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COMMENTARY

Pharmacogenomics: Relevance and opportunities for clinical pharmacology

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Pharmacogenomics (PGx) is the intersection of genomic medicine and pharmacology whereby knowledge of variation in an individual's genome is utilized to inform prescribing practice. The variation can affect genes responsible for determining either the pharmacokinetics or pharmacodynamics of a drug, and in some cases (for example, warfarin or phenytoin), response may be due to both pharmacokinetic and pharmacodynamic gene variation. The genomic variation may lead to reduction-of-function (RoF) or complete loss of function (LoF), while in other cases, there may be a gain-of-function (GoF). Thus, patients carrying RoF genetic variants in a drug-metabolizing enzyme gene will metabolize substrate drugs more slowly than noncarriers, increasing their risk of toxicity. Conversely, for prodrugs, RoF variation will result in reduced biotransformation to the active compound, resulting in reduced efficacy.

Clinically actionable PGx recommendations have now been developed by international guideline committees for over 90 prescribed drugs.[1] The evidence for these recommendations is usually derived from the totality of available research ranging from case reports, mechanistic investigations and pharmacokinetic studies to prospective comparative studies, implementation initiatives and randomized controlled trials (RCTs). Pivotal RCTs sit atop the medical evidence hierarchy, yet the growing number of approved drugs, genomic complexity and the costs involved in undertaking RCTs mean that, unfortunately, not all drug-gene variant combinations will be investigated through RCTs. Thus, the varied range of evidence types and their sometime inconsistent results need to be appraised in a dispassionate but reasoned manner, and intelligent analysis of real-world PGx data as it accumulates is crucial.

PGx variation is common in the human genome—almost 99% of people carry at least one PGx variant. Furthermore, as we get older and accumulate diseases, the resultant polypharmacy means that almost 90% of patients over the age of 70 are exposed to at least one drug with PGx guidance.[2] PGx can therefore be regarded as an important tool to help optimize prescribing through dose modification, drug choice and/or monitoring decisions to reduce adverse drug reactions (ADRs) and/or improve drug efficacy. Clearly, variability in drug response can also be due to non-genetic factors, for example renal function, but to date, we have largely ignored the importance of genetic variation on drug response. PGx when implemented 'at-scale', together with other factors affecting drug response, has the potential to lead to healthcare system-wide improvements in the quality of prescribing practice, which can improve drug efficacy, reduce ADRs, improve clinical outcomes and ultimately reduce cost.

Despite such potential, PGx has been inconsistently and slowly implemented into routine clinical care. Some sentinel sites in the United States have started implementing multiple drug-gene pair PGx testing into their hospitals, but at a whole healthcare system level, there are only a few examples, most notably the use of *HLA-B*57:01* genotyping to prevent abacavir hypersensitivity. In 2020, the European Medicines Agency recommended testing for dihydropyrimidine dehydrogenase (DPD) deficiency prior to starting fluoropyrimidine treatment. Later that year, the UK NHS commissioned genetic testing for four established RoF variants in *DPYD*, the gene encoding DPD. DPD deactivates fluoropyrimidine chemotherapeutics and RoF *DPYD* genetic variants significantly increase the risk

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of severe, and even fatal, toxicity following fluoropyrimidine exposure. Thus, appropriate dose modifications in patients with *DPYD* variants can prevent severe adverse events.[3] The United Kingdom is well positioned by virtue of the National Health Service (NHS) and well-developed genomic medicine services to implement PGx even further.[4]

In order to understand the scientific, clinical, lay and infrastructure issues that will be required for PGx implementation in the NHS, the Royal College of Physicians (RCP) and British Pharmacological Society (BPS) developed a joint multidisciplinary PGx Working Group, with representation from several physician specialties, other Royal Colleges (including the Royal College of General Practitioners), the Royal Pharmaceutical Society and other healthcare organizations. The output of this Working Group has culminated in a report, entitled 'Personalised prescribing: using pharmacogenomic information to improve patient outcomes'.[5] Several challenges are identified in the report that could hinder broader adoption of PGx if not appropriately considered and properly addressed. These include implementation strategies and PGx clinical service designs that do not take into account current healthcare system and staff pressures, prescribers' knowledge of PGx and associated education and training, managing stakeholder expectations, clinical governance and oversight and, crucially, funding. The report proposes mitigation strategies and provides recommendations to guide the equitable, manageable and appropriate implementation of PGx into the UK healthcare system.

The RCP/BPS Working Group report makes clear that widespread implementation of PGx into clinical practice will be a multidisciplinary and collective endeavour, especially as successful implementation requires agile systems responsive to novel robust research advances so that there is continual evaluation and optimization of PGx services. Thus, implementation will involve, but is not limited to, doctors, pharmacists and other healthcare prescribers from across both primary and secondary care; clinical geneticists, biochemists and clinical scientists involved in genetic testing (for both laboratory-based and potentially point-of-care testing); software engineers; informatics and applied healthcare researchers; healthcare commissioners; the public and most importantly, patients.

Within this complex system, clinical pharmacologists are well suited to support PGx in both healthcare and industry (Figure 1) to improve the use of existing drugs and develop new drugs. Clinical pharmacologists focus on safe and effective pharmacotherapy across diverse therapeutic areas combined with emphasis on both holistic patient care and scientific rigour. Clinical pharmacologists have also been pivotal in discovery and translational PGx research. Now, with growing clinical datasets, whole genome sequencing, artificial intelligence and other advanced computational methods, clinical pharmacologists should continue to be at the forefront of clinical academic PGx research, including the generation and refinement of PGx therapeutic guidelines. Despite the small size of the medical specialty of Clinical Pharmacology and Therapeutics in the United Kingdom, the skills, knowledge and experiences attained through broad clinical training and a focus on medicines places clinical pharmacologists in an excellent position to help coordinate and collaborate in the multi-organizational development and monitoring of PGx services within integrated care systems involving primary and secondary UK healthcare organizations linked to the national network of Genomic Laboratory Hubs (GLHs) in England and the centralized genomic testing facilities in Northern Ireland, Scotland and Wales. Clinical pharmacologists will need to work closely with physician colleagues, pharmacists, clinical scientists and others in multidisciplinary teams to establish new PGx services and, in the future, contribute to the design of intelligent and user-friendly clinical decision support systems. The development of PGx services also represents an opportunity for clinical pharmacologists to contribute to the evaluation of cost-effectiveness and real-world clinical effectiveness to ensure that PGx implementation is continually refined and optimized.

The implementation of PGx into the NHS also provides an opportunity to develop the speciality. For instance, it is possible that some clinical pharmacologists with a particular interest in PGx may become PGx specialists, similar to how some clinical pharmacologists have specialized in hypertension or clinical toxicology. PGx specialists could provide input into particularly complex individual patient cases referred to them by other healthcare professionals and provide advice either remotely and/or by reviewing the patient in a dedicated clinical

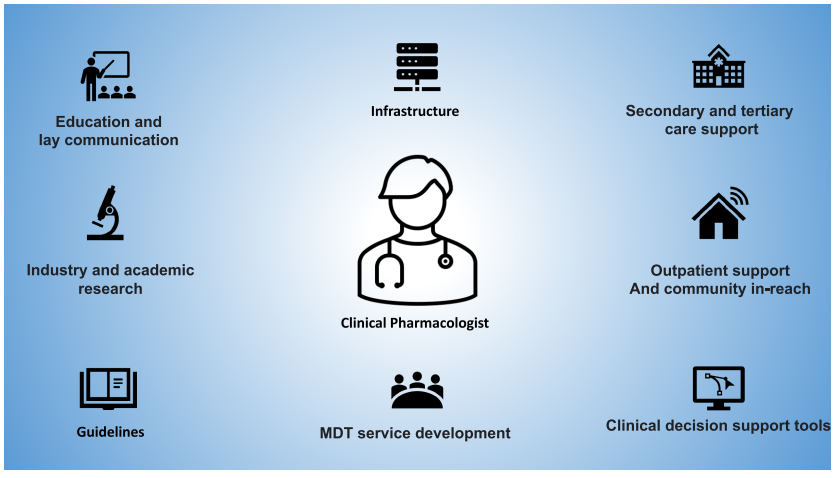

FIGURE 1 Opportunities for clinical pharmacologists to contribute to pharmacogenomics. Clinical pharmacologists working in academia, industry and the NHS can all make important contributions to pharmacogenomics. These range from novel therapeutic development to speciality pharmacogenomics consult services, in addition to education and public outreach

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pharmacology clinic. The dramatic increase in multimorbidity and polypharmacy rates represent a major challenge to prescribing pharmacotherapy safely and effectively because of the complex and dynamic interplay of drug–drug, drug–disease, drug–gene, drug–drug–gene and other types of interactions that can coalesce within the same individual. Thus, clinical pharmacologists with their broad and deep understanding of pharmacology, combined with expertise in PGx, are ideally equipped to serve patients with the most complex prescribing needs. It should also be noted that there is a role for clinical pharmacologists to communicate the merits and limitations of genomic science, and PGx in particular, to the general public. It is also of paramount importance that clinical pharmacologists help upskill colleagues in PGx and contribute to training the next generation of healthcare professionals in pharmacology and PGx.

In industry, there has been increasing interest in using genomic information to identify new drug targets, as it has been estimated that selecting targets supported by human genetic evidence could double the success rate in clinical development.[6] Academic and industry researchers are therefore increasingly leveraging large scale human genetic datasets (for example, in the UK Biobank) to catalyse and support target discovery and prioritization efforts. Sometimes, no further genetic-enabled stratification will occur following target selection and drugs can be developed for the broad patient population with the disease of interest. However, drugs have also been developed to target molecules resulting from specific pathogenic variants. One example is ivacaftor, which potentiates the opening of cystic fibrosis transmembrane conductance regulator (CFTR) protein channels in patients with cystic fibrosis that carry specific *CFTR* variants, such as G551D.[7]

Looking to the future, more than a million people will have undergone whole genome sequencing in the United Kingdom in the next few years, and this is likely to increase as prices fall and sequencing technology improves. There is of course a wealth of PGx information contained within whole human genomes, and it is important that this is extracted, interpreted and made available clinically to guide medicines prescribing. Another rapidly emerging technology with the potential to improve drug response, through patient stratification, is the development of polygenic risk scores (PRSs). Large disease-susceptibility PRSs involving millions of variants have been developed for several common conditions and can identify subgroups at elevated risk.[8] For example, individuals within the top 8% of the polygenic risk burden for coronary artery disease (CAD) have an average 3-fold increased risk of CAD, equivalent to the risk conferred by a familial hypercholesterolaemia mutation.[8] Importantly, the CAD PRS significantly influences the magnitude of benefit patients receive from PCSK9 inhibitors, such as alirocumab, in a secondary prevention setting.[9] Overall, taking into account the polygenic nature of disease alongside drug-specific pharmacokinetic and pharmacodynamic factors offers a novel approach to potentially improve drug effectiveness in certain settings, for example, in the use of more expensive medicines, but requires further research. One major current limitation is the reliance of genomic and PGx research on European-ancestry individuals, which limits target discovery opportunities, the ability to translate PGx discoveries from one ethnic group to another and the generalizability of PRSs. Examples in the PGx field include: (a) the lack of warfarin PGx data in Black Africans,[10] given that this is the most common oral anticoagulant used because of affordability, and (b) the four *DPYD* genetic variants tested in the United Kingdom and many parts of the world are derived from European populations,[3] and are not likely to capture genetic variants in other ethnic groups. The lack of genomic data on diverse ancestral populations therefore has the potential to exacerbate existing health inequalities if not addressed and hamper implementation initiatives.

In conclusion, PGx represents a novel piece in the jigsaw of factors that should be collectively considered when developing novel drugs and prescribing current drugs to improve the safety and efficacy of pharmacotherapy. The hurdles to broad uptake of PGx remain considerable. Nevertheless, healthcare systems are adapting, and the RCP/BPS PGx Working Group report should catalyse dialogue between stakeholders with the overall aim of progressing inclusive and equitable PGx implementation.

COMPETING INTERESTS

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REFERENCES

1. PharmGKB. Clinical guidance annotations. 2022. Accessed March 8, 2022. https://www.pharmgkb.org/guidelineAnnotations
2. Kimpton JE, Carey IM, Threapleton CJD, et al. Longitudinal exposure of English primary care patients to pharmacogenomic drugs: an analysis to inform design of pre-emptive pharmacogenomic testing. *Br J Clin Pharmacol*. 2019;85(12):2734-2746. doi:10.1111/bcp.14100
3. Henricks LM, Lunenburg C, de Man FM, et al. DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. *Lancet Oncol*. 2018;19(11):1459-1467. doi:10.1016/S1470-2045(18)30686-7
4. Turner RM, Newman WG, Bramon E, et al. Pharmacogenomics in the UK National Health Service: opportunities and challenges. *Pharmacogenomics*. 2020;21(17):1237-1246. doi:10.2217/pgs-2020-0091
5. Royal College of Physicians and British Pharmacological Society. *Personalised Prescribing: Using Pharmacogenomics to Patient Outcomes*.

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London: Royal College of Physicians and British Pharmacological Society; 2022. 53 pages.
6. Nelson MR, Tipney H, Painter JL, et al. The support of human genetic evidence for approved drug indications. *Nat Genet*. 2015;47(8):856-860. doi:10.1038/ng.3314
7. Ramsey BW, Davies J, McElvaney NG, et al. VX08-770-102 Study Group. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med*. 2011;365(18):1663-1672. doi:10.1056/NEJMoa1105185
8. Khera AV, Chaffin M, Aragam KG, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet*. 2018;50(9):1219-1224. doi:10.1038/s41588-018-0183-z
9. Damask A, Steg PG, Schwartz GG, et al. Patients with high genome-wide polygenic risk scores for coronary artery disease may receive greater clinical benefit from alirocumab treatment in the ODYSSEY OUTCOMES trial. *Circulation*. 2020;141(8):624-636. doi:10.1161/CIRCULATIONAHA.119.044434
10. Asiimwe IG, Zhang EJ, Osanlou R, et al. Genetic factors influencing warfarin dose in black-african patients: a systematic review and meta-analysis. *Clin Pharmacol Ther*. 2020;107(6):1420-1433. doi:10.1002/cpt.1755

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