need clear guidance on how results should inform prescribing decisions. This is where the UK Centre of Excellence in Regulatory Science and Innovation in Pharmacogenomics (UK-CERSI PGx) plays an important role. Bringing together academia, industry, regulators, healthcare professionals, and patients, UK-CERSI-PGx aims to accelerate the adoption of pharmacogenomics across the UK.

Importantly, this multiprofessional committee, has now published **five pharmacogenetic guidelines**, including guidance for including guidance for *UGT1A1*. So, what do these UK guidelines aim to achieve? I explore this further in this issue. A key feature that distinguishes them from many international guidelines is their focus on clinical pathways and practical implementation, helping to support equitable access to pharmacogenetic testing across healthcare settings.

Also in this issue, we shine the gene spotlight on ***HLA***, examining how targeted testing can reduce the risk of severe Type B adverse drug reactions. We also explore how other countries have successfully implemented HLA testing programmes and the lessons that can be applied within the UK.

Finally, within North Thames GMS, we are keen to involve more healthcare professionals in upcoming pharmacogenomic events and discussions on best-practice implementation. If you would like to contribute, learn from colleagues, and help shape the future of pharmacogenomics, we encourage you to join our multiprofessional **Pharmacogenomics Community of Practice**.

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INSIDE

More than recommendations: what is a guideline?

Clinical guidelines (and we use a lot of them) are often viewed as documents that summarise evidence and provide recommendations, but their true value lies in helping healthcare professionals translate evidence into everyday practice. In pharmacogenetics, where implementation remains a key challenge, guidelines play an essential role in supporting testing pathways, interpreting results and informing prescribing guidelines. **Importantly, guidelines are not the final destination**. They provide a foundation upon which clinical experience can grow. As healthcare professionals gain confidence in pharmacogenetic testing, they can better recognise where testing adds value for patients and where further evidence is needed to address remaining research gaps.

The UK CERSI-PGx pharmacogenetic guidelines represent this important starting point and to date five guidelines have been published (table 1). These guidelines differ from many other international recommendations by adopting a UK-focused approach, addressing practical considerations, such as appropriate testing turnaround times, how results should be recorded, and which patient populations are most likely to benefit from testing.

Another distinctive feature is their multiprofessional authorship. The guidelines have been developed with contributions from laboratory scientists, health economists, doctors, pharmacists, nurses, academics, and patients, ensuring that both the clinical and non-clinical aspects of implementation are represented.

Importantly, these guidelines also identify key research gaps and highlight the studies needed to address unanswered questions. While many pharmacogenetic tests are not yet centrally commissioned, the guidelines support future implementation by **promoting system readiness** across healthcare settings.

There are plans to produce more, with a focus on anti-depressants, cancer pharmacogenetics and testing for non-malignant gastrointestinal conditions. These guidelines can all be found centrally as open access within the British Journal of Clinical Pharmacology.

Gene	Drug(s)	Clinical area	NHSE centrally commissioned†	Guideline link
ACKR1	Clozapine	Treatment resistant psychosis	No	DOI: 10.1002/bcp.70576
CYP2C19	Clopidogrel	Stroke and cardiovascular disease	No	DOI: 10.1002/bcp.70370
HLA	Carbamazepine, oxcarbazepine, eslicarbazepine	Epilepsy, trigeminal neuralgia, manic-depressive psychosis	No	DOI: 10.1002/bcp.70559
UGT1A1	Irinotecan	Solid malignancies	No	DOI: 10.1002/bcp.70659
MT-RNR1	Aminoglycosides	Infectious diseases/cystic fibrosis	Yes*	DOI: 10.1002/bcp.70712

Table 1: Summary of published UK-CERSI guidelines. †Centrally commissioning information for England; ***criteria as per the National Genomic Test Directory for England **:** 1. individuals with a predisposition to gram negative infections for example due to known respiratory disease (e.g. bronchiectasis, cystic fibrosis) or due to structural or voiding genitourinary tract disorders, OR 2. individuals with hearing loss who have been exposed to aminoglycosides.

Gene Spotlight

Type B reactions and *HLA* genotyping

Adverse drug reactions (ADRs) can be broadly divided into two main categories, type A and type B. We routinely see **type A reactions** as they relate to the pharmacology of the drug, are dose-related and predictable. In contrast, **type B reactions** are unpredictable and related to severe reactions such as hypersensitivity drug reactions (HDRs) or other idiosyncratic adverse drug reactions. These type B reactions can be pre-emptively identified with *HLA* genotyping.

HLA genotyping identifies the variations within the Human Leukocyte Antigen (HLA) genes. HLA helps the body distinguish self from foreign bodies and used within organ and bone marrow transplantation. The *HLA* genes are found as a cluster on chromosome 6 and encode the major histocompatibility complex (MHC) proteins which are cell surface proteins and regulate immune system to identify the body's own proteins (self) from foreign proteins and in some cases drugs (non-self).

The class 1 *HLA* genes are frequently associated with pharmacogenetic drug interactions, with strong clinical actionability evidence for *HLA-B* gene variants.

The most well-known *HLA-B* gene and drug interaction is *HLA-B*57:01* and abacavir which causes hypersensitivity in 4-8% of patients. It is a delayed presentation but can be fatal if abacavir is not discontinued. The symptoms include fever, rash, fatigue, diarrhoea, abdominal pain, nausea and vomiting. In UK clinical practice, patients are routinely pre-emptively tested for *HLA-B*57:01* prior to starting abacavir.

In 2014, the MHRA published two drug safety updates for phenytoin, carbamazepine, oxcarbazepine and eslicarbazepine due to risk of severe cutaneous adverse reactions (SCAR).

These serious *HLA* skin reactions include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia (DRESS), and the less severe reactions include acute generalised exanthematous pustulosis (AGEP) and maculopapular rash.

The *HLA* gene like all other pharmacogenes are highly polymorphic, which means that the prevalence of variants differ between different populations. As an example, *HLA-B*15:02* is more commonly identified within Thai, Taiwanese, Singaporean and Chinese South Han populations compared to *HLA-A*3101* identified in individuals of European ancestry.

Within the UK, *HLA* genotyping is not routinely commissioned as a nationally funded service, although there is growing recognition of its potential role in preventing severe drug-induced HDRs. International experience demonstrates the benefits of pre-emptive testing. In Thailand, implementation of a national *HLA* screening programme has been associated with a substantial reduction in SJS and TEN cases, with reported reductions exceeding 70% within the first few years of implementation. In Singapore, where *HLA-B*58:01* testing before prescribing allopurinol is available but not universally mandated and the burden of allopurinol-related severe cutaneous adverse reactions (SCARs) remains significant. Ongoing discussions have focused on whether broader implementation would be cost-effective, particularly given that the costs associated with SCAR-related hospitalisation substantially exceed the cost of *HLA* testing.

For the UK, implementation strategies require careful consideration. The UK population is ethnically diverse and increasingly admixed,

meaning that restricting testing to individuals with self-reported East Asian ancestry may miss patients carrying clinically relevant *HLA* at risk variants. Consequently, approaches based solely on ethnicity risk perpetuating inequities in care and reducing the effectiveness of pharmacogenomic testing programmes.

A more equitable long-term strategy may involve broader pre-emptive pharmacogenomic testing integrated into routine healthcare pathways, enabling *HLA* results to be available at the point of prescribing irrespective of a patient's reported ancestry.

Drug	Allele	Example of adverse drug reaction	MHRA alert	Information within SmPC	SmPC testing recommendation
Abacavir	*HLA-B*57:01*	ABC-HSR	No	Yes	Yes
Carbamazepine	*HLA-B*15:02*	SJS/TEN	Yes	Yes	Clinical decision
	*HLA-B*15:11*		No	No	Clinical decision
	*HLA-A*31:01*	SJS, TEN and DRESS	Yes	Yes	No
Oxcarbamazepine	*HLA-B*15:02*	SJS/TEN	Yes	Yes	Clinical decision
	*HLA-A*31:01*	SJS, TEN and DRESS	Yes	Yes	Clinical decision
Eslicarbazepine	*HLA-B*15:02*	SJS/TEN	Yes	Yes	Not specified
	*HLA-A*31:01*	SJS, TEN and DRESS	Yes	Yes	Not specified
Lamotrigine	*HLA-B*15:02*	SJS/TEN	No	No	No
Phenytoin	*HLA-B*15:02*	SJS/TEN	Yes	Yes	Not specified
Allopurinol	*HLA-B*58:01*	SJS and other severe reactions	No	Yes	Clinical decision for individuals of Thai, Han Chinese or Korean descent.

Table 2: List of reported drug-*HLA* gene matches. ABA-HSR; Abacavir hypersensitivity syndrome, SJS; Stevens-Johnson Syndrome, TEN; toxic epidermal necrolysis, DRESS; drug reaction with eosinophilia and systemic symptoms, SmPC; Summary of product characteristics.

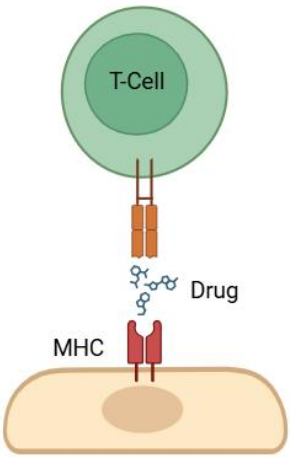


Figure 1: The MHC protein presents the drug to the T-cell which in turn will stimulate an immune or type B adverse drug reaction.

Pharmacogenomics Community of Practice – join us!!

This year we launched the new **Pharmacogenetics Community of Practice** (or PGx CoP for short), and we will be using this network to:

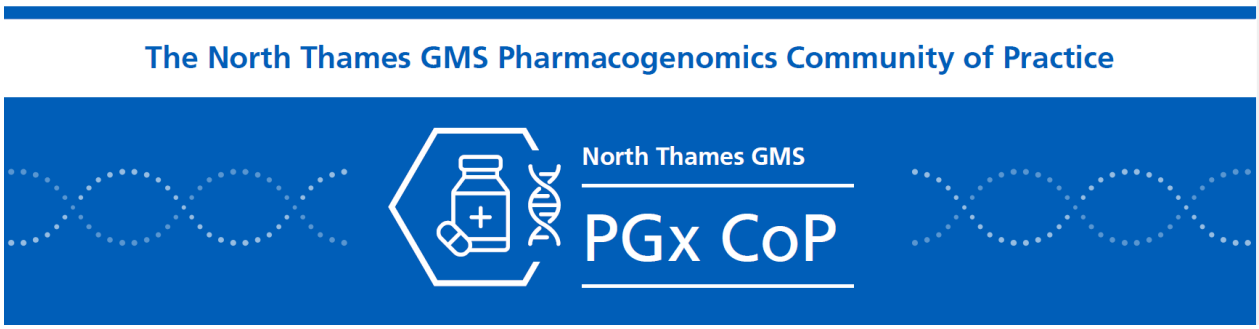
- Strengthen our understanding and application of pharmacogenomics
- Create a collaborative platform for shared learning
- Support evidence-based practice
- Accelerate clinical implementation

This PGx CoP will cover the North Thames GMS geographical footprint of North London, Hertfordshire and Mid and South Essex.

Our next meeting is on the 30th September from 1 to 2pm via Microsoft Teams.

If you are interested in joining, please contact me – Dharmisha.Chauhan1@nhs.net, will be great to have you on board!

We welcome all healthcare professionals from across all clinical sectors.



The NT-GMS team 😊

Within the North Thames Genomic Medicine Service (NT-GMS), I am privileged to work alongside an incredible multiprofessional team committed to delivering equitable access to genomic testing and innovation across our region.

In the field of pharmacogenomics, I work closely with our Programme Director, mental health leads, GP leads, nurses, pharmacists, laboratory leads, and many other colleagues to support the implementation and integration of genomic testing across clinical systems. Together, we are helping to ensure that genomic medicine can be translated into meaningful improvements in patient care.

To learn more about our team, our projects, and our education and training events, please visit and follow our LinkedIn page **@NorthThamesGenomics**. We regularly share updates on our work, opportunities on how to get involved, and developments in genomic medicine across North Thames.