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Pharmacogenomics and Community Pharmacy

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Abstract

We provide insight into the potential role that pharmacogenomic (PGx) certified pharmacists can contribute towards the integration of community based personalized health care through clinical research and services. A blue print for such clinical feasibility studies is presented and discussed in relation to providing more precise diagnostic, counselling and treatment services with potential overall economic benefit to the general population.

Keywords: Pharmacogenomics; Certified PGx pharmacists; Community pharmacies; Mental health; Precision medicine

Introduction

Pharmacogenomics (PGx) holds great promise in optimizing drug dosing and selection. The implementation of pharmacogenomics and global precision medicine over the next decade presents both opportunities and challenges [1,2]. Modifying medications based on polymorphic drug metabolizing enzymes, drug transporters and receptors has the potential to avoid side-effects, improve the efficacy of medications, and reduce time and money wasted for patients and the health care system. Uptake and application of these technologies has been slow, due to the high cost of testing, and the amount of knowledge required of medications and PGx to implement test results.

One solution in part to these bottlenecks would be the implementation of streamlined PGx testing in a community pharmacy by consultant pharmacists. Pharmacists are highly accessible, trusted medication experts. They are in the prime location to provide medication optimization services using PGx testing. Furthermore, testing that conforms to easily used clinical guidelines such as Clinical Pharmacogenetics Implementation Consortium (CPIC) or Dutch Pharmacogenetic Working Group [3] and tests for only major single nucleotide polymorphisms (SNPs) would facilitate the uptake of testing while driving down cost [4].

Feasibility studies

Clinical trials that incorporate pharmacogenomic testing feasibility studies to affirm clinical and economic benefit could be carried out by consultant pharmacists who are trained in PGx at a number of different partner community pharmacies. Briefly, such a blueprint would entail the following approach: Patients would be recruited for this service by pharmacists at their respective partner pharmacies by identifying side effects and in-efficacious medicines. The general scheme for this service would follows four points of contact after recruitment with the pharmacist who is certified in pharmacogenomics. Testing would be carried out in the pharmacy and then sent to a lab. After receipt of test results, pharmaceutical opinions/therapy changes would be generated by the pharmacist using current evidence based guidelines (like those created by CPIC) and suggestions would be communicated to the patient's family physician or the physician who prescribed the medication.

A number of feasibility trials have been carried out in the past few years in the United States and now in Canada. They confirm that this method of delivering personalized medicine does in fact work. Kerr Drug successfully implemented a pharmacist lead program which screened patients started on Plavix for CYP2C19 in 2013[5]. British Columbia has implemented a two phase study called "Genomics for Precision Drug Therapy in the Community Pharmacy" [6].

The first phase was completed in Fall 2016 which involved 29 community pharmacists in locations across British Columbia and recruited 200 patients - the program focused on patient education, developing standard operating procedures and collecting samples from their communities.

Finally, a paper published by Elliot et al. in February of 2017 showed the potential benefits of genetic testing combined with a clinical support tool [7]. Providers who combined genetic testing with a clinical support tool to treat home health patients using multiple medications were able to reduce hospital readmission rates by 52 percent and cut emergency department visits by 42 percent. This last paper highlights the necessity for a robust support tool to be able to integrate pharmacogenetic data into clinical practice. Vast amounts of data can be created from pharmacogenetic testing (especially whole genome sequencing) and as such, collating, storing and reporting SNP and haplotype information in an actionable way to clinicians becomes extremely important. It also necessitates secure database storage and privacy/consent from the patient to be able to surmount legal and ethical issues surrounding using this information. Lipton [8], in the journal Nature, provides a good overview of the ethical issues surrounding pharmacogenetic testing. Again, pharmacists and community pharmacy provide a way around some of these challenges. As more and more information is added to the clinicians workload, a provider who is well versed in pharmacogenetics, drug interactions and medications will put pharmacists at a logical juxtaposition to handle this role.

Similarly, increased access to pharmacogenetic testing and therefore information in the form of Direct to Consumer testing (DTC) also complicates clinician's roles. Pharmacogenetic testing as it currently stands can be obtained through direct to consumer companies (e.g.

23andMe) without the intervention of a clinician to either recommend or interpret these results. At first, the FDA banned 23andme's ability to offer health risk assessments to patients in the US. This was lifted in 2015 and they were once again able to sell directly to consumers [9]. To be able to implement DTC results the clinician must verify the testing being used, which SNPs are being tested for and their applicability to current evidence based guidelines. Unfortunately, the SNPs of many of these panels are not published and their utility could be brought into question if they do not test for the right SNPs or if they categorize haplotypes incorrectly.

Mental health

In the area of mental health the promise of psychiatric pharmacogenomics is becoming a reality where pharmacogenetics studies are the platform for discovering the DNA determinants of variability in drug response and tolerability [10]. Molecular variation can occur in the genes that code CYP450 drug metabolizing enzyme components, the enzyme products themselves and targets associated with synaptic transmission [11]. For example, genetic variation can be found in both the neurotransmitter and their receptors for GABAA where particular contributions of these GABAA isoforms are in control over the functioning of brain circuits, especially the mesolimbic system, [12] and dopamine D2 (D2R) [13] that have a direct effect on substance abuse and addictive behaviours Stephens et al. suggest there may be an opportunity for therapeutic targeting since genetic variation in expression of specific receptor types ($GABA_AR$) can show alteration of function associated with drug exposure and can involve a change in polarity of Cl- flux [12]. A reduction in D2R levels in the striatum is a determining factor that confers vulnerability to abuse substances. The authors also note a circuit-wide restructuring of local and long-range inhibitory connectivity within the basal ganglia. This is observed in response to manipulation of striatal D2R levels and is accompanied by multiple alterations in dopamine-dependent behaviours such that long term reduction of D2R expression occurs in substance use disorder populations [13].

Table 1 provides a list of drug classes used in the treatment of mental health conditions that are associated with genetic variation for CYP450 enzymes [14]. This table does not include any drug transporters although polymorphisms do exist in transporters which affect psychiatric medications (e.g. COMT). Another transporter important in drug metabolism (although not directly linked to mental health) is SLCO-1B1 which is important for the statin family of drugs. There are actionable pharmacogenetic guidelines based around SNPs in these transporters and related myalgia, myopathy and rhabdomyolysis.

Pharmacogenomic information

For those who want to validate raw data for the interpretation of diagnostic alleles/genotyping /phenotyping from commercial lab reports as part of quality control (QC) and be aware of currently annotated relevant databases, this information in part can be obtained through the dbSNP database [15] or by accessing haplotype information from CPIC [16]. Haplotype information for allelic combinations can be linked to rs numbers which in turn can be used as tags to search dbSNP directly for detailed information on their complete molecular/genetic/cytogenetic characterization. For instance, a report may state the individual has an haplotype allelic combination for CYP2D6 (Cytochrome P450, family 2, subfamily D, polypeptide 6) such as *4/*4 (see Beoris et al. for a recent review), [17]. This is one of the haplotypes that can define the slow metaboliser phenotype for codeine metabolism (to morphine) and requires a change in therapeutic pain medication intervention. Further, significant differences in allelic frequencies may also occur for various ethnic groups or within families/sib ships. Such differences may warrant proactive surveillance, testing and counselling of requisite populations at risk.

Table 1: Psychiatric medications and their metabolizing enzymes - Modified from FDA [14].

Drug	Drug metabolizing enzyme
Amitriptyline	CYP2C19
Aripiprazole	CYP2D6
Atomoxetine	CYP2D6
Citalopram	CYP2C19
Clomipramine	CYP2D6
Clozapine	CYP2D6
Desipramine	CYP2D6
Diazepam	CYP2C19
Doxepin	CYP2D6
Escitalopram	CYP2C19
Fluoxetine	CYP2D6
Flupenthixol	CYP2D6
Fluvoxamine	CYP2D6
Haloperidol	CYP2D6
Iloperidone	CYP2D6
Imipramine	CYP2D6
Mirtazapine	CYP2D6
Moclobemide	CYP2C19
Modafinil	CYP2D6
Nefazodone	CYP2D6
Olanzapine	CYP2D6
Paroxetine	CYP2D6
Perphenazine	CYP2D6
Pimozide	CYP2D6
Protriptyline	CYP2D6
Risperidone	CYP2D6
Sertraline	CYP2C19
Thioridazine	CYP2D6
Trimipramine	CYP2D6
Venlafaxine	CYP2D6
Zuclopenthixol	CYP2D6
Duloxetine	CYP2D6
Nortriptyline	CYP2D6

Discussion and Conclusion

Currently over 400 clinical trials utilize pharmacogenomic testing to investigate the role of genetic variability in assessing drug efficacy and side effects for various conditions/diseases [18].

We expect pharmacists will continue to be accepted in the role of PGx expert and that these feasibility studies will further provide the basis for pharmacist lead PGx and future research. These types of PGx services will likely lead to the prevention of adverse drug reactions (ADRs), giving patients more efficacious medicine and saving them and the healthcare system time and money. If successful, such studies will also show a potential alternate mode of health services delivery- this type of service will be needed for both the short and long term. Service gaps will occur in pharmacy/medical doctors/clinical setting personnel who will not take on intensive training required to provide such service in the short term. In the long term, as diagnostic technologies are integrated, such a healthcare model will have the capacity to integrate seamlessly these advances in diagnostic techniques and their practical applications. PGx certified personnel will have the requisite education/expertise to interpret results and provide appropriate therapeutic drug advice as the application

of potentially diagnostic epigenomic/methylome, micro RNA [19] and proteomic/metabolomic biomarkers [20] come online through their clinical use and standardization.

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