Case Series

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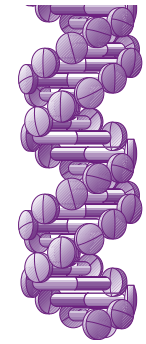
Pharmacogenomics



Clinical and educational impact of pharmacogenomics testing: a case series from the INGENIOUS trial

Pharmacogenomic testing has become increasingly widespread. However, there remains a need to bridge the gap between test results and providers lacking the expertise required to interpret these results. The Indiana Genomics Implementation trial is underway at our institution to examine total healthcare cost and patient outcomes after genotyping in a safety-net healthcare system. As part of the study, trial investigators and clinical pharmacology fellows interpret genotype results, review patient histories and medication lists and evaluate potential drug–drug interactions. We present a case series of patients in whom pharmacogenomic consultations aided providers in appropriately applying pharmacogenomic results within the clinical context. Formal consultations not only provide valuable patient care information but educational opportunities for the fellows to cement pharmacogenomic concepts.

First draft submitted: 3 March 2017; Accepted for publication: 18 April 2017;
Published online: 8 June 2017

Keywords: clinical • education • genetic testing • pharmacogenetics • pharmacology • precision medicine

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The Indiana Genomics Implementation (INGENIOUS) trial was initiated to examine the impact of genotyping and subsequent genotype-driven changes in care on total healthcare cost and long-term outcomes in a low income, safety-net population [1]. Subjects are genotyped for approximately 40 variants in response to a new prescription of 1 of 28 drugs. Although the electronic medical record (EMR) system is capable of delivering general recommendations through automated interruptive alerts for future prescriptions, the computer algorithms are not yet sophisticated enough to account for incidental findings related to existing prescriptions, concomitant drug–drug interactions (DDIs), or drug–disease interactions. These EMR alerts are also not present for the initial prescription that prompted trial enrollment since genotyping is completed 1 week following enrollment.

A component of the study is the Adjudication Committee, composed of a study principal investigator, a physician, and a clinical pharmacology fellow. The Committee is supported by a pharmacogenomics consult physician with clinical pharmacology hospital privileges. The Committee meets on a weekly basis to review pharmacogenomic results generated by the trial; fellows are responsible for pre-reviewing the patients' genotypes, demographics, clinical history, medication profiles and adverse drug responses. These data are then reviewed by the committee and recommendations are made regarding medication choice and dosage for any medications that may be affected by genotype results or known DDIs. Any patient with a significant actionable mutation or complicated clinical picture is referred to the consult physician and a formal consultation is performed. The fellow

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typically prepares the consult note and reviews it with the supervising physician, evaluating the patient in person if necessary. We present a series of four patients for whom formal consult services were provided, illustrating both medications with well-known guidelines and medications for which established guidelines do not exist. Details of the INGENIOUS trial have been previously published [1,2]. The INGENIOUS trial was approved by the Indiana University IRB and is registered on ClinicalTrials.gov (NCT02297126). The trial is ongoing with a projected completion date of June 2018.

Case 1: citalopram

Case 1 provides an important example in which following the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines proved challenging for a patient prescribed citalopram. The guidelines recommended selecting an alternative agent to citalopram based on the patient's genotype. However, prior alternate agent inefficacy and possible DDIs limited practical therapeutic options.

A 54-year-old male patient presented to the neurology clinic with chronic encephalopathy following a motor vehicle accident that occurred 2 years prior to trial enrollment. The patient had been previously evaluated in the outpatient neurology clinic with symptoms of memory loss, depression and anxiety. His response to venlafaxine (Effexor® [Pfizer, NY, USA]) therapy was inadequate. As a result, the patient was tapered from venlafaxine and citalopram (Celexa® [Forest Laboratories, Inc., NY, USA], a selective serotonin reuptake inhibitor, SSRI) was prescribed as a replacement, prompting enrollment in the INGENIOUS trial and acquisition of his genotype. The neurology team requested a consult in response to the patient's CYP2C19 ultrarapid metabolizer status and poor response to prior venlafaxine therapy.

Concomitant medications included donepezil (Aricept® [Pfizer, NY, USA]), lisinopril (Zestril® [AstraZeneca, Cambridge, UK]), and glipizide (Glucotrol® [Pfizer, NY, USA]). Laboratory and physical findings were unremarkable and noncontributory to selection of an appropriate antidepressant agent.

Pharmacogenetic testing revealed that this patient is homozygous for the *CYP2C19*17* allele indicating that two gain-of-function alleles are present. The prevalence of the **17* allele varies widely across populations: it is reported at <5% frequency in populations of Asian descent and >20% frequency in Caucasian, eastern European and African populations [3]. A major side effect of citalopram is its corrected QT interval (QT_c) prolongation. The CPIC guidelines for this mutation suggest use of an alternative drug not predominantly metabolized by CYP2C19 (Level of evidence: moderate) [4] while the Royal Dutch Association for the Advancement of Pharmacy – Pharmacogenetics Working Group (DPWG) guidelines suggest therapeutic drug monitoring in conjunction with dose titration to a maximum of 150% of the typical therapeutic dose [5]. According to the DPWG, dose titrations are recommended based upon clinical efficacy or adverse events with a recommendation to select an alternative agent upon occurrence of the later at maximal dosages. Alternative agents not metabolized predominantly by CYP2C19 include paroxetine (Paxil® [GlaxoSmithKline, London, UK]) and bupropion (Wellbutrin® [GlaxoSmithKline]). Because this patient was already taking a stable dose of donepezil, paroxetine and bupropion may not be ideal options for this patient as they are potent inhibitors of CYP2D6, the enzyme that metabolizes donepezil, CYP2D6. However, there is limited evidence to support the clinical relevance of this DDI.

One potential drug–disease interaction includes the evidence for the use of methylphenidate in patients with traumatic brain injury [6–8]. Ultimately the consult service recommended switching antidepressant agents to a drug not metabolized predominantly by CYP2C19 or titration of the citalopram dosing beyond typical dosing requirements in an attempt to overcome the patient's ultrarapid metabolism of the drug while monitoring for QT_c prolongation.

This case illustrates two key points. The first is that the CPIC and DPWG guidelines do not always align. In this circumstance, the consult team followed the CPIC guidelines, recommending drug substitution rather than dose titration. A second key point is that it is not always straightforward to recommend an alternative agent. In this case the patient had previously failed venlafaxine therapy and had potential drug interactions with donepezil, significantly limiting therapeutic options.

Importantly, the patient and primary care provider both were provided with the pharmacogenetics results and educated about potential implications for future prescribing. Specifically the provider was notified of a potential increased bleeding risk that should be carefully considered if prescribing clopidogrel (Plavix® [Sanofi-Aventis, NJ, USA]) in the future [9]. This patient was also found to have a reduced activity variant in the *SLCO1B1* gene which would be relevant to future statin prescriptions, particularly simvastatin (Zocor® [Merck and Co., Inc., NJ, USA]), as this patient could be at increased risk for statin-induced myopathy.

Case 2: clopidogrel

Case 2 illustrates how pharmacogenomic testing can retrospectively explain significant adverse events, reinforcing the need for alternative agent selection. It also relays the importance of considering DDIs with drug–gene interactions.

A 65-year-old woman with a past medical history of diabetes mellitus, hypertension, chronic obstructive pulmonary disease, gastro-esophageal reflux disease, and coronary artery disease presented with recurrent chest pain. Two years prior, the patient underwent a percutaneous coronary intervention with placement of a drug-eluting stent in her left anterior descending (LAD) coronary artery. She was started on the anticoagulant clopidogrel, an inhibitor of platelet adenosine diphosphate receptors. Within 30 days of revascularization, the patient experienced stent thrombosis associated with a ST-elevation myocardial infarction and culminating in a single vessel coronary artery bypass graft. Now, 2 years later, the patient again underwent a left heart catheterization with balloon angioplasty and stent placement in her LAD graft. She was once again prescribed clopidogrel. The clopidogrel order triggered trial enrollment followed by pharmacogenomic testing revealing a *CYP2C19 *1/*2* genotype. The patient's primary provider requested a formal consult to better understand the implications of this genotype.

The combination of one functional allele (**1*) and one loss-of-function allele (**2*) predicts that this patient has reduced CYP2C19 metabolic activity. Reduced CYP2C19 activity impairs conversion of clopidogrel to the pharmacologically active metabolite responsible for inhibition of platelet aggregation. Dose escalation for patients with reduced CYP2C19 function may overcome the lack of platelet aggregation inhibition but does not appear to translate to improved patient outcomes [10,11]. As a result, both CPIC and DPWG guidelines recommend that patients with reduced CYP2C19 activity receive alternative antiplatelet therapy [5,12]. Ultimately, antiplatelet agent selection depended upon consideration of the patient's *CYP2C19* genotype in addition to individual clinical characteristics.

Diabetes mellitus Type 2 with poor control, hypertension, and a long smoking history are likely to contribute to high residual platelet aggregation for this patient, further underscoring the importance of optimal antiplatelet therapy. The patient's medication list at the time of genotyping consisted of 23 additional medications including esomeprazole (Nexium® [AstraZeneca, Cambridge, UK]). Esomeprazole inhibition of CYP2C19 in conjunction with reduced CYP2C19 activity may further decrease the metabolic activation of clopidogrel. The combination of disease–drug, drug–drug and gene–drug interactions placed this patient at high risk for clopidogrel therapeutic failure. As a result, the consult committee recommended use of an alternative agent such as prasugrel (Effient® [Eli Lilly and Company, IN, USA]) or ticagrelor (Brilinta® [AstraZeneca]). Although platelet reactivity testing can be used to determine the degree of platelet inhibition resulting from anticoagulation therapy, reduction in bleeding events has not been shown after medication adjustments and further information is needed regarding the utility of routine use of these tests in patient care [13].

The majority of medication changes recommended by the consult service fall within our health system's formulary. Prasugrel is an exception but is available through patient assistance programs with prior authorization. The patient and provider are not burdened by the medication cost, but the health system is impacted by the cost.

Case 3: tramadol

Case 3 demonstrates an important rationale for pharmaco-genotyping patients receiving codeine or tramadol for pain management. The patient's primary service requested a pharmacogenomics consult to interpret genomic results after encountering difficulty achieving pain control.

A 67-year-old Caucasian male with a history of bilateral venous stasis ulcers of the ankles had been admitted for debridement with Integra™ Matrix Wound Dressing placement and subsequently developed a wound infection. Outpatient treatment was ineffective and he was readmitted for parenteral antibiotic therapy. During his admission, he received tramadol (Ultram® [Ortho-McNeil Pharmaceutical, Inc., NJ, USA]) for pain; the tramadol order triggered his study enrollment. He was found to have a *CYP2D6* mutation consistent with a reduced metabolism phenotype and his pain had been difficult to control over the long course of his ulcer treatment; a consult was requested to assist in determination of a pain control regimen.

On review of his medical record, the patient's medication list included acetaminophen (Tylenol® [Johnson & Johnson, NJ, USA]), aspirin (81 mg), hydrocodone/acetaminophen (Vicodin® [AbbVie Inc., IL, USA), oxycodone (OxyContin® [Purdue Pharma, CT, USA]) and tramadol, a synthetic low potency opioid pain medication. His serum creatinine was 1.36 mg/dl with an eGFR of 52 ml/min and a recent ECG showed a QTc of 473 ms. Pharmacogenomic testing revealed a *CYP2D6 *4/*41* genotype.

The patient's slightly prolonged QTc were discussed in relation to other medications but was not pertinent to his pain regimen. It was confirmed that the tramadol was ordered at the recommended extended dosing

interval of every 12 h for patients with reduced kidney function [14]. Also included in his consult note were three low level DDIs; concomitant use of tramadol with opioids and the resulting decreased seizure threshold was discussed [15]. The patient was not taking any known *CYP2D6* inhibitors.

The *CYP2D6 *4* allele is a nonfunctional allele and the **41* allele is a reduced function allele. These alleles combined equal an activity score of 0.5 [16] and confer a reduced function phenotype. The activity scoring system for *CYP2D6* was generated from analyses of paired genotype and phenotype information and provides a method of predicting phenotype based on specific known alleles. A score is assigned to each allele (0, 0.5, 1 or 2) based on published phenotype data and the activity score for the individual is the sum of the scores of both alleles. Given that CYP2D6 plays a role in the metabolism of a multitude of clinically useful medications [17], including codeine, hydrocodone, oxycodone and tramadol, this may explain at least in part the patient's difficulty achieving pain control: he may not be experiencing the full benefit of his analgesic medications. These medications are metabolized in part by CYP2D6 into active metabolites with higher binding affinity to opioid receptors than the parent compounds and reduced or defective CYP2D6 metabolic status may result in less than the expected level of analgesia. Current evidence only exists regarding the association of poor metabolizer phenotypes (two nonfunctional alleles) and reduced response to pain medications [18,19], but on an individual level, these genetic results may help explain the patient's lack of response and provide guidance for alternative therapies. Hydrocodone is the least affected by *CYP2D6* mutations as alternative metabolic pathways exist; morphine is active as the parent compound and thus response should not be affected; transdermal and transmucosal fentanyl (Duragesic® [Janssen Pharmaceuticals, Inc., NJ, USA], Actiq® [Teva Pharmaceutical Industries Ltd., Petah Tikva, Israel]) are metabolized primarily via CYP3A4 [20] and would be reasonable alternatives.

This case demonstrates an important rationale for pharmacogenotyping patients receiving codeine or tramadol for pain management. The patient's pain was not controlled on tramadol therapy alone. Genotyping supported the escalation of pain management with hydrocodone. Although this patient did not convey nonadherence or drug-seeking behavior, providers may include these behaviors on their differential of uncontrolled pain, disproportionate to their expectations. At times, a history is insufficient to distinguish patients with persistent pain and those with drug-seeking behavior [21]. Genotyping provides an additional rationale for escalation of pain management and may expedite opiate titration for future episodes of significant pain by bypassing those medications known to be ineffectively metabolized [22–24].

Case 4: venlafaxine

Case four reveals a potential limitation of pharmacogenomic testing, wherein the patient's genotype predicted adverse effects to an existing venlafaxine prescription, but the patient had maintained a favorable clinical response for some time. The primary care provider questioned how to properly utilize these results.

A 50-year-old white woman was evaluated by her primary care physician for depression. She had recently changed primary providers and health systems. She reported a history of past depression; other medical issues included essential hypertension, iron deficiency anemia, obesity and gastroesophageal reflux. As a result of this visit, the provider renewed the patient's antidepressant venlafaxine (a serotonin-norepinephrine reuptake inhibitor [SNRI]). Since this was an initial venlafaxine prescription in our health system, the order prompted study enrollment.

This patient's *CYP2D6* mutation (**5/*29*) predicts a reduced function metabolizer phenotype with an activity score of 0.5 [16]. The **5* allele is a complete deletion mutation and in combination with the **29* allele (results in a reduced function protein) predicts decreased CYP2D6 activity. The primary metabolic pathway for venlafaxine (VEN) is via *CYP2D6* into O-desmethylvenlafaxine (ODV) during first pass hepatic metabolism. ODV is also active as an SNRI; better treatment response has been shown to be associated with a higher ODV/VEN ratio [25,26] and patients with low ODV/VEN ratios may have an unfavorable adverse effect profile [27]. The DPWG recommends that an alternate drug be chosen for patients with predicted poor or intermediate phenotype as there is insufficient data available to calculate dose adjustment based on genotype [5]; if venlafaxine is prescribed, the dose should be carefully titrated to clinical response and ODV levels should be monitored (level of evidence: 4, good).

This patient was also taking amlodipine (Norvasc® [Pfizer Inc., NY, USA]), ferrous sulfate (Feosol® [Meda Consumer Healthcare, NJ, USA]) and omeprazole. No other drug–gene interactions were identified. Her serum creatinine was 0.7 mg/dl and liver function testing was normal. An electrocardiogram was not available.

The consult service recommended no change in medications: the patient reported that she had tolerated the medication in the past, though she did not remember the dose. Her clinical response and lack of side effects

may be influenced by several factors: she may have sufficient CYP2D6 activity to exhibit a normal phenotype for this particular drug-gene pair, her severity of symptoms may only necessitate a low level of active drug, she may have a high tolerance for the known side effects of venlafaxine, and/or she may have sufficient shunting through alternate metabolic pathways (e.g., CYP2C19) to produce a favorable ODV/VEN ratio and relieve her symptoms. Though her *CYP2C19* genotype is normal, it is important to realize that she is now taking omeprazole, a known CYP2C19 inhibitor.

This case illustrates the need for interpretive services when pharmacogenetic information is available as multiple variables contribute to an individual's response to treatment. In this example, the patient's prior tolerance of venlafaxine outweighs the pharmacogenotyping result predicting adverse effects to venlafaxine. The patient's new primary care provider questioned how to properly utilize the genotype results. She felt more comfortable making the decision to continue venlafaxine after a pharmacogenomics consultation concurred with her assessment that the patient had a favorable clinical response with acceptable tolerance. The patient's prescription would not have been questioned without pharmacogenomic testing, and this is a cautionary example to avoid over-reliance on testing results.

If the patient did develop intolerable side effects or did not respond to venlafaxine, possible alternatives include sertraline (Zoloft® [Pfizer Inc., NY, USA]) and citalopram. As these are metabolized predominantly by CYP2C19, the patient should be switched to an alternate proton pump inhibitor known to have less CYP2C19 inhibitory activity (e.g., pantoprazole, Protonix® [Pfizer Inc.]) or to an alternate acid suppression agent (e.g., ranitidine, Zantac® [Pfizer Inc.]).

Discussion

Other large-scale pharmacogenomics implementations exist [28] but the INGENIOUS trial is the only one in the USA to specifically enroll an underserved population and to target a large number of medications with genotyping results available in the patient medical record to all providers. Our study is also, to our knowledge, the only one that reviews each set of results in the context of the individual clinical situation in order to provide information about the primary medication of interest as well as incidental findings related to other medications and DDIs. Automated systems are excellent for reporting genotypes or gene-drug pairs with solid evidence to guide drug choice and dose such as *CYP2C9* influences on warfarin (Coumadin) dose [29]. Such systems can streamline the return of information to the EMR [30] and the INGENIOUS study alerts providers to drug–gene interactions through the EMR. However, individual review is necessary because these automated systems are not yet sophisticated enough to interpret gene-drug pair recommendations in concert with drug–drug and drug–disease interactions.

Another well-known issue addressed by our structure is the interpretation of results by providers who have not been trained in this area and/or who have limited experience and are not comfortable with the translation of genotyping data into patient care recommendations and clinical decision-making [31–33]. Our Committee bridges this gap and provides not only the pertinent information but is available for further provider support if needed [1].

The Committee serves a dual purpose in our project: it also provides a training and educational opportunity for the NIH-sponsored Clinical Pharmacology Fellows. Fellows improve their understanding of drug–gene interactions and metabolism pathways during their prereview of patient information and genotype results. The review of data with the project PI and faculty physician creates an active learning experience that makes pharmacogenomics more relevant, illustrates concepts learned in didactic curricula, and provides continued exposure that may lead to increased retention of information. Others have shown that involvement of trainees in active interpretation of genotype results leads to a more favorable experience and increased knowledge gain [34–36]; our study, however, avoids the ethical and philosophical sticky wickets that are inherent with using one's own DNA for genotyping.

The INGENIOUS study also provides our fellows with a service learning modality: enrollment data, medication lists, genotype results and formal consult notes are maintained within a REDCap (Research Electronic Data Capture) database [37]. REDCap is a secure, web-based application designed to support data capture for research studies. Our REDCap database was created by and is continually curated by the fellows to review and document all patient genotyping results, even those that do not result in a formal clinical pharmacology consult. This responsibility allows the fellows to gain practical understanding of the logistics of a large pharmacogenomic trial.

In this case series, we present four varied examples of patients with clinically actionable genotypes that illustrate both the educational value for the fellows and the impact of pharmacogenomics testing at the patient level. Though the INGENIOUS trial is ongoing, we provide a brief overview of the logistics of reviewing genotype data obtained as part of the study. A significant limitation of this study is that clinical outcomes have not yet been assessed; thus, caution should be exercised when interpreting the data in this case series until the study itself is published.

We illustrate the uniqueness of the INGENIOUS trial in that the Clinical Pharmacology Fellows are critically involved in the process of reviewing genotype data and making clinical recommendations. The Adjudication Committee provides critical applied learning opportunities for the Fellows as we have outlined in this case series. We also demonstrate the value of our unique Adjudication Committee in assessing multiple aspects of the clinical situation for each individual patient. As shown by our example cases, clinical situations are often complex and genotype information must be considered in the context of the larger clinical picture. The final outcomes of the INGENIOUS trial will provide insight regarding the impact of genotyping on long-term outcomes and healthcare expenditure at the population level, in this series we provide examples of the impact of genotyping at an individual level.

Financial & competing interests disclosure

This project was supported by NIH-NIGMS: Indiana University Comprehensive Training in Clinical Pharmacology (T32GM008425) which provided stipend support to RC Pierson and BT Gufford. The INGENIOUS trial (NCT02297126) is sponsored by an NIH/NHGRI U01-grant (HG007762). Z Desta is supported by the NIH-U01 HG007762. MT Eadon was supported by the PhRMA foundation (Clinical Pharmacology Young Investigator Award), the Norman S Coplon Satellite Health Extramural Grant Program, and an NIH/NIDDK award (K08DK107864–01). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Large-scale pharmacogenomics studies can provide valuable educational opportunities for learners.
- This case series illustrates the impact of large pharmacogenomics studies on the care of individual patients.
- Support systems for individual prescribers are critical as many providers do not have the training or knowledge base to incorporate pharmacogenomic results into everyday practice.

References

1 Eadon MT, Desta Z, Levy KD *et al.* Implementation of a pharmacogenomics consult service to support the INGENIOUS trial. *Clin. Pharmacol. Ther.* 100(1), 63–66 (2016).

2 Weitzel KW, Alexander M, Bernhardt BA *et al.* The IGNITE network: a model for genomic medicine implementation and research. *BMC Med. Genomics.* 9(1), 1 (2016).

3 Li-Wan-Po A, Girard T, Farndon P, Cooley C, Lithgow J. Pharmacogenetics of CYP2C19: functional and clinical implications of a new variant *CYP2C19*17*. *Br. J. Clin. Pharmacol.* 69(3), 222–230 (2010).

4 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.* 98(2), 127–134 (2015).

5 Swen JJ, Nijenhuis M, de Boer A *et al.* Pharmacogenetics: from bench to byte-an update of guidelines. *Clin. Pharmacol. Ther.* 89(5), 662–673 (2011).

6 Johansson B, Wentzel A-P, Andréll P, Rönnbäck L, Mannheimer C. Long-term treatment with methylphenidate for fatigue after traumatic brain injury. *Acta Neurol. Scand.* 135(1), 100–107 (2016).

7 Lee H, Kim SW, Shin IS, Yang SJ, Yoon JS. Comparing effects of methylphenidate, sertraline and placebo on neuropsychiatric sequelae in patients with traumatic brain injury. *Hum. Psychopharmacol.* 20(2), 97–104 (2005).

8 Siddall OM. Use of methylphenidate in traumatic brain injury. *Ann. Pharmacother.* 39(7–8), 1309–1313 (2005).

9 Sibbing D, Koch W, Gebhard D *et al.* Cytochrome *2C19*17* allelic variant, platelet aggregation, bleeding events, and stent thrombosis in clopidogrel-treated patients with coronary stent placement. *Circulation* 121(4), 512–518 (2010).

10 Collet J-P, Cuisset T, Rangé G *et al.* Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N. Engl. J. Med.* 367(22), 2100–2109 (2012).

11 Price MJ, Berger PB, Teirstein PS *et al.* Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA* 305(11), 1097–1105 (2011).

12 Scott SA, Sangkuhl K, Stein CM *et al.* Clinical pharmacogenetics implementation consortium guidelines for *CYP2C19* genotype and clopidogrel therapy: 2013 update. *Clin. Pharmacol. Ther.* 94(3), 317–323 (2013).

13 Leunissen TC, Janssen PWA, Ten Berg JM *et al.* The use of platelet reactivity testing in patients on antiplatelet therapy for prediction of bleeding events after cardiac surgery. *Vascul. Pharmacol.* 77, 19–27 (2016).

14 Tramadol hydrochloride, package insert. Ortho-McNeil Pharmaceutical, Inc., NJ, USA.

15 Kahn LH, Alderfer RJ, Graham DJ. Seizures reported with tramadol. *JAMA* 278(20), 1661 (1997).

16 Gaedigk A, Simon SD, Pearce RE, Bradford LD, Kennedy MJ, Leeder JS. The *CYP2D6* activity score: translating genotype information into a qualitative measure of phenotype. *Clin. Pharmacol. Ther.* 83(2), 234–242 (2008).

17 Zhou S-F. Polymorphism of human cytochrome *P450 2D6* and its clinical significance. *Clin. Pharmacokinet.* 48(11), 689–723 (2012).

18 Lötsch J, Rohrbacher M, Schmidt H *et al.* Can extremely low or high morphine formation from codeine be predicted prior to therapy initiation? *Pain* 144(1–2), 119–124 (2009).

19 Stamer UM, Lehnen K, Höthker F *et al.* Impact of *CYP2D6* genotype on postoperative tramadol analgesia. *Pain* 105(1–2), 231–238 (2003).

20 Labroo RB, Paine MF, Thummel KE, Kharasch ED. Fentanyl metabolism by human hepatic and intestinal cytochrome P450 3A4: implications for individual variablity in disposition, efficacy, and drug interactions. *Drug Metab. Dispos.* 25(9), 1072–1080 (1997).

21 Grover CA, Elder JW, Close RJ, Curry SM. How frequently are 'classic' drug-seeking behaviors used by drug-seeking patients in the emergency department? *West. J. Emerg. Med.* 13(5), 416–421 (2012).

22 Davis MP, Homsi J. The importance of cytochrome P450 monooxygenase *CYP2D6* in palliative medicine. *Support. Care Cancer.* 9(6), 442–451 (2001).

23 Kapur BM, Lala PK, Shaw JLV. Pharmacogenetics of chronic pain management. *Clin. Biochem.* 47(13–14), 1169–1187 (2014).

24 Somogyi AA, Barratt DT, Coller JK. Pharmacogenetics of opioids. *Clin. Pharmacol. Ther.* 81(3), 429–444 (2007).

25 Nichols AI, Focht K, Jiang Q, Preskorn SH, Kane CP. Pharmacokinetics of venlafaxine extended release 75 mg and desvenlafaxine 50 mg in healthy *CYP2D6* extensive and poor metabolizers: a randomized, open-label, two-period, parallel-group, crossover study. *Clin. Drug Investig.* 31(3), 155–167 (2011).

26 Lobello KW, Preskorn SH, Guico-Pabia CJ *et al.* Cytochrome P450 2D6 phenotype predicts antidepressant efficacy of venlafaxine: a secondary analysis of 4 studies in major depressive disorder. *J. Clin. Psychiatry.* 71(11), 1482–1487 (2010).

27 McAlpine DE, O'Kane DJ, Black JL, Mrazek DA. Cytochrome *P450 2D6* genotype variation and venlafaxine dosage. *Mayo Clin. Proc.* 82(9), 1065–1068 (2007).

28 van der Wouden CH, Cambon-Thomsen A, Cecchin E *et al.* Implementing pharmacogenomics in Europe: design and implementation strategy of the ubiquitous pharmacogenomics consortium. *Clin. Pharmacol. Ther.* 101(3), 341–358 (2017).

29 Johnson JA, Gong L, Whirl-Carrillo M *et al.* Clinical pharmacogenetics implementation consortium guidelines for *CYP2C9* and *VKORC1* genotypes and warfarin dosing. *Clin. Pharmacol. Ther.* 90(4), 625–629 (2011).

30 Hicks JK, Crews KR, Hoffman JM *et al.* A clinician-driven automated system for integration of pharmacogenetic interpretations into an electronic medical record. *Clin. Pharmacol. Ther.* 92(5), 563–566 (2012).

31 Dodson C. Knowledge and attitudes concerning pharmacogenomics among healthcare professionals. *Per. Med.* 8(4), 421–428 (2011).

32 Stanek EJ, Sanders CL, Taber K a J *et al.* Adoption of pharmacogenomic testing by US physicians: results of a nationwide survey. *Clin. Pharmacol. Ther.* 91(3), 450–458 (2012).

33 Selkirk CG, Weissman SM, Anderson A, Hulick PJ. Physicians' preparedness for integration of genomic and pharmacogenetic testing into practice within a major healthcare system. *Genet. Test. Mol. Biomarkers.* 17(3), 219–225 (2013).

34 O'Brien TJ, LeLacheur S, Ward C *et al.* Impact of a personal *CYP2D6* testing workshop on physician assistant student attitudes toward pharmacogenetics. *Pharmacogenomics.* 17(4), 341–352 (2016).

35 Perry CG, Maloney KA, Beitelshees AL *et al.* Educational innovations in clinical pharmacogenomics. *Clin. Pharmacol. Ther.* 99(6), 582–584 (2016).

36 Adams SM, Anderson KB, Coons JC *et al.* Advancing pharmacogenomics education in the core pharmd curriculum through student personal genomic testing. *Am. J. Pharm. Educ.* 80(1), 3 (2016).

37 Harris PA, Taylor R, Thielke R *et al.* Research electronic data capture (REDCap)-a metadata-driven methodology and workflow process for providing translational research informatics support. *J. Biomed. Inform.* 42(2), 377–381 (2009).