Pharmacogenetic testing to optimise prescribing – the future standard of care?

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The goal of delivering personalised medicine is closer than ever before. Pharmacogenetic (PGx) testing to guide the prescribing of certain medicines can improve patient outcomes and reduce adverse drug reactions. The PGx Impact study was designed to estimate the impact of pre-emptive genetic testing on prescribing activities in UK primary care. This article summarises the key findings of the study and discusses potential ways in which pharmacogenetic testing can optimise prescribing, and what this may mean for general practice in the near future.

Case 1
Mr Khan is a 60-year-old man with a medical history of obesity, type 2 diabetes mellitus, hypertension, dyslipidaemia and depression. He is currently prescribed metformin 500mg BD, amlodipine 10mg OD, atorvastatin 20mg OD and citalopram 20mg ON.

During a medication review, with pharmacogenetic testing, a clinician identifies Mr Khan is a CYP2C19 intermediate metaboliser. CYP2C19 enzyme metabolises citalopram and in intermediate metabolisers like Mr Khan, the drug is metabolised slower resulting in accumulation and potential toxicity. Pharmacogenetic prescribing guidelines of the Dutch Pharmacogenetic Working Group (DPWG)[1] recommend half the maximum daily dose of citalopram in intermediate metabolisers, so in adults this would be a daily maximum of 20mg and for the elderly this would be 10mg. As Mr Khan has been established on this dose of citalopram for a couple of years, the clinician discusses benefit and risk of continuing this dose given Mr Khans age. On exploration, Mr Khan does describe increasing drowsiness and agrees to a trial reduction to citalopram 10mg OD.

Case 2
Mrs Jones is a 40-year-old woman with a medical history of obesity, gout and hypertension. She is currently prescribed ramipril 5mg OD. She comes to the practice complaining of new onset gout. eGFR >90

*The clinician notes this is the third gout attack in the last 12 months for Mrs Jones and decides to initiate a medicine to prevent future episodes. Mrs Jones has recently had pharmacogentic testing through a clinical trial and her report states she carries the HLA-B*58:01 gene variant predicting she has an increased risk to be hypersensitive to allopurinol. The report states to avoid allopurinol and prescribe an alternative urate lowering medicine. The clinician initiates the second line agent febuxostat which does not have a drug-gene interaction with the HLA-B variant.*

Box 1. Examples of pharmacogenetic testing in general practice.

Whenever a new medicine is initiated, the prescription is written knowing that while it is likely to work for most patients, for a proportion it will be ineffective or cause side effects. The current methods used to increase the likelihood of achieving benefit over harm are to prescribe for licensed indications, at the recommended dose and following evidence-based guidelines for that disease. Unfortunately, a lot of the assumptions underpinning these recommendations are based on characteristics of the average patient presenting in clinic, requiring treatment for a condition, with standard treatment guidelines for drug and dose. Not many patients are average, but thankfully many are not too far from it.

Pharmacogenetic testing is a form of genetic testing that focuses on identifying gene variants related to drug response. This knowledge can help personalise the prescribing process and potentially improve the safety and efficacy of medicines. Just as it is common to test liver and kidney function before prescribing certain medicines, pharmacogenetic testing is likely to become routine medical care to inform drug and dose selection for patients.

Pharmacogenetics

Pharmacogenetics describes the relationship between genes and drug response. At the simplest level, genes are short sections of DNA that code for the production of proteins. These proteins independently or in combination with the environment lead to a variety of different observable characteristics. In the world of pharmacogenetics or PGx for short, the genes of interest relate predominately to those which produce drug metabolising enzymes, drug receptors and drug transporters. Normal variations in these genes can influence both dose-related and non-dose related drug toxicity. For example, nearly 7% of European populations carry a non-functional gene for the CYP2D6 enzyme, making them poor metabolisers (PM) of common drugs like codeine and tramadol.[2] Individuals who are CYP2D6 PMs, are unable to break down codeine into morphine and therefore derive little to no analgesic effect irrespective of dosing. Additional examples of drug-gene interactions encountered in general practice are shown in Box 1.

Genetic variability is common, and most studies estimate more than 95% of any given population, carry at least one gene variant that predicts an altered response to one or more medicines.[3] Additionally, over a patient's lifetime, the likelihood of being prescribed a drug with a notable drug-gene interaction is high with one study finding nearly 80% of English primary care patients are prescribed at least one PGx drug over a 20-year period.[4] With genetic testing costs reducing, the high incidence of drug-gene interactions and the immutability of the germline genome, implementing a panel, pre-emptive pharmacogenomic testing strategy seems to be the future (See Box 2).

The PGx Impact Study

The PGx Impact study used a modelling approach to estimate the annual prescribing volumes of medicines affected by high impact drug-gene interactions in UK primary care. The authors used a large community pharmacy database to estimate annual prescription volumes of newly initiated medicines in UK primary care with published PGx prescribing guidelines. These volumes were combined with population frequency data of pharmacogenetic variants relevant to drug response to estimate the volume of prescribing activity that could be optimised through pharmacogenetic testing.[5]

The PGx Impact study involved reviewing all relevant published pharmacogenetic prescribing recommendations from two international organisations. A total of 56 medicines were identified relevant to UK primary care. The authors estimate that annually, current international PGx prescribing recommendations would advise a direct dose or drug change for 1 in 11 new prescriptions for this group of medicines. Nearly 21% of new prescriptions for these 56 medicines would recommend action from the prescriber which includes drug/dose changes and/or additional monitoring. This translated to nearly 6 million patients annually in UK primary care having a drug-gene interaction according to the main PGx prescribing guidelines available to date.[5]

The most commonly prescribed medicines with drug-gene interactions included antidepressants, analgesics, anti-epileptics, antibiotics and statins. Interestingly, the majority of these drug-gene interactions occurring in primary care could be identified by testing for variants within four genes only

suggesting implementing a panel testing approach in UK primary care need not include an extensive list of gene panel, in order to potentially provide benefit to the majority of the population. Furthermore, these genetic variants provide information with regards to prescribing only and do not determine disease incidence or inheritance.

Is PGx the answer?
Whilst not a magic bullet, PGx provides an additional layer of information prescribers can use to holistically prescribe medicines for patients in a more personalised way. Genetic information highlighting a patient's drug metabolising profile ~~can~~ could potentially be used in the same way as a renal function test. PGx prescribing guidelines describe how to use the results of a genetic test, be it to avoid certain medicines (contra-indications), prescribe medicines with enhanced monitoring (cautions) or prescribe at a lower or higher initial dose. Much like other clinical tests, PGx tests cannot be used in isolation for most cases. Instead reflecting the complexity of drug response, PGx tests like other clinical tests should be considered as part of the whole clinical picture to guide prescribing safely and effectively.

There is growing evidence supporting the clinical utility of multi-drug or panel PGx testing. For example, a meta-analysis showed that PGx guided decision support (to aid prescribing), improved the incidence of remission in individuals with major depressive disorder by 5-fold, when compared to usual standards of care.[6] In Europe, the PREmptive Pharmacogenomic Testing for Preventing Adverse Drug REactions clinical trial (PREPARE) is a large multi-centre open, randomised study including almost 7,000 patients and investigating the effect of pre-emptive panel PGx testing on adverse event incidence. The panel of genes included is extensive and covers genes affecting a wide range of therapeutic areas including primary care, general medicine, cardiology, oncology, psychiatry, neurology, and transplantation. Results for the trial are expected later this year and if favourable, could provide a catalyst for wider PGx clinical implementation.

Translating pharmacogenetics in the clinic
Genomic medicine is already embedded within the NHS. A legacy of the 100,000 genome project is establishing a NHS Genomic Medicine Service (GMS) in England with seven NHS Genomic Medicine Service Alliances overseeing and co-ordinating the embedding of genomics into mainstream clinical care.[7] The NHS GMS aims to provide access to genomic technologies across the whole population. ~~established regional genomic medicine centres with the capability to provide whole genome sequencing and interpretation for the population.~~ Currently the majority of genetic tests available to order on the national genomic test directory are for cancers and rare and inherited diseases. A pharmacogenetic testing panel has however been developed for piloting later this year. Few details have been published on which drug-gene pairs the panel will cover and which patient groups will be eligible. However, given the immutable nature of genetics, it is likely that general practitioners will start to encounter pharmacogenetics, even if testing is initiated in secondary care. This will then give prescribers in the UK access to pharmacogenetic testing which is already available to prescribers either publicly or privately in counties like Australia, Canada, the Netherlands, and the USA.[8]

Education and training have always been one of the forefront concerns for clinical implementation of pharmacogenetics. A recent qualitative study of general practitioners in UK primary care corroborates this, with a key theme being the level of pharmacogenetic education necessary to support clinical management.[9] Education and training of allied health professionals like pharmacists or nurse practitioners could support a multidisciplinary team approach to pharmacogenetic interpretation. This is particularly important, as pharmacogenetic test results have lifelong relevance and so healthcare professionals across settings will encounter these results in the patient's clinical management. Genetic literacy of allied health professionals along with prescribing clinicians could distribute any additional workload appropriately thereby minimising the impact on the general practitioners' workload.

In addition to training and education, clinical informatics is also important. Personal genetic information needs to be recorded in a patients primary care electronic health record so that it 'follows' the patient throughout their lifetime. In addition, this information should ideally be incorporated in clinical decision support so that pharmacogenetic information is flagged up at the point of prescribing. For example, in the Netherlands pharmacogenetic information is recorded on one central system called the G-Standard.[10]

This system is used both for prescribing and dispensing medicines. Logistically this is more challenging to implement in the UK, as general practices will have different coding and prescribing systems. In the interim, a pharmacogenetic passport could be trialled. The PREPARE study are using this in Europe as part of their clinical trial. Patients are given a smart card with the results of the genetic variants tested and affected drugs. The card also has information on when testing took place and in which laboratory. In addition, practitioners can also scan a QR code on the card which directs them to a website with further up to date information supporting the clinical management of any drug-gene interactions.[10]

The future
The challenge of prescribing safely and efficiently is complex. Like most interventions, pharmacogenetics may help improve the safety and efficiency of prescribing for some patients, but not for all. More importantly, in the majority of cases a patients' genetic profile is only useful when used in conjunction with the wider clinical picture. Nonetheless, the ability to access genetic information and use it in the context of prescribing, brings us one step closer to realising the benefits of personalised medicine.

The PGx Impact study predicts that drug-gene interactions occur frequently in UK primary care. Utilising pharmacogenetic in this setting may provide patient benefit to a large proportion of the population on multiple occasions. Moving forward policymakers need to consider the impact of pharmacogenetic testing not only for secondary settings but also primary care where the majority of prescribing takes place. A pharmacogenetic panel of genes that cover both primary and secondary care drugs will be the ideal mode for implementation.

Education, training, and clinical informatics represent some of the greatest challenges to widespread adoption. Prescribers require clear, simple, clinically relevant information at the point of prescribing to facilitate implementation.[11] Incorporating models of care, where pharmacologists, pharmacists and other healthcare professionals work in multi-disciplinary teams providing PGx interpretation could support primary care doctors to improve patient care without additional workload.[12]

Pre-emptive pharmacogenetic testing refers to genetically testing a patient before any known prescribing activity takes place. This is different to a 'reactive' testing model where a genetic test is ordered prior to prescribing a particular medicine. Pre-emptive testing offers the opportunity to utilise pharmacogenetics at the point of prescribing if the genetic test results are stored and integrated into the primary health care record.

Box 2. What is 'pre-emptive' pharmacogenomic testing?

- Lots of factors influence drug response with genetics being one of them.
- Variants in single genes with a large effect size on drug response affect a small percentage ($\approx$10%) of all medicines on the market. However, these medicines are often prescribed frequently in primary care.
- Common medicines affected by drug-gene interactions include analgesics, antidepressants, statins, and proton pump inhibitors.
- Pharmacogenetic information, in tandem with other patient factors can guide better dose and drug selection, thereby improving the safety and efficiency of prescribing.
- Prescribing decision support tools with pharmacogenetic information could help support ease of implementation in primary care.

Box 3. Key messages for clinicians

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