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RESEARCH ARTICLE

Pharmacogenetics Implementation in Primary Care

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ABSTRACT
Pharmacogenetics is being considered as a pre-emptive test for the National Health Service in the United Kingdom. Primary care is a key clinical service for the use of this technology due to the large number of medications prescribed in this setting. Given the volume of prescribing and the prevalence of pharmacogenetic variants an average GP will be using pharmacogenetics approximately 12 times per week. The current high workload in primary care means that a time of only a minute or two at most is available for the physician to use this new information. Pharmacogenetics is only one data point in identifying drug options for a patient. In determining those options physicians also consider drug-drug, drug-condition, drug-liver and drug-renal potential interactions. Clinical Decision Support Systems exist that use pharmacogenetic and other information to help identify safer and more effective medication options for an individual.
The aim of this review was to assess the role of pharmacogenetics in primary care and review implementation strategies with special reference to the recent report from the National Health Service in the United Kingdom.

Primary Care Pharmacogenetics: Key Points

- Significant Pharmacogenetic evidence for many primary care prescribed drugs
- Guidelines are available for clinical interpretation of pharmacogenetic genotypes
- High prevalence of pharmacogenetic variants in primary care population
- Pharmacogenetics is only one factor influencing medication response along with renal, hepatic, other drugs, conditions.
- Personalised prescribing including pharmacogenetics interpretation should only take one to two minutes
- Electronic medical record integrated Clinical Decision Support Systems are part of the process for personalised prescribing
- Education, both just in time and more comprehensive, are necessary elements.

Introduction

Depending on an individual's genes and other factors, some medications may work more effectively, less effectively, or cause an adverse reaction. Adverse drug reactions (ADRs) are the cause of 197,000 deaths in Europe annually[1]. Between 40,000 and 400,000 deaths in hospital in Europe per year are caused by adverse drug reactions[2] and ADRs account for approximately 3.5% of hospital admission [3,4]. It is estimated that nearly half of ADRs may be preventable [5,6] The desired therapeutic outcome occurs between 50–75% of the time a prescription is given. It varies according to the medication and the reason it is being given, and the characteristics of the individual[7].

For over thirty years the evidence about drug-gene interactions has been increasing as the costs of testing has come down and the number of studies increased. The most well described interactions relate to P450 metabolism pathways in the liver and the impact single nucleotide polymorphisms (SNPs) have on these pathways, and the resulting drug serum level, and drug response. Nearly everyone has one or more genetic variants associated with documented drug-gene interactions[8]. The drugs impacted by these genetic variations are very commonly used. Several thousand drug-gene association studies have been published along with large numbers of randomised controlled trials using pharmacogenetics[9].

Technologies exist that use pharmacogenetic and other information to help identify safer and more effective medication options for an individual[10]. The large number of rigorous evidence-based guidelines about drug-gene interactions[11] combined with the prevalence of these pharmacogenetic variations [12] has reached a level such that the United Kingdom (UK) is planning how to make it available to everyone[13]. The implementation of this technology in European Primary Care is not without its challenges and this review identifies and addresses these.

Methods

This is a narrative literature review. The information for this review was gathered from searches of the National Library of Medicine (NLM) of pharmacogenetics and primary care performed over the last five years, and reviewing references from articles found during these searches. Information on prescribing in primary care, adverse drug reactions, and evidence of drug-gene interactions was identified from searches of NLM using a combination of MESH and keywords as well as reviewing information from PharmGKB (www.pharmgkb.com). 'Adverse drug reaction[MeSH Terms]) OR adverse drug reaction reporting systems[MeSH Terms]' in PubMed; '(((Pharmacogenetic*) OR (Pharmacogenomics*)) and ((((primary care) OR (family practice)) OR (family medicine)) OR (general practice)))' in PubMed and '("Genetics"[Mesh]) AND ("General Practice"[Mesh] OR "Primary Health Care"[Mesh])' in PubMed. Both authors developed and wrote the paper.

Results

One of the challenges of pharmacogenetics is the translation of the large and growing volume of evidence-based information into the multiple clinical settings where prescribing takes place, and for the many conditions that pharmacogenetics can be used. This need has been addressed through development of gene-drug guidelines by several international working groups that provide a standardized approach to translating drug-gene association into actionable prescribing recommendation based on the latest collective evidence available. These groups include the Clinical Pharmacogenetics Implementation Consortium (CPIC)[11] and the Dutch Pharmacogenetics Working Group (DPWG)[14].

There are two major reasons for implementation of pharmacogenetics in primary care. First is the high volume of prescribing that takes place in this setting compared to other specialties. In developed countries, most drugs are prescribed in primary care. More than 50% of consultations result in a prescription and individual family physicians prescribe 233 different drugs per year [15]. The second reason is that pharmacogenetic variants in primary care are common. For example, CYP2C19 has strong drug-gene associations with selective serotonin reuptake inhibitors[16] and proton pump inhibitors[17] with Clinical Pharmacogenetics Implementation Consortium (CPIC) level A evidence. Clinically important variants in CYP2C19 are seen in 27% in primary care patients[10] though a lower prevalence of 11% -24% was seen in Mediterranean South Europeans[18].

Initially one focus of the clinical use of pharmacogenetics was on improving drug therapy within the field of oncology, where several

pharmacogenetic tests have been studied for single drugs and a single genetic variation[19]. General Practitioners (GPs) do not have the same support as hospital colleagues, and use of pharmacogenetics has had slower adoption in the community setting[20]. Recently there has been assessment of pharmacogenetic clinical application in the primary care setting in countries such as Canada, US, UK, and Netherlands. Panels of genes with evidence of clinically significant drug-gene interactions for drugs used in primary care and the cost of testing were evaluated[10,21,22]. The drugs are commonly prescribed in primary care and an example of the prevalence of variants and the drugs impacted is shown in Table 1.

Table 1. Frequency of alleles, diplotypes, phenotypes, and CPIC A&B drugs with known drug-gene interactions for fully genotyped patients tested in primary care. [10]

Gene	**Alleles/ Diplotypes**	**Phenotype**	**Frequency of Alleles/ Diplotypes**		CPIC A&B Drugs
			No. of patients	**% (95%CI)**	
SLCO1B1 rs4149056	T/T (*1/*1)	Normal function	132	71 (64-77)	Atorvastatin Fluvastatin Lovastatin Pitavastatin Pravastatin Rosuvastatin Simvastatin
	T/C (*1/*5)	Intermediate function	49	27 (21-33)	
	C/C (*5/*5)	Low activity	4	2 (0-4)	
VKORC1 rs9923231	G/G	Normal activity	38	21(15-27)	*Warfarin*
	G/A	Intermediate activity	89	48 (41-55)	
	A/A	Low activity	58	31 (25-38)	
CYP2C19	*1/*1	Extensive metabolizer	80	43 (36-50)	Amitriptyline Citalopram Clopidogrel Dexlansoprazole Doxepin Escitalopram Lansoprazole Omeprazole Pantoprazole Voriconazole Lornoxicam
	*1/*2,*2/*17,*1/*4,*1/*8	Intermediate metabolizer	55	30 (24-37)	
	*2/*2,*2/*3,*3/*3 Canada	Poor metabolizer	8	4 (2-8)	
	*1/*17,*17/*17	Ultra-rapid metabolizer	42	23 (17-29)	
CYP2C9	*1/*1,	Extensive metabolizer	118	64 (57-70)	Celecoxib Flurbiprofen Fluvastatin Fosphenytoin Ibuprofen Lornoxicam Meloxicam Phenytoin Piroxicam Siponimod Tenoxicam Lenoxicam Warfarin
	*1/*2,*1/*3,*2/*2,*2/*3	Intermediate metabolizer	62	33 (27-41)	
	*3/*3	Poor metabolizer	5	3 (1-6)	

Although health providers acknowledge that a large opportunity lies in using pharmacogenetic knowledge to optimize and personalise prescribing, implementation remains a great challenge in the primary care setting[8,23–27]. Given the volume of prescribing in primary care and the prevalence of pharmacogenetic variants an important question is how often pharmacogenetics would be used in primary care if pharmacogenetic testing was done pre-emptively for the population. A group in the United Kingdom modelled the use of a pre-emptive pharmacogenetic programme for 9 genes related to 56 drugs frequently dispensed in primary care[8]. Using data from the UK biobank to give the prevalence of variants, and the UK prescribing data to identify the incidence of prescribing of drugs with established drug gene interactions, they estimated that approximately 20% of all new prescriptions of these 56 drugs an actionable drug-gene interaction (DGI) is likely to be present. A general practitioner with 1500 patients will initiate 604 prescriptions of these 56 drugs per year. That means they would be using pharmacogenetics 12 times per week. The current high workload in primary care means that a time of only a minute or two at most is available for the GP to use this new information.

Implementation of pharmacogenetics in primary care that works within this time limitation has also shone the spotlight on the prescribing process. It has highlighted the need for the integration not only of pharmacogenetic data, but drug-drug interaction data, liver and renal function, as well as drug-condition such as QTc or heart failure interaction data. The clinical decisions support system needs to do this seamlessly taking information from the electronic medical record and providing the user with a list of medication options that have been through a filter of all the variables including pharmacogenetics. This challenge has been identified in a recent report from the Royal College of Physicians and British Pharmacological Society joint working party that provides evidence on the use of pharmacogenetic information and the template for widescale implementation[13]. The challenge is making sure that genetic information is available to the healthcare professionals wherever and whenever they are prescribing, in a format that is usable, and that they know how to use it. The report highlights that the use of pharmacogenetics is equivalent to carrying out renal or liver function tests to guide drug prescribing decisions, and that analogy might conceivably aid understanding.

Once the UK National Health Service (NHS) has determined the pharmacogenetic test panel, it may be included in the National Genomic Test Directory, which will outline eligibility, testing scope, and actionability within the whole of the UK NHS. Building on the success of the 100,000 Genomes Project, NHS England launched the Genomic Medicine Service (GMS) in October 2018 to further embed genomics into the NHS. Prior to this, genomic testing facilities across England were reconfigured into seven regional genomic laboratory hubs (GLHs) to consolidate and enhance genomic testing capacity and capability. The GLHs provide a national testing network that underpins the GMS as it strives to meet its commitment to the NHS Long Term Plan to sequence 500,000 whole genomes from patients as part of their routine NHS care by 2023–24.

Some of the key tenets of the UK plan include, but aren't limited to:

- Developing clinical pharmacogenomics guidance
- Developing a report structure that is easy to interpret, strives to avoid user alert fatigue, and contains links to further information (for example just-in-time learning resources)
- Developing methods of providing reports across the spectrum of patient record systems, from paper-based to interruptive electronic systems
- Developing coding for genetic variants to allow for incorporation into the Electronic Health Record (EHR)
- Ensuring that data are stored securely and confidentially
- Building interconnected systems that enable community-based services and hospitals to access clinically relevant pharmacogenomic results for patients
- Future-proofing the systems so that pharmacogenomic-based recommendations can be added/amended as the research base grows

Given that most of the prescribing occurs in primary care, primary care doctors and pharmacists will be an essential component of an interdisciplinary pharmacogenetics service. Primary care is likely the preferred setting for implementing pharmacogenomics clinical decision support systems at scale over the short term, particularly because most of the prescribing happens in primary care.

Any first step in the implementation of pharmacogenomics must be accompanied by a targeted education and training package[28]. Support for clinicians must be provided as pharmacogenomic testing is rolled out. The education must be tailored to the clinical setting and the healthcare professional. It is not a genomics course but knowledge about pharmacogenetic variants and how they can be used for those patients seen by that clinic/hospital/health network organization. There are many examples of pharmacogenetic education from the hundreds of randomised controlled trials on the use of pharmacogenetics. From the trials in primary care and in our experience an hour of education is sufficient for people to start using pharmacogenetic knowledge that is presented in a format that works for this clinical setting.

Pharmacogenetics has traditionally been provided as a lab report. GP's use lab reports every working day and with the concise evidence-based information pharmacogenetic reports have a place within the decision support. They summarise the number and type of the pharmacogenetic variants for that individual, and the drug-gene interactions associated with those variants. In a sense it is no different from looking up a potential drug-drug interaction showing a scale of the clinical impact of the interaction. However, the evidence is growing for drug-gene interactions, so a static printed report is not optimal or clinically actionable. The pharmacogenetic information must be available wherever the patient is being seen for prescriptions, from the community pharmacist to the general practitioners' offices, so some secure cloud process that ensures patient privacy is needed. The technology for this already exists for a lot of health care information.

At the heart of many of the steps identified by the NHS is the Clinical Decision Support System (CDSS). The CDSS should help health care professionals identify medication options and doses for that patient. An alert at the time of prescribing, after patient shared decision making has resulted in a choice of medication, is not the most helpful decision support. Prescribing alerts provided by CDSS have been shown to be ignored in 88% of circumstances. False positive alerts were caused by a too broad screening interval and lack of incorporation of patient-specific variables[29].

An alternative to providing alerts is to provide a list of condition-specific personalised drug options for the patient. The drug management of disease and the dose of medication are two key questions facing general practitioners[30]. For each condition there is a list of guideline-based drug options. Personalised prescribing is the process that applies the patient expectations and characteristics including pharmacogenetics to that list. The result is a filtering of the list, identifying the potential interactions with liver-drug, renal-drug, condition-drug, drug-drug interactions, and drug-gene interactions. This results in the exclusion of some drugs due to critical interactions, and identification of drugs with less severe potential interactions. The impact of all these interactions can be displayed to the health care professional before they discuss the options with the patient. For the most frequently seen conditions pharmacogenetic informed clinical decision support system software can pull information from electronic medical records and provide the options in seconds providing the health care professional with a list of medication options for the condition, based on all the patient variables including the pharmacogenetics.

Conclusion

There is now a significant body of pharmacogenetic evidence for many primary-care prescribed drugs. These are in the format of guidelines and on-line databases and contain the information required to translate a genotype to a specific dose of a medication. Combining the pharmacogenetics with renal, hepatic, other drugs, and other conditions is necessary for a comprehensive personalised approach to prescribing.

Given the high prevalence of pharmacogenetic variants pre-emptive testing will lead to the use of pharmacogenetics between ten and fifteen times per week for an average GP. Given this demand personalised prescribing including pharmacogenetics interpretation should only take one to two minutes. Electronic medical record integrated Clinical Decision Support Systems are part of the process that enable this fast process of personalised prescribing. Education, both just in time and more comprehensive, are necessary elements for the confident use of pharmacogenetics in primary care.

Prescribing is a complex process with multiple factors to consider on top of the three primary questions about effectiveness, harm, and cost.

Pharmacogenetics has put this complexity under the spotlight and prompted educational programs and the development of new clinical decision support systems. The use of pharmacogenetics is a step on the path to safer, more effective, prescribing.

Conflicts of Interest

Dr Dawes is founder and Chief Scientific Officer at GenXys Health Care Systems

Dr Esquivel is Chief Medical Officer at GenXys Health Care Systems

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