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SPOTLIGHT COMMENTARY

Pharmacogenomics spotlight commentary: From the United Kingdom to global populations

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1 | INTRODUCTION

There has been a flurry of genomic activity in the United Kingdom, which has led to expanded discussions regarding feasibility of national implementation of personalised medicine using genomic data to guide prescribing. By implementing current scientific knowledge of pharmacogenes, which influence the pharmacokinetics and pharmacodynamics of medicines, it would be possible to reduce the risk of adverse drug reactions and associated morbidity and mortality, decrease use of less effective drugs in certain individuals, and increase efficacy of chosen therapeutics, with less guesswork in dose titration. Where dose changes are indicated, clinical algorithms which consider pharmacogenetics are increasingly available. To fully mine the potential of such genomic knowledge, pharmacogenomics would need to be utilized on a population level. However, this raises a host of systems-related implementation considerations for which there is very limited experience in a national context. Multidisciplinary implementation science has made strides in improving understanding of how to translate important scientific gains to complex clinical care systems. Plans to apply pharmacogenomic testing on a large scale, such as in national health systems, may benefit from such an approach.[1]

In this Spotlight Commentary, we discuss several articles recently published in the *British Journal of Clinical Pharmacology*, which highlight the potential for pharmacogenomics actionability within the UK prescribing sphere, clearly demonstrating scope for improvement in clinical care.[2–4] Global research has also highlighted the importance of validating the genomic evidence base across diverse groups, which will be crucial to the ethical implementation of a stratified medicine programme within the United Kingdom as well as in other nations across the globe.

2 | PRE-EMPTIVE PHARMACOGENOMICS POTENTIAL IN UNITED KINGDOM

Providing fuel to the fire for moving towards pre-emptive pharmacogenomic testing is a recent publication indicating that 80% of patients were exposed to at least 1 drug associated with an actionable pharmacogenomic variant over a 20-year period.[3] The researchers looked at exposure to these drugs both retrospectively (2, 10, and 20 years) and prospectively (5 years) using data from the Clinical Practice Research Datalink (CPRD). This database includes anonymized, longitudinal medical records from primary care practices in the United Kingdom. As a result, the analysis focused on drugs initiated, or continued in primary care and thus does not contain drugs for specialist indications such as cancer. Kimpton et al. found exposure of primary care patients to pharmacogenomic drugs to be very common, with 74% exposed in the 10 years prior and 71% exposed in the 5 years post study initiation.[3] The top drugs prescribed were codeine, omeprazole, simvastatin, lansoprazole, amitriptyline, tramadol, citalopram, warfarin, paroxetine, and clopidogrel. Several of these

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drugs are the same as those found in a study by Samwald et al. who analysed prescribing data in the United States between 2009 and 2012 using healthcare administrative claims data.[5] From an initial list of 19 genes with drug/gene pharmacogenomics-based dosing guidelines, Kimpton et al. found that just three genes (*CYP2D6*, *CYP2C19*, and *SLCO1B1*) accounted for virtually all (>95%) pharmacogenomic drug prescribing across all periods.[3] This is in line with the results from Youssef et al. who found that *CYP2D6* accounts for 61.3%, *CYP2C19* for 25.0%, and *SLCO1B1* for 8.3% of the estimated 5 780 595 medicines prescribed in 2019.[2] The study by Kimpton et al. did not look at genomic data, but noted other studies have shown actionable variants to be frequently present in these genes.[3] This work supports development and implementation of a pre-emptive multi-gene pharmacogenomics panel to be utilized in a primary care setting to enhance prescribing decisions based on a patients' genetic background.

3 | MANAGING THE POTENTIAL DEMANDS OF PHARMACOGENOMIC SERVICES

The mainstreaming of pharmacogenomic services poses a number of challenges, not least in meeting the significant demand that could result if pre-emptive testing were offered routinely in relation to pharmacogenomic drugs. Youssef et al. estimated that around 4 million people would need to be tested annually in primary care in the UK.[2] Clearly, this may not be practicable, and suitable eligibility criteria will need to be specified to contain volume and costs. This may involve prioritizing patients based on other risk factors, limiting testing to situations where high doses are indicated, or to medicines associated with the most severe or common adverse drug reactions.

There may be significant advantages in panel tests, where a number of genes can be assessed simultaneously, and data stored in patients' electronic health records for when they might be eligible for a given medicine in the future. Based on Youssef et al., a panel test for nine genes (*CYP2D6*, *CYP2C19*, *HLA-B*, *SLCO1B1*, *CYP2C9*, *F5*, *HLA-A*, *TPMT*, and *VKORC1*) could inform one in every 11 new prescriptions issued in primary care in the United Kingdom.[2]

Challenges to implementing pharmacogenomics may be somewhat different in hospital settings. In the context of more specialized care in a children's hospital setting, Mizuno et al. describe how precision dosing can be achieved by embedding clinical decision support tools that consider pharmacogenomics, pharmacokinetics, and pharmacodynamics, within electronic health records.[6] They illustrate applications of pharmacogenomics with examples of medicines with low therapeutic indices—sirolimus, hydroxycarbamide, methotrexate, and morphine. However, they highlight an important barrier to more widespread implementation, noting that expertise spanning relevant clinical pharmacology domains have been mostly confined to relatively few academic institutions. A wider adoption of model-informed precision dosing would require more user-friendly decision support tools.

4 | GLOBAL PHARMACOGENOMICS AND CHALLENGES TO IMPLEMENTATION WORLDWIDE

There is continuing interest in studying pharmacogenomics worldwide and understanding of both ethnic differences and local challenges is increasing. A recent article reviewed current pharmacogenomics knowledge and clinical adoption in Oceania, Africa, Latin America, and Asia.[7] Data from Oceania nicely illustrated local challenges in terms of both the limited number of pharmacogenes studied to date and the differences in genetic repertoire between different Pacific regions, as described previously in more detail.[8] These differences have implications for use of pharmacogenomics in treatment of infectious disease, particularly malaria, tuberculosis and HIV. Similar problems with pharmacogenomics implementation in infectious disease treatment exist in Africa, but the development of the African Pharmacogenomics Consortium may help overcome them. Implementation of pharmacogenomics in Africa for other drug classes including codeine is already underway, at least in some hospitals. Warfarin is used widely in Africa, and a systematic review of genetic factors affecting warfarin dosing in Africans has recently been completed.[9,10] This shows the complexity of factors affecting dosing, with these factors now being investigated further in Uganda and South Africa (War-PATH http://warpath.info/) to develop specific clinical and genetic dosing algorithms in the longer term.

Latin American populations pose special problems for implementation of pharmacogenomics due to the large degree of population admixture within the various countries.[7] The nature of admixture is such that even guidelines for pharmacogenomics dosing based on "continental ancestry" may not be sufficient to deal with the complexity of population admixture.[11] Admixture is likely to also be increasingly relevant to the United Kingdom and other European countries.

Pharmacogenomics implementation in Asia continues, with one important local example being implementation of HLA genotyping to prevent cutaneous adverse reactions linked to anticonvulsants in the regions where *HLA-B*15:02* is common.[7] Irinotecan is another interesting example where treatment-related neutropenia is more common in those with certain UGT1A1 genotypes. The global pharmacogenomics article highlights the fact that the allele associated with decreased UGT1A1 activity phenotype (Gilbert's syndrome) is different in Asians (*UGT1A1*6*) compared with Europeans (*UGT1A1*28*), but worldwide, the drug label does not mention both alleles, except in Japan and Singapore.[7]

Despite these challenges, it is clear that pharmacogenomic testing is available in a range of countries worldwide, though this availability is not yet widespread, and implementation is still limited, in both highly developed and less well-developed regions.[12]

5 | CONCLUSION

Though challenges must be overcome in pharmacogenomic implementation on a national and international level, the National Health Services in the United Kingdom are uniquely well positioned to lead

integration of genomic information with mainstream clinical prescribing. Initiatives from Genomics England and elsewhere across the United Kingdom in cooperation with the National Health Services will have the opportunity to proactively address potential barriers to implementation and drive forward clinical translation of pharmacogenomics.[13] Pharmacogenomic testing would be recommended in line with emerging NHS guidance within the United Kingdom and as an amalgam of existing knowledge as reflected by the PharmGKB resource globally.[14] This has already started with the introduction of *DPYD* pharmacogene testing for cancer patients across the United Kingdom, which may inform altered chemotherapeutic regimes to decrease risk of toxicity from 5-fluorouracil or capecitabine.[4,13] Regulators have a role in increasingly adding pharmacogenomic information to summary of product characteristics (SmPC) and updating prescribing guidance concurrently. In the United Kingdom, for example, the genetic update to the SmPC was accompanied by a MHRA safety update on testing for dihydropyrimidine dehydrogenase (DPD) deficiency prior to prescribing intravenous 5-fluorouracil, capecitabine, or tegafur.[15] Globally driven work highlights the importance of validating the pharmacogenomics evidence base in diverse populations, and underlines the fallacy of pure ethnic categories, therefore mandating a more complex approach to understanding of ancestry in pharmacogenomics. This will ensure equity in care resulting from a well-balanced evidence base.

COMPETING INTERESTS

E.F.M. is a member of the NHS England and NHS Improvement pharmacogenetics test evaluation working group. A.K.D. is a member of the NHS England and NHS Improvement pharmacogenetics test evaluation working group. D.A.H. is chair of the NHS England and NHS Improvement pharmacogenetics test evaluation working group.

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