Pharmacogenomic testing and its future in community pharmacy

The Pharmaceutical Journal 15 NOV 2019
By Essra Youssef
, Sam Mostafa
, David Wright

Although it is common to see pharmacogenomic testing used North America and Australia, it is not yet part of practice in the UK. With the promise of genomic screening becoming part of the NHS, pharmacists must equip themselves with a knowledge of how the process works.

Source: Shutterstock.com

In January 2019, the UK government unveiled its ten-year plan for NHS England and emphasised the role pharmacists can play in promoting patient self-care[1]. There was also a focus on delivering value from medicines and reducing avoidable medicines related-harm, which costs the NHS a minimum of £98.5m per year[2]. This coincides with the NHS Genomic Medicine Service, which will be rolled out across England from April 2020, meaning that the routine use of genomic screening and personalised treatments will be the new normal in the NHS[3],[4].

Pharmacists' advice currently relies on knowledge of observable patient characteristics, such as age, weight, comorbidities and concurrent medicines, while largely disregarding genetics. However, it is estimated that genetic factors could contribute to between 25–50% of inappropriate drug responses[5].

Knowing exactly which medicine to use for a patient and which to avoid can be a challenging task in clinical practice. However, pharmacogenomics can provide the prescriber with additional information on some of the unobserved patient characteristics that affect drug response — this can assist with both drug selection and safety. Therefore, the combination of this pharmacogenomic information along with other factors influencing pharmaceutical care may provide an opportunity to deliver more 'personalised' medicine, facilitating better selection and reducing the need for 'trial and error' prescribing.

Pharmacogenomics is an emerging field that studies how genes affect a person's response to medicines[6]. It looks at how an individual's genes influence a particular biological process that mediates the effects of a medicine[7].

One of the main barriers to the implementation of pharmacogenomics in clinical practice has been the translation of pharmacogenomic knowledge to that which is actionable and usable in the clinic[8]. Fortunately, progress has been made in this area and several organisations now develop guidance to support prescribing where a drug–gene association is established. Examples include:

- The Clinical Pharmacogenetics Implementation Consortium;
- The Dutch Pharmacogenetics Working Group;
- The Canada Pharmacogenomics Network for Drug Safety.

The most extensively studied genetic polymorphisms in pharmacogenes (genes involved in pharmaceutically relevant biological pathways affecting the response of one or several drugs) that are now being used in practice can be seen in Table 1. These variations are found in in the genes encoding:

1. Cytochrome P450 drug metabolising enzymes;
2. Drug transporters;
3. The human leukocyte antigen B proteins[9].

The extent to which an individual pharmacogene influences overall drug response is dependent on the gene in question, in addition to other factors known to influence the drug's pharmacokinetic and/or pharmacodynamic properties. For example, if the gene in question controls the production of a particular drug-metabolising enzyme, then the significance of this will depend on:

- Whether the drug is metabolised primarily by the enzyme in question;
- The relationship between plasma concentration and efficacy/toxicity;
- Whether the drug is an active drug or a prodrug;
- Whether there are any inhibitors or inducers of the drug-metabolising enzyme present, which can further alter the phenotype of the enzyme by a process known as phenoconversion[10].

Table 1: Examples of important pharmacogenes

Important pharmacogenes	Examples of clinical impact
Cytochrome P450 genes e.g. *CYP2D6, CYP2C19, CYP2C9*	The CYP2D6 enzyme metabolises around 25% of drugs in clinical use, including many psychotropics, opioid analgesics and other classes of medicines. Poor metabolisers of the CYP2D6 enzyme have been found to be at increased risk of side effects when taking medicines like venlafaxine, aripiprazole and amitriptyline. The CYP2C19 metaboliser state has implications for the antiplatelet drug clopidogrel, many of the proton pump inhibitors and many antidepressants. CYP2C9 is important for calculating the starting daily dose for warfarin and is useful for predicting the risk of side effects for several non-steroidal anti-inflammatory drugs.
Drug transporter genes e.g. *SLCO1B1*	Drug transporters mediate the active transport of both endogenous substrates and xenobiotic compounds. One of the most extensively

Table 1: Examples of important pharmacogenes

Important pharmacogenes	Examples of clinical impact
	studied genes is *SLCO1B1*, which encodes the OATP1B1 drug transporter responsible for statin uptake into the liver. People who carry a particular genetic variant in the *SLC01B1* gene produce a transporter with reduced function. This increases the circulating plasma concentration of statins which is associated with an increased risk of myopathy. The association is strongest with simvastatin, for which pharmacogenomic guidelines exist recommending drug/dose changes.
Human leukocyte antigen-B (HLA-B) genes e.g. *HLA-B*1502*	The human leucocyte antigen-B gene codes for cell-surface molecules that are responsible for presenting endogenous peptides to circulating T-cells. Variants of this gene have been associated with Type B adverse drug reactions in a wide number of drugs including abacivir, flucloxacillin, allopurinol, carbamazepine and phenytoin. For example, the presence of the *HLA-B*1502* allele in those of a Han Chinese, Hong Kong Chinese or Thai origin is associated with an increased risk of carbamazepine-induced Stevens–Johnson syndrome.
Sources: Policy Research Unit in Economic Evaluation of Health and Care Interventions[2]; American College of Clinical Pharmacy[7]; *AAPS J*[9]; *J Neural Transm*[10]; *Aust New Zeal J Psychiatry*[11]; *J Clin Pharm Ther*[12],[13],[14],[15],[16],[20]; US Food and Drug Administration[17]; *Naunyn Schmiedebergs Arch Pharmacol*[18]; *Pharmacogenet Genomics*[19],[21]; *N Engl J Med*[22]; *Nat Genet*[23]; *Int J Immunogenet*[24]; *Epilepsia*[25]	

There are guidelines to support the prescribing of more than 50 medicines where pharmacogenomic biomarkers are predicted to be of clinical relevance (see Table 2).

Table 2: Medicines where actionable pharmacogenomic prescribing guidelines are available

Therapeutic class	List of medicines
Cardiovascular system	Acenocoumarol Atorvastatin Clopidogrel Fleicanide Metoprolol Propafenone Simvastatin

Table 2: Medicines where actionable pharmacogenomic prescribing guidelines are available

Therapeutic class	List of medicines
	Warfarin
Central nervous system	Amitriptyline Aripiprazole Atomoxetine Carbamazepine Citalopram Clomipramine Codeine Desipramine Doxepin Escitalopram Fluvoxamine Haloperidol Imipramine Ondansetron Oxcarbazepine Nortriptyline Paroxetine Phenytoin Pimozide Sertraline Tramadol Trimipramine Tropisetron Venlafaxine Zuclopentixol

Table 2: Medicines where actionable pharmacogenomic prescribing guidelines are available

Therapeutic class	List of medicines
Gastrointestinal system	Azathioprine Lansoprazole Omeprazole Pantoprazole
Infections	Abacavir Atazanavir Efavirenz Flucloxacillin Ivacaftor Peginterferon alfa-2a Peginterferon alfa-2b Ribavrin Voriconazole
Malignant disease and immunosuppression	Capecitabine Cisplatin Daunorubicin Doxorubicin Flurorouracil Mercaptopurine Tacrolimus Tamoxifen Tegafur Thioguanine Rasburicase
Other	Allopurinol

Table 2: Medicines where actionable pharmacogenomic prescribing guidelines are available

Therapeutic class	List of medicines
	Desflurane
	Enflurane
	Halothane
	Isoflurane
	Methoxyflurane
	Sevoflurane
	Succinylcholine

Source: PharmGKB[26]

Community pharmacy pharmacogenomic testing model

Worldwide, the implementation of pharmacogenomic testing has largely been located in specialist academic centres[27]. These centres have adopted a pre-emptive panel approach to testing, which is where patients are tested for the presence of multiple pharmacogenes on admission[28]. The results are then entered into the patient's electronic health record and integrated into clinical decision support systems. This way, prescribers are alerted to the patient's pharmacogenomic result when prescribing a medicine that is impacted by the tested gene.

Outside of these environments, examples are emerging of community pharmacy pharmacogenomic testing models[29],[30]. These models use commercial testing services (paid for by the customer) that provide laboratory testing, evidence-based interpretation, recommendations for clinical decision making and online platforms to store and report test results[31]. There is a range of services that employ pharmacists to deliver test results, available in the United States, Canada and Australia.

Benefits of pharmacogenomic testing

The aims of pharmacogenomic testing can be divided into two broad categories:

1. Improving safety by reducing the incidence of adverse drug reactions;
2. Improving the chance of therapeutic efficacy.

Around 20 genes have been identified as having established clinical significance for more than 80 medicines[32]. Randomised controlled trials support the use of pharmacogenomic testing to inform the prescribing of warfarin, abacivir and antidepressants[22],[33],[34].

There is evidence that suggests pharmacogenomic testing could have an effect on improving medicines adherence, improving confidence in deprescribing and facilitating shared decision making[35],[36],[37],[38]. These are all mechanisms that could support medicines optimisation[39].

However, patients may not want to be involved with pharmacogenomic testing as they may not necessarily connect the benefits of testing to their health[40]. Patients have shown an interest, but willingness to pay for a service varies[40].

Training and end-to-end process

Education and training are essential to the delivery of pharmacogenomic testing. Pharmacist training can come in the form of formal postgraduate programmes and online modules designed by the company performing the testing[41].

As part of the service set-up, pharmacists are encouraged to get in touch with local practices to educate them on pharmacogenomic testing. This is important as the pharmacogenomic test results need to be reviewed by a clinician if the results are to be actioned (see Box 1). Experience shows that doctors are receptive to pharmacogenomic advice offered by pharmacists[42]. However, it is important that these relationships are built early, especially if the report results are sent directly to the patient's doctor.

This model of testing carried out in Australia, Canada and America is not publicly funded and typically requires payment from the patient.

Box 1: Example of steps involved in a commercial pharmacogenomic testing model

1. The pharmacist identifies patients that may benefit from testing. These may be patients who have experienced therapeutic inefficacy or side effects with past medicines and have yet to find a medicine that works for them.
2. The pharmacist explains what pharmacogenomic testing is and gives an overview of the testing process.
3. The pharmacist takes consent for testing and a DNA sample (e.g. a cheek swab) from the patient.
4. The pharmacist sends the swab to the laboratory along with the details of the patient and their doctor (who has been previously engaged with pharmacogenomic testing). The pharmacist makes a follow-up appointment with the patient to explain and deliver the test results.
5. Test results are electronically sent to the doctor and the pharmacist to deliver to the patient. The patient does not gain access to their results prior to having them explained by their nominated healthcare practitioner (pharmacist or doctor).
6. In the follow-up appointment, the pharmacist talks to the patient about how their pharmacogenomic results are likely to impact their current and potential future medicines, and discuss any non-genetic factors that may also influence drug response. If the pharmacist identifies any potential problems with the patient's medicines, they will contact the patient's doctor to discuss further.
7. After the appointment, the patient is provided with access to their results through an online patient portal. The pharmacy at which the patient had their testing performed maintains a record of the results to help with alerting on significant gene–drug interactions for future medicines prescribed for the patient.

How is testing carried out

Commercial pharmacogenomic testing kits use different DNA collection methods. A popular method employed is a buccal (cheek) swab, owing to its simplicity and non-invasive nature[43]. A typical testing kit will be composed of a swab with a container to collect DNA and a pre-addressed envelope to send the sample to a laboratory.

Example process for DNA collection:

1. Open the pouch to remove the swab tube. The swab tube can be opened by pressing the upper part of the cap. The swab can then be removed by holding the cap and tube (it is important that the swab head is not touched with fingers because this would risk contamination);
2. Insert the swab between cheek and lower gums of the patient and roll the swab ten times on the inner of both cheeks;
3. The swab should be placed back into the tube firmly, until there is a click.

Following these steps, there may be a need to fill out a form and return the swab to the testing facility. The facility will notify the pharmacist of the results after analysing the sample.

Data protection

In the UK, the EU General Data Protection Regulation (GDPR) governs data processing and protection[44]. The main implications for genetic testing in community pharmacy is to ensure consent for testing is 'freely given, specific, informed and unambiguous'[45]. In addition, community pharmacies should ensure the company which is offering the pharmacogenomic testing service is GDPR compliant.

How this could work in practice

Although the process of pharmacogenomic testing is not currently carried out in community pharmacies in the UK, it may be part of future NHS services[3]. Therefore, it is important to understand how a development of this nature may impact future practice. The following example consultations are derived from experiences of that in Australia using paid-for pharmacogenomic testing kits through community pharmacy.

Case study 1: genomic testing in an older person with depression

Gary Jones, a retired teacher, has been referred to his pharmacy for a pharmacogenomic test by his GP. He is aged 62 years, recently widowed and is prescribed a standard starting dose of sertraline for depression[46]. The GP referred him to the pharmacy for a pharmacogenomic test because, after two months of treatment, he is still experiencing poor symptom control at night.

Receiving consent and information giving

You receive consent from the patient, collect a cheek swab sample and make an appointment for one weeks' time, where you will review the test results with the patient.

Results of the test

The test results show the patient to carry the *CYP2C19 *17/*17* genotype, which predicts the patient to have an ultra-rapid metaboliser phenotype for the CYP2C19 enzyme[44]. This makes him metabolise and clear sertraline very rapidly, reducing drug exposure and increasing the risk of therapeutic failure.

Outcome of the test

You explain to the patient that his gene results suggest that his body processes sertraline at a faster rate than other people, which may explain why the medicine's effect wears off quickly compared to those who do not have the same gene variation.

Options could be to increase the dosing frequency to twice a day, increase the daily dose, or change to another antidepressant that is not metabolised by CYP2C19. You contact the patient's GP and forward them a copy of his report. The GP makes an appointment with the patient and decides to change the patient's antidepressant from sertraline to venlafaxine. As the report suggests, the patient should have normal metabolism of venlafaxine via the CYP2D6 enzyme. The patient comes back to the pharmacy three months later and explains that he has responded well and that his depression is well managed by his new medication.

The CYP2C19 genotype the patient carries also predicts a sub-therapeutic response to amitriptyline, citalopram, escitalopram, omeprazole and voriconazole at usual doses, with recommendations to increase the dose or choose alternative therapies in some cases, based on current pharmacogenomic guidelines[13],[14],[47],[48].

Case study 2: genomic testing for a patient taking warfarin

Mary Thompson, aged 75 years, has been referred by her GP to her pharmacy for pharmacogenomic testing. She is due to have a tissue valve replacement in one month and her surgeon has explained that she will need three months of post-operative warfarin therapy[49]. Her GP wants her to have pharmacogenomic testing to help guide the initial dosing of warfarin.

Receiving consent and information giving

You talk her through the process of testing (see Box 1), take her consent and arrange a follow up appointment in a week's time.

Results of the test

The report shows that she carries the *CYP2C9*2/*3* genotype, which predicts her to have a CYP2C9 poor metaboliser phenotype[16]. This results in significantly reduced metabolism of warfarin and increased anticoagulant effect. Her *VKORC1 AA* genotype predicts significantly reduced amount of VKORC1 (the enzyme warfarin inhibits), which is associated with an increased risk of warfarin sensitivity and lower daily dose requirements. Overall, reduced warfarin metabolism and increased warfarin sensitivity are predicted[16],[50].

Outcome of the test

You explain to the patient that her genetic results predict her daily warfarin requirements to be between 0.5–2.0mg per day[51]. Many factors can influence warfarin dosing, such as diet, alcohol, weight and concurrent medications. However, when initiating warfarin, having knowledge of the genetic profile can optimise dosing[33]. You give a copy of the report to the patient to take to the hospital. You ensure that the GP also receives a copy of the report and ask them to inform the relevant anticoagulant clinic.

After the operation, the consultant in the hospital started her on warfarin 1.0mg/day. The patient was able to get into the required international normalised ratio range of between 2.0 to 3.0 with no complications. In this instance, the availability of the pharmacogenomic result ensured the patient was prescribed a much lower starting daily dose and, therefore, encountered minimal adverse effects.

The patient's CYP2C9 genotype also predicts reduced phenytoin metabolism, leading to higher plasma concentrations and increased probability of toxicity[52].

Case study 3: genomic testing on pain relief

Sheila Smith, a Caucasian woman aged 40 years, asks to speak to you as she is frustrated that her current medicines are not working — she is currently taking co-codamol to alleviate her “severe” lower-back pain. She is unable to take non-steroidal anti-inflammatory drugs as she gets a rash.

Receiving consent and information giving

You explain to her that her lack of pain relief from her current medicines may be influenced by her genes and a pharmacogenomic test can help determine if they appropriate. You talk her through the process of testing (see Box 1), take her consent and arrange a follow up appointment in a week’s time.

Results of the test

The report shows that the patient carries two non-functioning alleles for the CYP2D6 enzyme (*CYP2D6*4/*4*), which confers a poor metaboliser phenotype[53].

Outcome of the test

You explain to the patient that codeine (as a prodrug) needs to be converted into morphine by the CYP2D6 enzyme, for which she has no function, and that she is unlikely to get sufficient pain relief from codeine-based analgesics. You reassure her that this is relatively common and that it occurs in about 5–10% of Caucasians[53].

You discuss the results with her GP and explain that tramadol and to a lesser extent oxycodone are unlikely to provide adequate pain relief as both drugs are metabolised to varying degrees by CYP2D6[53]. You suggest that potential alternatives that may be suitable for this patient are: regular use of paracetamol; low-dose morphine on an as-required basis; or a trial of buprenorphine if clinically applicable[13],[53].

Upon reviewing her results, the GP decided to switch her to regular paracetamol and a when required low dose of oral morphine. The doctor scheduled a review of her progress in a week’s time and, upon her return a week later, she reported much improved pain control with regular paracetamol and low-dose morphine when required.

The CYP2D6 genotype also predicts increased risk of side effects to tricyclic antidepressants, paroxetine, fluvoxamine, aripiprazole with recommendations to reduce doses or switch to alternative therapies[13],[14],[47].

Conflict of interest

Sam Mostafa is an employee of myDNA Life Australia, a company that provides pharmacogenomic testing.

David Wright and Essra Youssef have a research collaboration with myDNA Life Australia, but have no financial interests in the company.

References:

[1] Alderwick H & Dixon J. The NHS long term plan. *BMJ* 2019;364:l84. doi: 10.1136/bmj.l84

[2] Elliott RA, Camacho E, Campbell F *et al.* Prevalence and economic burden of medication errors in the NHS in England: rapid evidence synthesis and economic analysis of the prevalence and burden of

medication error in the UK. 2018. Available at: http://www.eepru.org.uk/wp-content/uploads/2018/02/eepru-report-medication-error-feb-2018.pdf (accessed January 2020)

[3] West Midlands Genomic Medicine Centre. Rare Disease boards transform genomic results process. 2019. Available at: https://www.westmidsgmc.nhs.uk/rare-disease-boards-transform-genomic-results-process (accessed January 2020)

[4] Health Education England. Pharmacogenomics: a new normal for the NHS? 2019. Available at: https://www.genomicseducation.hee.nhs.uk/blog/pharmacogenomics-a-new-normal-for-the-nhs (accessed January 2020)

[5] Spear BB, Heath-Chiozzi M & Huff J. Clinical application of pharmacogenetics. *Trends Mol Med* 2001;7(5):201–204. doi: 10.1016/s1471-4914(01)01986-4

[6] Evans WE & McLeod HL. Pharmacogenomics — drug disposition, drug targets, and side effects. *N Engl J Med* 2003;348:538–549. doi: 10.1056/NEJMra020526

[7] Lam SW, in *Critical Care Self-Assessment Program Book* 2:7–25. American College of Clinical Pharmacy. 2016. Available at: https://www.accp.com/store/product.aspx?pc=CCSAP_2019-2021 (accessed January 2020)

[8] Johansen Taber KA & Dickinson BD. Pharmacogenomic knowledge gaps and educational resource needs among physicians in selected specialties. *Pharmgenomics Pers Med* 2014;7:145–162. doi: 10.2147/PGPM.S63715

[9] Lauschke VM, Milani L & Ingelman-Sundberg M. Pharmacogenomic biomarkers for improved drug therapy — recent progress and future developments. *AAPS J* 2017;20(1):4. doi: 10.1208/s12248-017-0161-x

[10] Mostafa S, Kirkpatrick CMJ, Byron K & Sheffield L. An analysis of allele, genotype and phenotype frequencies, actionable pharmacogenomic (PGx) variants and phenoconversion in 5408 Australian patients genotyped for CYP2D6, CYP2C19, CYP2C9 and VKORC1 genes. *J Neural Transm* 2019;126(1):5–18. doi: 10.1007/s00702-018-1922-0

[11] Foulds JA, Maggo SD & Kennedy MA. Personalised prescribing in psychiatry: Has pharmacogenomics delivered on its promise? *Aust New Zeal J Psychiatry* 2016;50(6):509–510. doi: 10.1177/0004867416640099

[12] Shams ME, Arneth B, Hiemke C *et al.* CYP2D6 polymorphism and clinical effect of the antidepressant venlafaxine. *J Clin Pharm Ther* 2006;31(5):493–502. doi: 10.1111/j.1365-2710.2006.00763.x

[13] Swen JJ, Nijenhuis M, de Boer A *et al*. Pharmacogenetics: From bench to byte — an update of guidelines. *Clin Pharmacol Ther* 2011;89:662–673. doi: 10.1038/clpt.2011.34

[14] Hicks JK, Sangkuhl K, Swen JJ *et al*. Clinical Pharmacogenetics Implementation Consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. *Clin Pharmacol Ther* 2017;102(1):37–44. doi: 10.1002/cpt.597

[15] Scott SA, Sangkuhl K, Stein CM *et al*. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. *Clin Pharmacol Ther* 2013;94(3):317–323. doi: 10.1038/clpt.2013.105

[16] Johnson JA, Caudle KE, Gong L *et al.* Clinical Pharmacogenetics Implementation Consortium guideline for pharmacogenetics —guided warfarin dosing. *Clin Pharmacol Ther* 2017;102:397–404. doi: 10.1002/cpt.668

[17] US Food and Drug Administration. Table of pharmacogenomic biomarkers in drug labelling. 2019. Available at: https://www.fda.gov/drugs/science-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling (accessed January 2020)

[18] Petzinger E & Geyer J. Drug transporters in pharmacokinetics. *Naunyn Schmiedebergs Arch Pharmacol* 2006;372(6):465–475. doi: 10.1007/s00210-006-0042-9

[19] Oshiro C, Mangravite L, Klein T & Altman R. PharmGKB very important pharmacogene: SLCO1B1. *Pharmacogenet Genomics* 2010;20:211–216. doi: 10.1097/FPC.0b013e328333b99c

[20] Ramsey LB, Johnson SG, Caudle KE *et al.* The Clinical Pharmacogenetics Implementation Consortium guideline for SLCO1B1 and simvastatin-induced myopathy. *Clin Pharmacol Ther* 2014;96:423–428. doi: 10.1038/clpt.2014.125

[21] Barbarino J, Kroetz D, Klein T & Altman R. PharmGKB summary: very important pharmacogene information for human leukocyte antigen B. *Pharmacogenet Genomics* 2015;25(4):205–221. doi: 10.1097/FPC.0000000000000118

[22] Mallal S, Phillips E, Carosi G *et al*. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med* 2008;358:568–579. doi: 10.1056/NEJMoa0706135

[23] Daly AK, Donaldson PT, Bhatnagar P *et al*. HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. *Nat Genet* 2009;41:816–819. doi: 10.1038/ng.379

[24] Cristallo AF, Schroeder J, Citterio A *et al*. A study of HLA class I and class II 4-digit allele level in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Int J Immunogenet* 2011;38:303–309. doi: 10.1111/j.1744-313X.2011.01011.x

[25] Locharernkul C, Loplumlert J, Limotai C *et al*. Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B*1502 allele in Thai population. *Epilepsia* 2008;49:2087–2091. doi: 10.1111/j.1528-1167.2008.01719.x

[26] PharmGKB. Clinical Guideline Annotations. 2019. Available at: https://www.pharmgkb.org/guidelineAnnotations (accessed January 2020)

[27] Klein ME, Parvez MM & Shin JG. Clinical Implementation of Pharmacogenomics for Personalized Precision Medicine: Barriers and Solutions. *J Pharm Sci* 2017;106:2368–2379. doi: 10.1016/j.xphs.2017.04.051

[28] Rasmussen-Torvik LJ, Stallings SC, Gordon AS *et al*. Design and Anticipated Outcomes of the eMERGE-PGx Project: A Multicenter Pilot for Preemptive Pharmacogenomics in Electronic Health Record Systems. *Clin Pharmacol Ther* 2014;96(4):482–489. doi: 10.1038/clpt.2014.137

[29] Ferreri SP, Greco AJ, Michaels NM *et al*. Implementation of a pharmacogenomics service in a community pharmacy. *J Am Pharm Assoc* 2014;54(2):172–180. doi: 10.1331/JAPhA.2014.13033

[30] Haga SB, Moaddeb J, Mills R & Voora D. Assessing feasibility of delivering pharmacogenetic testing in a community pharmacy setting. *Pharmacogenomics* 2017;18:327–335. doi: 10.2217/pgs-2016-0175

[31] Weitzel KW, Cavallari L H & Lesko LJ. Preemptive Panel-Based Pharmacogenetic Testing: The Time is Now. *Pharm Res* 2017;34(8):1551–1555. doi: 10.1007/s11095-017-2163-x

[32] Relling MV & Evans WE. Pharmacogenomics in the clinic. *Nature* 2015;526(7573):343–350. doi: 10.1038/nature15817

[33] Pirmohamed M, Burnside G & Eriksson N *et al*. A Randomized Trial of Genotype-Guided Dosing of Warfarin. *N Engl J Med* 2013;369(24):2294–2303. doi: 10.1056/NEJMoa1311386

[34] Bousman CA, Arandjelovic K, Mancuso SG *et al*. Pharmacogenetic tests and depressive symptom remission: a meta-analysis of randomized controlled trials. *Pharmacogenomics* 2019;20:37–47. doi: 10.2217/pgs-2018-0142

[35] Charland SL, Agatep BC, Herrera V *et al*. Providing patients with pharmacogenetic test results affects adherence to statin therapy: results of the Additional KIF6 Risk Offers Better Adherence to Statins (AKROBATS) trial. *Pharmacogenomics J* 2014;14(3):272–280. doi: 10.1038/tpj.2013.27

[36] Winner JG, Carhart JM, Altar CA *et al*. Combinatorial pharmacogenomic guidance for psychiatric medications reduces overall pharmacy costs in a 1 year prospective evaluation. *Curr Med Res Opin* 2015;31(9):1633–1643. doi: 10.1185/03007995.2015.1063483

[37] Tannenbaum C, Farrell B, Shaw J *et al*. An Ecological Approach to Reducing Potentially Inappropriate Medication Use: Canadian Deprescribing Network. *Can J Aging* 2017;36:97–107. doi: 10.1017/S0714980816000702

[38] Arandjelovic K, Eyre HA, Lenze E *et al*. The role of depression pharmacogenetic decision support tools in shared decision making. *J Neural Transm* 2019;126:87–94. doi: 10.1007/s00702-017-1806-8

[39] Heaton J, Britten N, Krska J & Reeve J. Person-centred medicines optimisation policy in England: an agenda for research on polypharmacy. *Prim Health Care Res Dev* 2017;18:24–34. doi: 10.1017/S1463423616000207

[40] Gibson ML, Hohmeier KC & Smith CT. Pharmacogenomics testing in a community pharmacy: patient perceptions and willingness-to-pay. *Pharmacogenomics* 2017;18(3):227-233. doi: 10.2217/pgs-2016-0161

[41] Kennedy MJ. Personalized medicines- are pharmacists ready for the challenge? 2018. *Integr Pharm Res Pract* 2018;7:113–123. doi: 10.2147/IPRP.S133083

[42] Papastergiou J, Tolios P, Li W & Li J. The Innovative Canadian Pharmacogenomic Screening Initiative in Community Pharmacy (ICANPIC) study. *J Am Pharm Assoc* 2017;57(5):624–629. doi: 10.1016/j.japh.2017.05.006

[43] Ang JS, Aloise MN, Dawes D *et al*. Evaluation of buccal swabs for pharmacogenetics. *BMC Res Notes* 2018;11(1):382. doi: 10.1186/s13104-018-3476-5

[44] Raza S & Hall A. Genomic medicine and data sharing. *Br Med Bull* 2017;123(1):35–45. doi: 10.1093/bmb/ldx024

[45] Royal College of Physicians, Royal College of Pathologists & British Society for Genetic Medicine. Consent and confidentiality in genomic medicine: Guidance on the use of genetic and genomic information in the clinic. London: RCP, RCPath and BGSM; 2019.

[46] National Institute for Health and Care Excellence. Depression in adults: recognition and management (NICE Clinical Guideline 90). 2018. Available at: https://www.nice.org.uk/guidance/cg90/chapter/1-Guidance (accessed January 2020)

[47] Hicks JK, Bishop JR, Sangkuhl K *et al*. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. *Clin Pharmacol Ther* 2015;98:127–134. doi: 10.1002/cpt.147

[48] Moriyama B, Obeng AO, Barbarino J *et al*. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP2C19 and Voriconazole Therapy. *Clin Pharmacol Ther* 2017;102(1):45–51. doi: 10.1002/cpt.583

[49] Baumgartner H, Falk V, Bax JJ *et al*. 2017 ESC/EACTS Guidelines for the Management of Valvular Heart Disease. *Eur Heart J* 2017;38(36):2739–2791. doi: 10.1093/eurheartj/ehx391

[50] Dailymed. WARFARIN SODIUM-warfarin tablet. 2018. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=541c9a70-adaf-4ef3-94ba-ad4e70dfa057 (accessed January 2020)

[51] Dean L. Warfarin therapy and VKORC1 and CYP genotype. 2018. Available at: https://www.ncbi.nlm.nih.gov/books/NBK84174/ (accessed January 2020)

[52] Caudle KE, Rettie AE, Whirl-Carrillo M *et al*. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and HLA-B Genotypes and Phenytoin Dosing. *Clin Pharmacol Ther* 2014;96(5):542–548. doi: 10.1038/clpt.2014

[53] Crews KR, Gaedigk A, Dunnenberger *et al*. Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450 2D6 Genotype and Codeine Therapy: 2014 update. *Clin Pharmacol Ther* 2014;95(4):376–382. doi: 10.1038/clpt.2013.254

Citation: *The Pharmaceutical Journal*, online, online | DOI: 10.1211/PJ.2019.20207342