Spotlight Commentary

Pharmacogenomics; From the UK to global populations

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There has been a flurry of genomic activity in the UK, 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. 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. In several recent articles, the potential for pharmacogenomics actionability within the UK prescribing sphere has been highlighted, clearly demonstrating scope for improvement in clinical care[1–3]. 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 UK as well as in other nations across the globe.

Pre-emptive pharmacogenomics potential in UK

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[2]. 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 UK. 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[2]. The top drugs prescribed were codeine, omeprazole, simvastatin, lansoprazole, amitriptyline, tramadol, citalopram, warfarin, paroxetine, and clopidogrel. Several of these drugs are the same as those found in a study by Samwald *et al.* who analysed prescribing data in the US between 2009 and 2012 using healthcare administrative claims data[4]. 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. 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[1]. 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[2]. 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.

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[1]. 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*, *VKORC1*) could inform one in every 11 new prescriptions issued in primary care in the UK[1].

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[5]. 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.

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[6]. Data from Oceania nicely illustrated local challenges both in terms of the limited number of pharmacogenes studied to date and the differences in genetic repertoire between different Pacific regions, as described previously in more detail[7]. 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[8,9]. 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[6]. 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[10]. Admixture is likely to also be increasingly relevant to the UK 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[6]. 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[6].

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[11].

Conclusion

Though challenges must be overcome in pharmacogenomic implementation on a national and international level, the National Health Services in the UK are uniquely well positioned to lead integration of genomic information with mainstream clinical prescribing. Initiatives from Genomics England and elsewhere across the UK, 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 [12]. This has already started with the introduction of *DPYD* pharmacogene testing for cancer patients across the UK, which may inform altered chemotherapeutic regimes to decrease risk of toxicity from 5-fluorouracil or capecitabine[3,12]. 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.

Disclosures/COI

EFM is a member of the NHS England and NHS Improvement pharmacogenetics test evaluation working group.

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