VOLUME - 12, ISSUE - 05, MAY - 2023 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper | Clinical Research

THE SIGNIFICANCE AND POTENTIAL FOR CLINICAL PHARMACOLOGY IN RELATION TO PHARMACOGENOMICS.

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ABSTRACT This paper discusses the potential of pharmacogenomics to improve the safety and efficacy of drug therapy, as well as the challenges and opportunities for clinical pharmacologists in this field. With the increasing availability of genomic data and advances in sequencing technology, pharmacogenomics has the potential to personalize treatment plans for individual patients based on their genetic profiles. However, the complexity of genetic variation and the need for robust clinical evidence are some of the challenges that the field faces. Nonetheless, there are opportunities for clinical pharmacologists to contribute to the development and implementation of personalized medicine, ranging from research to specialty pharmacogenomics consult services. Additionally, the paper highlights the potential of whole genome sequencing and polygenic risk scores in improving drug response and patient stratification, while emphasizing the need for more diverse genomic data to ensure equitable implementation of pharmacogenomics. In conclusion, incorporating pharmacogenomics into clinical practice has the potential to revolutionize the field of pharmacotherapy, and healthcare professionals must continue to advocate for its integration to improve patient outcomes.

KEYWORDS : Pharmacogenomics, Drug response, Personalized medicine, Clinical pharmacology, Genetic variation

BACKGROUND

Pharmacogenomics is the study of the genetic basis for variations in drug response among individuals. It involves the identification and characterization of genetic variations that may impact how individuals metabolize drugs, as well as how drugs affect their bodies. Pharmacogenomics has the potential to improve the safety and efficacy of drug therapy by helping healthcare providers tailor treatment plans to individual patients, thereby reducing the risk of adverse drug reactions and improving treatment outcomes.

Clinical pharmacology is the medical specialty that focuses on the safe and effective use of drugs in patients. Clinical pharmacologists are experts in drug interactions, pharmacokinetics, and pharmacodynamics. They are responsible for optimizing drug therapy in patients by considering a range of factors such as age, sex, weight, and comorbidities. Clinical pharmacologists are uniquely positioned to contribute to the field of pharmacogenomics, given their deep understanding of drug pharmacology and their experience in clinical practice.

In recent years, there has been a growing interest in the potential of pharmacogenomics to improve drug therapy. The increasing availability of genomic data and advances in sequencing technology have made it possible to identify genetic variants that influence drug response and to use this information to guide treatment decisions. For example, genetic testing can be used to identify patients who may be at increased risk of adverse drug reactions, or who may require higher or lower doses of certain medications. Similarly, pharmacogenomic information can be used to select the most effective treatment for individual patients based on their genetic profiles.

The potential benefits of pharmacogenomics are substantial, but the field also faces a number of challenges. One key challenge is the complexity of genetic variation, which can influence drug response in multiple ways. In addition, many genetic variants that affect drug response are relatively rare, making it difficult to study them in large patient populations. Another challenge is the need for robust clinical evidence to support the use of pharmacogenomic information in clinical practice. While there are a growing number of studies demonstrating the clinical utility of pharmacogenomics, more research is needed to fully understand how best to integrate this information into clinical decision-making.

Despite these challenges, there are a number of opportunities for clinical pharmacologists to contribute to the field of pharmacogenomics. These range from novel therapeutic development to specialty pharmacogenomics consult services, education, and public outreach. For example, clinical pharmacologists working in academia can conduct research on the pharmacogenomic basis of drug response, and develop new drugs or drug targets based on this knowledge. Similarly, clinical pharmacologists working in the industry can use pharmacogenomic information to identify new drug targets or to stratify patient populations for clinical trials. In the NHS, clinical pharmacologists can provide specialist pharmacogenomics consult services to healthcare providers, helping to interpret genetic test results and develop personalized treatment plans for individual patients.

This paper will explore the relevance and opportunities for clinical pharmacology in the field of pharmacogenomics. We will discuss the current state of the field, including key challenges and opportunities for future research. We will also highlight examples of how clinical pharmacologists are currently contributing to the field of pharmacogenomics, and provide recommendations for how the specialty can continue to play a leading role in the development and implementation of personalized medicine.

Understanding Pharmacogenomics and its Impact on Prescribing Practices

Pharmacogenomics (PGx) utilizes an individual's genomic information to inform prescribing practices by identifying genetic variation that can impact a drug's pharmacokinetics or pharmacodynamics, potentially leading to reduced or complete loss of function, as well as gain-of-function effects, and the presence of RoF genetic variants can increase the risk of toxicity while RoF variation in prodrugs can reduce efficacy. [1], [2]

The Development and Evaluation of Clinically Actionable PGx Recommendations for Prescribed Drugs

International guideline committees have developed over 90 clinically actionable pharmacogenomics (PGx) recommendations for prescribed drugs based on various sources of evidence, including case reports, pharmacokinetic studies, and randomized controlled trials (RCTs), with RCTs being the most highly valued, although not all drug-gene variants can be investigated in this manner due to factors such as genomic complexity and cost. Therefore, it is important to objectively evaluate the various types of evidence and analyze real-world PGx data as it becomes available. [3]

The Significance of PGx in Optimizing Prescribing Practices

PGx is prevalent in almost 99% of individuals due to genomic variation, which becomes more pronounced with age and disease. This makes PGx an important tool for optimizing drug prescription by aiding in dose modification, drug selection, and monitoring decisions, ultimately leading to reduced adverse drug reactions and improved drug efficacy. Although non-genetic factors can also affect drug response, the importance of genetic variation in drug response has been largely overlooked. Implementing PGx at scale, along with other factors influencing drug response, can potentially improve the quality of prescribing practice, enhance clinical outcomes, and reduce healthcare costs. [4]

Slow and Inconsistent Implementation of PGx in Clinical Care\

Despite the potential benefits of PGx, its implementation into routine clinical care has been inconsistent and slow. While some sentinel sites in the United States have started implementing multiple drug-gene pair PGx testing in their hospitals, there are only a few examples of whole healthcare system-level implementation. One notable example is 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 of severe, and even fatal, toxicity following fluoropyrimidine exposure. Thus, appropriate dose modifications in patients with DPYD variants can prevent severe adverse events. The United Kingdom, with its National Health Service (NHS) and well-developed genomic medicine services, is well-positioned to implement PGx even further. [5]

A multidisciplinary approach to PGx implementation in the NHS

The Royal College of Physicians (RCP) and the British Pharmacological Society (BPS) collaborated to establish a multidisciplinary PGx Working Group that includes representatives from various healthcare organizations. The Working Group produced a report titled "Personalised Prescribing: using pharmacogenomic information to improve patient outcomes," which aims to address the challenges associated with the broader adoption of PGx in the UK healthcare system. The report identifies several obstacles that could impede the widespread implementation of PGx, including the current healthcare system's pressures, lack of prescribers' knowledge of PGx and relevant education and training, stakeholder expectations management, clinical governance and oversight, and funding. The report provides recommendations and mitigation strategies to facilitate the equitable, manageable, and appropriate implementation of PGx in the UK healthcare system. [6]

Clinical Pharmacologists as Key Players in PGx Implementation

Clinical Pharmacologists are well-positioned to support PGx implementation in healthcare and industry. They focus on safe and effective pharmacotherapy across various therapeutic areas while emphasizing holistic patient care and scientific rigor. They have also played a critical role in the discovery and translational research of PGx. [1, 7]

The Role of Clinical Pharmacologists in PGx Research

With the growing availability of clinical datasets, whole genome sequencing, artificial intelligence, and other advanced computational methods, Clinical Pharmacologists are at the forefront of clinical academic PGx research. They should continue to generate and refine PGx therapeutic guidelines. The diagram depicted in Figure 1 highlights the various opportunities available for clinical pharmacologists to contribute to the field of pharmacogenomics. These opportunities include, but are not limited to, involvement in therapeutic development, speciality pharmacogenomics consult services, and education and public outreach efforts. Clinical pharmacologists in academia, industry, and the NHS can all play important roles in advancing the field of pharmacogenomics. [1, 8]

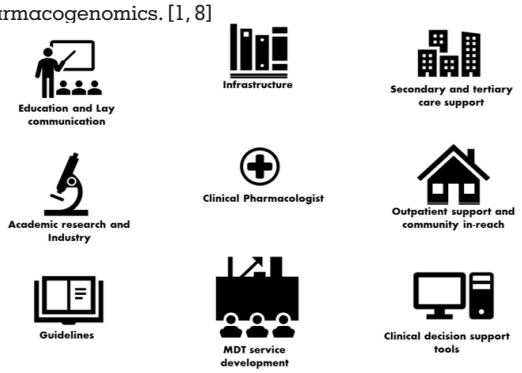

Figure-1: Ways in which clinical pharmacologists can contribute to pharmacogenomics.

Collaboration and Coordination for PGx Implementation

Clinical Pharmacologists, despite being a small medical specialty, are well-equipped to coordinate and collaborate in the multi-organizational development and monitoring of PGx services within integrated care systems. This involvement includes primary and secondary healthcare organizations, linked to the national network of Genomic Laboratory Hubs (GLHs) in England, and centralized genomic testing facilities in Northern Ireland, Scotland, and Wales. [1]

Working with Multidisciplinary Teams

Clinical Pharmacologists will work closely with physician colleagues, pharmacists, clinical scientists, and others in multidisciplinary teams to establish new PGx services. Furthermore, they can contribute to the design of intelligent and user-friendly clinical decision support systems. [1]

The Opportunity to Evaluate Cost-effectiveness

The development of PGx services presents 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. [1]

Specialization in PGx within Clinical Pharmacology

The implementation of PGx in the NHS presents an opportunity to develop the specialty of clinical pharmacology. With a particular interest in PGx, some clinical pharmacologists may become PGx specialists, similar to specialists in hypertension or clinical toxicology. [1]

Role of PGx Specialists

PGx specialists could provide input into complex individual patient cases referred to them by other healthcare professionals. They could also provide advice remotely and/or review the patient in a dedicated clinical setting. [1]

The role of clinical pharmacologists in implementing PGx in healthcare and industry

Clinical pharmacologists with their broad and deep understanding of pharmacology, combined with expertise in PGx, are ideally equipped to serve patients with complex prescribing needs. They can provide input into complex individual patient cases referred to them by other healthcare professionals and communicate the merits and limitations of genomic science, including PGx, to the general public. Additionally, clinical pharmacologists can 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. Academic and industry researchers are leveraging large-scale human genetic datasets to support target discovery and prioritization efforts. Drugs can be developed for the broad patient population with the disease of interest or to target specific pathogenic variants, such as ivacaftor, which potentiates the opening of cystic fibrosis transmembrane conductance regulator (CFTR) protein channels in patients with cystic fibrosis that carry specific CFTR variants. [1, 8]

Future of PGx and Genomics

In the near future, it is expected that more than a million people in the UK will have undergone whole genome sequencing, which will enable the extraction and interpretation of PGx information from their genomes. Additionally, the development of polygenic risk scores (PRSs) is another emerging technology with the potential to improve drug response and patient stratification. PRSs involve millions of variants and can identify subgroups at elevated risk for common conditions. However, the current limitation is the reliance on genomic and PGx research on European-ancestry individuals, which limits target discovery opportunities and the generalizability of PRSs. [1, 9]

Moreover, the lack of genomic data on diverse ancestral populations has the potential to worsen existing health inequalities and impede implementation initiatives. For instance, warfarin PGx data is lacking in Black Africans, despite being the most commonly used oral anticoagulant due to affordability. Similarly, the four DPYD genetic variants tested in the UK and other parts of the world are derived from European populations and may not capture genetic variants in other ethnic groups. [1] Despite these limitations, incorporating genomics and PGx into clinical practice has the potential to improve drug effectiveness, especially in the use of more expensive medicines. However, further research is required to understand the complex interplay between genetic factors and drug response and to ensure that the benefits of PGx are available to all patients regardless of their ethnic background.

CONCLUSION

Pharmacogenomics (PGx) is a critical component to consider when prescribing drugs to improve their safety and efficacy. While there are still significant barriers to the widespread implementation of PGx, healthcare systems are evolving to incorporate this technology. The RCP/BPS PGx Working Group report is expected to encourage communication and collaboration between stakeholders to promote the inclusive and equitable implementation of PGx. It is essential that healthcare professionals continue to advocate for the integration of PGx in clinical practice, as this has the potential to revolutionize the field of pharmacotherapy.

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