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Clinical application of pharmacogenetics in pain management

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Abstract

There is growing experience translating genomic data into clinical practice, as seen with the Implementing GeNomics In pracTice (IGNITE) network. A primary example is the influence of CYP2D6 genotype on the beneficial and adverse effects of some opioids. Clinical recommendations exist to guide drug therapy based on CYP2D6 genotype for codeine, tramadol, oxycodone and hydrocodone, although the level of supporting evidence differs by drug. Limited evidence also supports the use of genetic data to guide other medications in chronic pain therapy, including tricyclic antidepressants and celecoxib. Pragmatic clinical trial data are needed in this area to better understand the impact of diverse populations, therapeutic interventions and clinical care environments on genotype-guided drug therapy for chronic pain.

Keywords

CYP2D6; Implementation; opioids; pain management; pharmacogenetics; primary care

Taking a personalized approach to patient care can allow clinicians to use individuals' phenotype and genotype data (e.g., molecular profiling, medical imaging, lifestyle data) to identify the optimal treatment strategy, determine predisposition to disease and/or deliver targeted interventions [1]. Pharmacogenetics, or the use of genetic data to guide drug therapies, is a clinical tool within the personalized medicine toolbox [2]. Clinical evidence and resources that provide guidance to clinicians on the use of pharmacogenetic information for select gene–drug pairs are increasing [3]. These resources include pharmacogenetic data within the US FDA-labeling for nearly 200 medications and the availability of curated and ranked clinical pharmacogenetic evidence summaries in the Pharmacogenomics KnowledgeBase [4]. In addition, clinical guidelines that provide consensus recommendations on genotype-informed drug dosing are available for 35 drugs or drug classes from the Clinical Pharmacogenetics Implementation Consortium (CPIC), an international consortium developed in 2009 [5]. Additional clinical recommendations are provided for many gene–drug pairs from the Dutch Pharmacogenetics Working Group, the Canadian Pharmacogenomics Network for Drug Safety and the EMA [6,7].

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Although clinical information is increasingly available, routine adoption of pharmacogenomics in clinical practice remains limited due to implementation barriers such as clinician inexperience with pharmacogenetic information and lack of integration of genomic results within the electronic health record with clinical decision support [8]. The University of Florida (UF) Health Personalized Medicine Program (FL, USA), a member of the NIH-funded Implementing GeNomics In pracTice (IGNITE) network, was established to improve integration of genomic data into clinical practice. The UF Health Personalized Medicine Program launched in 2012 with *CYP2C19* testing to guide antiplatelet therapy in patients undergoing percutaneous coronary intervention [9]. We have since expanded on this initial implementation to include, among other areas, the treatment of chronic pain [10]. The purpose of this report is to summarize selected gene–drug pairs with clinical relevance in pain management and present an example of how these pharmacogenetic data have been used in practice.

Chronic pain management

Approximately 11% of adults in the USA experience some form of chronic pain [11]. Symptom assessment and treatment recommendations for pain are often based on subjective data, which lead to challenges clinically. The WHO analgesic ladder provides an approach to managing patients with malignant pain. In practice, this ladder is often applied to nonmalignant chronic pain, although its application in this setting is limited by its original design for a malignant pain model and omission of pain etiology or biological mechanism in symptom assessment [12–15]. The WHO analgesic ladder directs therapy based on pain severity and persistence, with drug therapy recommendations spanning from nonopioids (e.g., NSAIDs) for mild pain followed by ‘weak’ (e.g., codeine) and ‘strong’ opioids (e.g., morphine) for moderate to severe pain, with inclusion of adjuvant therapies (e.g., duloxetine) as appropriate.

One in five patients seen by a clinician for pain receives a prescription for opioids in the USA [16]. However, a Cochrane analysis found long-term opioid therapy was either ineffective or poorly tolerated by a third of patients with nonmalignant chronic pain [17]. This lack of evidence for long-term therapy is also problematic for nonopioid therapy. Short-term opioid therapy has been associated with an adverse effect (e.g., nausea, constipation, somnolence, dizziness and pruritus) in 50–80% of patients [18,19]. An additional concern is possible addiction to prescribed opioids, although current pharmacogenetic evidence is unable to identify populations at increased addiction risk [20].

Pharmacogenetics & chronic pain management

A portion of the variability in patients’ response to pain medications can be attributed to genetic factors, including variation in genes encoding drug metabolizing enzymes (e.g., CYP450 enzymes). Knowledge of an individual’s pharmacogenetic data can provide an objective measure to help predict effectiveness and tolerability of medications in chronic pain management. However, it is essential for clinicians to recognize that although the effect of genetic variability on drug levels and patient outcomes have been studied extensively, the level of evidence supporting the clinical usefulness of genotype-guided drug therapy differs

widely among gene–drug pairs. CPIC uses a systematic method to prioritize and assign evidence levels to gene–drug pairs, known as CPIC levels. CPIC levels are valuable tools that provide guidance for clinicians to interpret pharmacogenetic test results [21]. A CPIC level of ‘A’ or ‘B’ indicates that a gene–drug pair has ‘prescribing action recommended; alternative therapies or dosing are highly likely to be effective and safe’ [22].

To ensure a focus on current, clinically relevant pharmacogenetic information, this manuscript includes discussion of pain management gene–drug pairs that have a CPIC level of A or B (Table 2), including selected opioids, celecoxib, tricyclic antidepressants (TCAs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) [21,22].

CYP2D6 & opioids

CYP2D6 is drug-metabolizing enzyme encoded by a highly polymorphic gene. The CYP2D6 enzyme is involved in the metabolism of approximately 25% of clinically used medications, and genetic variations in the *CYP2D6* gene are associated with changes in enzyme activity [25]. CYP2D6 genetic variability can lead to patients having one of four CYP2D6 phenotypes (i.e., poor, intermediate, normal and ultrarapid metabolizers). Approximately 5–10% of patients have complete deletion of the *CYP2D6* gene (no CYP2D6 enzyme activity) and are classified as poor metabolizers. An estimated 1–2% of individuals have multiple copies of the *CYP2D6* gene with increased enzyme activity [23,26]. The phenotype frequencies vary by race with certain race groups displaying higher (e.g., ultrarapid metabolism in Middle Eastern populations) or lower (e.g., poor metabolism in east Asians) frequencies [27].

Codeine, tramadol, oxycodone and hydrocodone undergo bioactivation to more active forms via the CYP2D6 enzyme to varying extents. The clinical effects of genetic variability are especially important with codeine and tramadol, which are activated by CYP2D6 to morphine and O-desmethyltramadol, respectively [23,28]. These metabolites each have 200-fold greater affinity for the μ -opioid receptor than their parent compounds [29]. The CYP2D6-mediated metabolite is oxymorphone for oxycodone and hydromorphone for hydrocodone which have a 40-fold and 10- to 33-fold higher affinity for the μ -opioid receptor than their parent drug, respectively [23]. Patients who are CYP2D6 poor metabolizers have reduced concentrations of the active metabolites and are at risk for reduced analgesia with codeine, tramadol, oxycodone or hydrocodone [30–35]. Conversely, patients who are CYP2D6 ultra-rapid metabolizers have increased concentrations of the active metabolites and are at increased risk for toxicity [31–37]. There have been multiple cases of toxicity and/or death in pediatric patients receiving codeine post-tonsillectomy and/or adenoidectomy in which patients were discovered to be CYP2D6 ultra-rapid metabolizers postmortem [38,39]. The FDA added a boxed warning to codeine-containing products in light of these cases, which was subsequently updated to include a contraindication to codeine and tramadol use in patients <12 years of age in 2017 [40–42].

Although bioactivation of codeine, tramadol, oxycodone and hydrocodone is affected by CYP2D6 enzyme activity, the evidence supporting a link between *CYP2D6* genotype and clinically relevant outcomes (e.g., pain relief) differs by drug, with codeine having the

highest level of evidence, followed by tramadol, with lesser evidence supporting clinically relevant effects with oxycodone and hydrocodone. This is explained to a great extent by pharmacokinetic differences among these agents. The bioactivation processes for oxycodone and hydrocodone include enzymes other than CYP2D6, providing alternative metabolic pathways. In addition, the parent oxycodone and hydrocodone compounds themselves have analgesic activity, allowing them to provide therapeutic effects in the absence of CYP2D6 activity [43,44]. For oxycodone, alternative pathways appear to be important as decreased CYP2D6 activity has been associated with decreased metabolite levels without changes in clinical outcomes [34].

CPIC guidelines provide *CYP2D6* genotype-based recommendations for codeine (Table 1; CPIC level A), with additional recommendations included for tramadol, oxycodone and hydrocodone based on the strength of supporting clinical evidence [23]. Clinical recommendations based on *CYP2D6* genetic variability are also provided by the Dutch Pharmacogenetics Working Group and the Canadian Pharmacogenomics Network for Drug Safety and are generally aligned with CPIC guidance [6,7].

CYP2D6 & CYP2C19 & antidepressants

The CYP2C19 enzyme, which is encoded by the *CYP2C19* gene, and CYP2D6 are responsible for metabolizing many antidepressants, including drugs widely prescribed off label in the management of chronic pain (e.g., TCAs, SNRIs) [45]. *CYP2C19* possesses genetic variation associated with a range of CYP2C19 enzyme activities and corresponding phenotypes (i.e., poor metabolism, intermediate metabolism, normal metabolism, rapid metabolism and ultra-rapid metabolism) [24].

Both CYP2D6 and CYP2C19 affect the metabolism of TCAs. Tertiary amine TCAs (e.g., amitriptyline) are metabolized by CYP2C19 to secondary amine TCAs (e.g., nortriptyline) which also possess pharmacological activity [24]. Secondary amines (e.g., nortriptyline) are then converted to less active metabolites via CYP2D6. Clinical outcomes have been associated with TCA serum concentrations and genotype (e.g., poor metabolism is associated with higher TCA concentrations and increased risk of adverse effects) [45–47]. CPIC guidelines exist to guide TCA dosing based on *CYP2D6* and *CYP2C19* genotypes (Table 1), although the association between TCAs and genotype may vary based on specific agent, dose and indication (Table 2; CPIC level A or B) [24].

Similar to TCAs, venlafaxine was primarily developed for use in depression but has since expanded to off-label use in chronic pain. Venlafaxine is an SNRI primarily metabolized by CYP2D6 to the active metabolite, O-desmethylvenlafaxine (ODV) [48,49]. Venlafaxine metabolizer status is often classified by either *CYP2D6* genotype or the ODV/venlafaxine ratio [50,51]. One example of phenotype classification per ODV/venlafaxine ratio was a pooled analysis of four industry-sponsored studies that were initially used to gain FDA approval [50]. While there was no difference in dose between normal metabolizers and poor metabolizers, normal metabolizers were associated with higher ODV concentrations, and greater clinical improvement. The FDA package insert states CYP2D6 poor metabolizers have increased venlafaxine levels and reduced ODV levels compared with normal

metabolizers but does not recommend dose adjustments based on *CYP2D6* genotype [49]. The application of *CYP2D6*-guided venlafaxine therapy is complicated by factors including an additional active metabolite (i.e., desvenlafaxine), possible involvement of other hepatic enzymes (e.g., *CYP2C19*), and that the association with *CYP2D6* may vary based on dose or indication (Table 2; CPIC level B).

CYP2C9 & celecoxib

CYP2C9 is responsible for the metabolic clearance of 15–20% of all drugs that undergo Phase I metabolism and is encoded by the highly polymorphic *CYP2C9* gene [52]. FDA labeling for celecoxib indicates *CYP2C9* is predominantly responsible for its metabolism and recommends initiating treatment at half of the lowest recommended dose in known or suspected *CYP2C9* poor metabolizers [53]. Pharmacokinetic data have demonstrated that patients with decreased *CYP2C9* activity have greater plasma concentrations of celecoxib, especially patients who are *CYP2C9* poor metabolizers [54]. A randomized controlled trial of 282 children treated with a 3-day course of celecoxib after adenotonsillectomy found that patients who had a variant associated with a decreased function of the *CYP2C9* enzyme reported less pain than patients without this variant. CPIC guidelines are not yet available for celecoxib (Table 2; CPIC level B).

CYP2B6 & methadone

CYP2B6 has high interindividual variation in *CYP2B6* enzyme expression [55]. The *CYP2B6* enzyme is involved in the metabolism of 4% of the top 200 medications, including methadone (Table 2; CPIC level B). Predicting drug response for methadone based on pharmacogenetic data is complicated by methadone's complex pharmacokinetics and the number of enzymes involved in its metabolism. A systematic review and meta-analyses found that patients with decreased *CYP2B6* activity had higher trough levels of the (*R*)- and (*S*)-enantiomers of methadone, more so with (*S*)-methadone [56]. However, these findings are based on limited data, with the availability of a small number of cross-sectional ($n = 5$) and case-control ($n = 2$) studies. Based on these factors the clinical application of *CYP2B6* genotype in methadone therapy is debatable.

Translating pharmacogenetic data into practice: CYP2D6 codeine example

As the evidence supporting the role of genomic medicine mounts, the focus shifts to aid the development and investigation of genomic medicine practice models to enhance its implementation into routine clinical practice. Institutions affiliated with the IGNITE network and others have described such implementations [57–62]. Of the gene–drug pairs described in this report, clinical use of pharmacogenetic data to guide drug therapy is currently most prevalent with the *CYP2D6* testing to inform codeine and/or tramadol prescribing. Varying clinical models have been proposed for implementation of pharmacogenetic testing generally [58–60,63], or for genotype-guided codeine therapy specifically [61]. When approaching implementation of *CYP2D6* testing in practice to guide chronic pain management, some institutions have begun with a limited approach, such as targeting specific at-risk patient populations or limiting clinical recommendations to agents with the

highest level of clinical evidence (i.e., codeine, tramadol). Gammal *et al.* implemented a pharmacogenetics-based prescribing strategy using clinical decision support to prevent the use of codeine in high-risk populations based on surgical history (i.e., after tonsillectomy, adenoidectomy) or high-risk *CYP2D6* genotype (i.e., poor or ultra-rapid metabolism or indeterminate genotype) [61]. Their patient population consisted largely of patients with sickle cell disease in whom codeine was used extensively. Codeine was used in 173 of the 543 (32%) sickle cell disease patients without high-risk *CYP2D6* genotype compared with 1 of 53 (4%) patients with a high-risk *CYP2D6* genotype (the one patient with high-risk genotype who received codeine had previously tolerated codeine).

At UF Health, we are investigating a broader approach to use of pharmacogenetic testing through the Implementing Genomics in Practice (IGNITE) Proof of Concept Study: Genotyping in Family Medicine Clinics ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02335307) identifier NCT02335307). This ongoing pragmatic study compares pain management and pain control between patients with and without *CYP2D6* genotype information available [64]. Patients with chronic pain, defined as pain for at least 3 months, are eligible for participation. The study utilizes a prospective cluster design in which primary care clinics are assigned as implementation or control sites. After providing written informed consent, a buccal cell sample is collected from patients at implementation sites, with genotyping completed in approximately 1–2 weeks. At that time, the physician caring for the patient receives genotype results and a pharmacist consultation that includes test interpretation and recommendations, with the final therapeutic decision being made by the physician. Control patients are offered genotyping, with results provided at study completion. The study is examining patient-reported pain outcomes, assessed using the NIH Patient Reported Outcomes Measurement Information System measures at baseline and 3 months. Change in patient-reported pain will be compared between patients enrolled from implementation versus control sites. Additionally, this trial will determine physician-perceived usefulness of *CYP2D6* genotype results for prescribing decisions for chronic pain management.

Our experiences with this study to date have reinforced the importance of accounting for patient-specific factors that influence drug therapy selection, particularly in relation to medications that influence *CYP2D6* activity (Table 3) [65,66]. This is especially important in patients who are *CYP2D6* normal or intermediate metabolizers. In these patients, *CYP2D6* inhibitors (e.g., duloxetine) may phenotypically ‘convert’ patients to *CYP2D6* intermediate or poor metabolizers while the patient is taking the enzyme inhibitor. Second, several of the patients suspected to have abnormal *CYP2D6* function by clinical criteria (e.g., poor responders to tramadol or codeine) were found to have normal a *CYP2D6* genotype. This emphasizes the usefulness of genotyping to rule out an abnormal *CYP2D6* genotype as a factor influencing drug response. Additionally, options for alternative therapy are limited in *CYP2D6* poor and ultra-rapid metabolizers if a pain medication in the second step of the WHO analgesic ladder (e.g., codeine, tramadol, hydrocodone) is indicated. The primary alternatives for these patients require a step down (e.g., NSAIDs) or a step up (e.g., morphine), which may or may not be clinically appropriate [67]. For these patients, we have recommended an initial trial of oxycodone or hydrocodone with close monitoring, with step-up or step-down therapy to alternative medications as appropriate, since these opioids have the least evidence of clinically relevant effects caused by *CYP2D6* variability [23,68].

Clinical experience with applying pharmacogenetic data in a pragmatic environment provides an important piece of the puzzle for clinicians desiring to use such tests in practice.

Conclusion

Pharmacogenetic-guided therapy for chronic pain is now a reality at some institutions for select medications (e.g., codeine, tramadol) metabolized by CYP2D6. In addition to pharmacogenetic data, providers should continue to consider other patient-specific factors (e.g., previous opioid use, renal function, concomitant medications) to guide drug therapy. As pharmacogenetics is translated from the research to the clinical setting, it is essential that the approach remains grounded in published evidence. The CPIC levels provide a clinician-friendly, systematic, evidenced-based tool to facilitate the application of gene–drug pairs appropriate for clinical care.

Future perspective

Many factors point to an expanded use of clinical pharmacogenetics. An increased number of medical centers have started offering genetic testing (including CYP2D6 testing) to predict drug response [57]. Regulatory bodies are beginning to more widely allow expanded use of genetic information as the FDA recently announced it will allow marketing of a direct-to-consumer genetic tests for disease risk [70]. In the future, clinical use of pharmacogenetic tests will likely become more prevalent as patient access to testing improves and the associated cost of testing decreases.

Evidence generation that incorporates pragmatic design and diverse populations may expedite a translation of pharmacogenetics into clinical care across a variety of settings, including nonacademic institutions. Pharmacogenetics is often referred to as a science of the outliers. That is, it is the patients at the extremes regarding drug effectiveness and response who may gain the most benefit from pharmacogenetic testing. As such, pharmacogenetic studies may be limited by sample size, as genotype is not expected to have a major influence on drug response for most patients. Alternative approaches to the traditional randomized control trial design are warranted to evaluate the impact of genotype-guided therapy on important patient outcomes given the expense and time required to conduct an adequately powered pharmacogenetic clinical trial. A pragmatic approach to evidence development may allow for examination of pharmacogenetics intervention in a real-world setting [71]. The UF Health Proof of Concept study described above is one example of a pragmatic trial design relying on practice-based evidence. Another example of an ongoing pragmatic study is the large, PREmptive Pharmacogenomic testing for prevention of Adverse drug REactions (PREPARE) study conducted by the Ubiquitous Pharmacogenomics Consortium in Europe [72]. PREPARE will enroll over 8000 patients in an attempt to quantify the collective clinical utility of implementing a panel of pharmacogenomic markers, including CYP2D6 testing for opioid response, into routine clinical care.

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References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Nimmegern E, Benediktsson I, Norstedt I. Personalized medicine in Europe. Clin. Transl. Sci 10(2), 61–63 (2017). [PubMed: 28083940]
2. Ginsburg GS, Willard HF. Genomic and personalized medicine: foundations and applications. Transl. Res 154(6), 277–287 (2009). [PubMed: 19931193]
3. Implementing Genomics In Practice (IGNITE). IGNITE SPARK Toolbox <https://ignite-genomics.org/spark-toolbox/clinicians/>• Provides various tools to aid clinicians implementing personalized medicine.
4. PharmGKB. www.pharmgkb.org/
5. Clinical Pharmacogenetics Implementation Consortium (CPIC). Guidelines <https://cpicpgx.org/guidelines/>• Provides a comprehensive list and link to all published Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines.
6. Madadi P, Amstutz U, Rieder M et al. Clinical practice guideline: CYP2D6 genotyping for safe and efficacious codeine therapy. J. Popul. Ther. Clin. Pharmacol 20(3), e369–e396 (2013). [PubMed: 24214521]
7. 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). [PubMed: 21412232]
8. Manolio TA, Chisholm RL, Ozenberger B et al. Implementing genomic medicine in the clinic: the future is here. Genet. Med 15(4), 258–267 (2013). [PubMed: 23306799]
9. Owusu-Obeng A, Weitzel KW, Hatton RC et al. Emerging roles for pharmacists in clinical implementation of pharmacogenomics. Pharmacotherapy 34(10), 1102–1112 (2014). [PubMed: 25220280]
10. Cavallari LH, Weitzel KW, Elsey AR et al. Institutional profile: University of Florida Health Personalized Medicine Program. Pharmacogenomics 18(5), 421–426 (2017). [PubMed: 28346068]
11. Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012. J. Pain 16(8), 769–780 (2015). [PubMed: 26028573]
12. World Health Organization. Cancer pain relief Geneva: WHO (1986).
13. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) Adult Cancer Pain V 12017 ed. www.nccn.org/professionals/physician_gls/pdf/pain.pdf
14. Varrassi G Severe chronic pain – the reality of treatment in Europe. Curr. Med. Res. Opin 27(10), 2063–2064 (2011). [PubMed: 21929442]
15. Ballantyne JC, Kalso E, Stannard C. WHO analgesic ladder: a good concept gone astray. BMJ 352, i20 (2016). [PubMed: 26739664]
16. Daubresse M, Chang HY, Yu Y et al. Ambulatory diagnosis and treatment of nonmalignant pain in the United States, 2000–2010. Med. Care 51(10), 870–878 (2013). [PubMed: 24025657]
17. Noble M, Treadwell JR, Tregear SJ et al. Long-term opioid management for chronic noncancer pain. Cochrane Database Syst. Rev (1), CD006605 (2010).
18. Chou R, Fanciullo GJ, Fine PG et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J. Pain 10(2), 113–130 (2009). [PubMed: 19187889]
19. Manchikanti L, Kaye AM, Knezevic NN et al. Responsible, safe, and effective prescription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) guidelines. Pain Phys 20(2S), S3–S92 (2017).

20. Kranzler HR, Smith RV, Schnoll R, Moustafa A, Greenstreet-Akman E. Precision medicine and pharmacogenetics: what does oncology have that addiction medicine does not? *Addiction* 112(12), 2086–2094 (2017). [PubMed: 28431457]
21. Caudle KE, Klein TE, Hoffman JM et al. Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process. *Curr. Drug Metab* 15(2), 209–217 (2014). [PubMed: 24479687]
22. Clinical Pharmacogenetics Implementation Consortium (CPIC). Prioritization of genes/drugs <https://cpicpgx.org/prioritization/#flowchart>
23. Crews KR, Gaedigk A, Dunnenberger HM et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clin. Pharmacol. Ther* 95(4), 376–382 (2014). [PubMed: 24458010] •• The CPIC guidelines for CYP2D6 and codeine therapy provide commentary that extends to tramadol, oxycodone and hydrocodone.
24. Hicks JK, Sangkuhl K, Swen JJ et al. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. *Clin. Pharmacol. Ther* doi:10.1002/cpt.597 (2016) (Epub ahead of print).
25. Ingelman-Sundberg M Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. *Pharmacogenomics J* 5(1), 6–13 (2005). [PubMed: 15492763]
26. Aklillu E, Persson I, Bertilsson L, Johansson I, Rodrigues F, Ingelman-Sundberg M. Frequent distribution of ultrarapid metabolizers of debrisoquine in an ethiopian population carrying duplicated and multiduplicated functional CYP2D6 alleles. *J. Pharmacol. Exp. Ther* 278(1), 441–446 (1996). [PubMed: 8764380]
27. Gaedigk A, Sangkuhl K, Whirl-Carrillo M, Klein T, Leeder JS. Prediction of CYP2D6 phenotype from genotype across world populations. *Genet. Med* 19(1), 69–76 (2017). [PubMed: 27388693]
28. Thorn CF, Klein TE, Altman RB. Codeine and morphine pathway. *Pharmacogenet. Genomics* 19(7), 556–558 (2009). [PubMed: 19512957]
29. Volpe DA, McMahon Tobin GA, Mellon RD et al. Uniform assessment and ranking of opioid mu receptor binding constants for selected opioid drugs. *Regul. Toxicol. Pharmacol* 59(3), 385–390 (2011). [PubMed: 21215785]
30. Poulsen L, Arendt-Nielsen L, Brosen K, Sindrup SH. The hypoalgesic effect of tramadol in relation to CYP2D6. *Clin. Pharmacol. Ther* 60(6), 636–644 (1996). [PubMed: 8988065]
31. Stamer UM, Musshoff F, Kobilay M, Madea B, Hoeft A, Stuber F. Concentrations of tramadol and O-desmethyltramadol enantiomers in different CYP2D6 genotypes. *Clin. Pharmacol. Ther* 82(1), 41–47 (2007). [PubMed: 17361124]
32. Lotsch J, Rohrbacher M, Schmidt H, Doebering A, Brockmoller J, Geisslinger G. Can extremely low or high morphine formation from codeine be predicted prior to therapy initiation? *Pain* 144(1–2), 119–124 (2009). [PubMed: 19395173]
33. Stamer UM, Zhang L, Stuber F. Personalized therapy in pain management: where do we stand? *Pharmacogenomics* 11(6), 843–864 (2010). [PubMed: 20504256]
34. Andreassen TN, Eftedal I, Klepstad P et al. Do CYP2D6 genotypes reflect oxycodone requirements for cancer patients treated for cancer pain? A cross-sectional multicentre study. *Eur. J. Clin. Pharm* 68(1), 55–64 (2012).
35. Linares OA, Fudin J, Daly AL, Boston RC. Individualized hydrocodone therapy based on phenotype, pharmacogenetics, and pharmacokinetic dosing. *Clin. J. Pain* 31(12), 1026–1035 (2015). [PubMed: 25621429]
36. Eckhardt K, Li S, Ammon S, Schanzle G, Mikus G, Eichelbaum M. Same incidence of adverse drug events after codeine administration irrespective of the genetically determined differences in morphine formation. *Pain* 76(1–2), 27–33 (1998). [PubMed: 9696456]
37. Gasche Y, Daali Y, Fathi M et al. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. *N. Engl. J. Med* 351(27), 2827–2831 (2004). [PubMed: 15625333]
38. Ciszewski C, Madadi P, Phillips MS, Lauwers AE, Koren G. Codeine, ultrarapid-metabolism genotype, and postoperative death. *N. Engl. J. Med* 361(8), 827–828 (2009). [PubMed: 19692698]

39. Kelly LE, Rieder M, Van Den Anker J et al. More codeine fatalities after tonsillectomy in North American children. *Pediatrics* 129(5), e1343–e1347 (2012). [PubMed: 22492761]
40. US Food and Drug Administration. Safety review update of codeine use in children; new boxed warning and contraindication on use after tonsillectomy and/or adenoidectomy. FDA Drug Safety Communication www.fda.gov/drugs/drugsafety/ucm339112.htm
41. Acetaminophen and Codeine®, package insert Par Pharmaceutical, NY, USA.
42. US Food and Drug Administration. FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. FDA Drug Safety Communication www.fda.gov/Drugs/DrugSafety/ucm549679.htm
43. Davis MP, Varga J, Dickerson D, Walsh D, Legrand SB, Lagman R. Normal-release and controlled-release oxycodone: pharmacokinetics, pharmacodynamics, and controversy. *Support. Care Cancer* 11(2), 84–92 (2003). [PubMed: 12560936]
44. Otton SV, Schadel M, Cheung SW, Kaplan HL, Busto UE, Sellers EM. CYP2D6 phenotype determines the metabolic conversion of hydrocodone to hydromorphone. *Clin. Pharmacol. Ther* 54(5), 463–472 (1993). [PubMed: 7693389]
45. Dworkin RH, O'connor AB, Backonja M et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 132(3), 237–251 (2007). [PubMed: 17920770]
46. Steimer W, Zopf K, Von Amelnunxens et al. Amitriptyline or not, that is the question: pharmacogenetic testing of CYP2D6 and CYP2C19 identifies patients with low or high risk for side effects in amitriptyline therapy. *Clin. Chem* 51(2), 376–385 (2005). [PubMed: 15590749]
47. Chaudhry M, Alessandrini M, Rademan J et al. Impact of CYP2D6 genotype on amitriptyline efficacy for the treatment of diabetic peripheral neuropathy: a pilot study. *Pharmacogenomics* 18(5), 433–443 (2017). [PubMed: 28350251]
48. Sangkuhl K, Stingl JC, Turpeinen M, Altman RB, Klein TE. PharmGKB summary: venlafaxine pathway. *Pharmacogenet. Genomics* 24(1), 62–72 (2014). [PubMed: 24128936]
49. Effexor®, package insert. Wyeth Pharmaceuticals, Inc, PA, USA.
50. 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). [PubMed: 20441720]
51. Shams ME, Arneth B, Hiemke C et al. CYP2D6 polymorphism and clinical effect of the antidepressant venlafaxine. *J. Clin. Pharm. Ther* 31(5), 493–502 (2006). [PubMed: 16958828]
52. Van Booven D, Marsh S, McLeod H et al. Cytochrome P450 2C9-CYP2C9. *Pharmacogenet. Genomics* 20(4), 277–281 (2010). [PubMed: 20150829]
53. Celebrex®, package insert. Pfizer Pharmaceuticals, NY, USA.
54. Kirchheiner J, Stormer E, Meisel C, Steinbach N, Roots I, Brockmoller J. Influence of CYP2C9 genetic polymorphisms on pharmacokinetics of celecoxib and its metabolites. *Pharmacogenetics* 13(8), 473–480 (2003). [PubMed: 12893985]
55. Thorn CF, Lamba JK, Lamba V, Klein TE, Altman RB. PharmGKB summary: very important pharmacogene information for CYP2B6. *Pharmacogenet. Genomics* 20(8), 520–523 (2010). [PubMed: 20648701]
56. Dennis BB, Bawor M, Thabane L, Sohani Z, Samaan Z. Impact of ABCB1 and CYP2B6 genetic polymorphisms on methadone metabolism, dose and treatment response in patients with opioid addiction: a systematic review and meta-analysis. *PLoS ONE* 9(1), e86114 (2014). [PubMed: 24489693]
57. Cavallari LH, Beitelshes AL, Blake KV et al. The IGNITE Pharmacogenetics Working Group: an opportunity for building evidence with pharmacogenetic implementation in a real-world setting. *Clin. Transl. Sci* 10(3), 143–146 (2017). [PubMed: 28294551]
58. Dunnenberger HM, Biszewski M, Bell GC et al. Implementation of a multidisciplinary pharmacogenomics clinic in a community health system. *Am. J. Health Syst. Pharm* 73(23), 1956–1966 (2016). [PubMed: 27864203]
59. Hicks JK, Dunnenberger HM, Gumpfer KF, Haidar CE, Hoffman JM. Integrating pharmacogenomics into electronic health records with clinical decision support. *Am. J. Health Syst. Pharm* 73(23), 1967–1976 (2016). [PubMed: 27864204]

60. Nassan M, Nicholson WT, Elliott MA, Rohrer Vitek CR, Black JL, Frye MA. Pharmacokinetic pharmacogenetic prescribing guidelines for antidepressants: a template for psychiatric precision medicine. *Mayo Clin. Proc* 91(7), 897–907 (2016). [PubMed: 27289413]
61. Gammal RS, Crews KR, Haidar CE et al. Pharmacogenetics for safe codeine use in sickle cell disease. *Pediatrics* 138(1), pii:e20153479 (2016). [PubMed: 27335380] • A description of a clinical implementation of CYP2D6-guided codeine therapy in a pediatric sickle cell disease population.
62. Weitzel KW, Alexander M, Bernhardt BA et al. The IGNITE network: a model for genomic medicine implementation and research. *BMC Med. Genomics* 9, 1 (2016). [PubMed: 26729011]
63. Dunnenberger HM, Crews KR, Hoffman JM et al. Preemptive clinical pharmacogenetics implementation: current programs in five US medical centers. *Annu. Rev. Pharmacol. Toxicol* 55, 89–106 (2015). [PubMed: 25292429]
64. Clinical Trials database: NCT02335307. <https://clinicaltrials.gov/ct2/show/NCT02335307>
65. Borges S, Desta Z, Jin Y et al. Composite functional genetic and comedication CYP2D6 activity score in predicting tamoxifen drug exposure among breast cancer patients. *J. Clin. Pharm* 50(4), 450–458 (2010).
66. Storelli F, Matthey A, Lenglet S, Thomas A, Desmeules J, Daali Y. Impact of CYP2D6 functional allelic variations on phenoconversion and drug–drug interactions. *Clin. Pharmacol. Ther* doi: 10.1002/cpt.889 (2017) (Epub ahead of print).
67. Nicholson WT, Formea CM. Clinical perspective on the Clinical Pharmacogenetics Implementation Consortium updated 2014 guidelines for CYP2D6 and codeine. *Clin. Chem* 61(2), 319–321 (2015). [PubMed: 25301855] • A clinician’s commentary on CPIC’s guidelines for CYP2D6 and codeine.
68. Crews KR, Caudle KE, Dunnenberger HM, Sadhasivam S, Skaar TC. Considerations for the utility of the CPIC guideline for CYP2D6 genotype and codeine therapy. *Clin. Chem* 61(5), 775–776 (2015). [PubMed: 25770140] • CPIC’s response to the commentary by Nicholson and Formea.
69. US Food and Drug Administration. Table of pharmacogenomic biomarkers in drug labeling www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm
70. US Food and Drug Administration. FDA news release: FDA allows marketing of first direct-to-consumer tests that provide genetic risk information for certain conditions www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm551185.htm
71. Bruehl S, Apkarian AV, Ballantyne JC et al. Personalized medicine and opioid analgesic prescribing for chronic pain: opportunities and challenges. *J. Pain* 14(2), 103–113 (2013). [PubMed: 23374939]
72. 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). [PubMed: 28027596]

Executive summary

Chronic pain management

- Many patients and clinicians are faced with the difficulties of managing chronic pain.
- There is a need to improve evidence for long-term pharmacological pain management.

Pharmacogenetics & chronic pain management

- In clinical practice, pharmacogenetic tests for pain management are often ordered via commercial laboratories that use a panel-based approach that tests for multiple genes.
- The evidence varies for each gene–drug pair with select gene–drug pairs ready for implementation; every gene–drug pair is not created equally.
- Clinical Pharmacogenetics Implementation Consortium provides useful resources to guide evidence review and clinical implementation of pharmacogenetics.
- Recommendations are available for *CYP2D6*-guided therapy for codeine and tramadol; however, the evidence for hydrocodone and oxycodone are less strong.
- Of other available treatment options, *CYP2D6* and *CYP2C19* for tricyclic antidepressants, *CYP2D6*-venlafaxine, *CYP2C9*-celecoxib and *CYP2B6*-methadone have the best Clinical Pharmacogenetics Implementation Consortium level.

Translating pharmacogenetic data into practice: *CYP2D6* codeine example

- Clinical decisions related to *CYP2D6* genotype results must include patient factors that influence drug therapy selection, such as the patient's history of response or toxicity, drug allergies or intolerances, and concomitant medications.
- Abnormal *CYP2D6* enzyme function cannot be determined by clinical presentation alone; however, genotyping is able to rule out abnormal *CYP2D6* genotype as a factor influencing drug response.

Conclusion

- Pharmacogenetic-guided therapy for chronic pain is a reality for select medications while other medications have developing evidence.

Future perspective

- We expect an increased use of clinical pharmacogenetics as costs and regulatory restrictions decrease in combination with improved evidence and access to testing

Table 1.

Clinical Pharmacogenetic Implementation Consortium recommendations for medications by CYP2C19 and CYP2D6 phenotypes

Drugs	CYP2C19 phenotype	CYP2D6 phenotype	Recommendation
Codeine and tramadol	N/A	UM	Avoid due to increased risk of toxicity. Hydrocodone and oxycodone are also metabolized by CYP2D6 and are not good substitutes
		NM	Normal use of codeine and tramadol
		IM	Normal use but monitor for lack of response
		PM	Avoid due to risk of ineffective analgesia. Hydrocodone and oxycodone are also metabolized by CYP2D6 and are not good substitutes
TCAs – secondary amines (e.g., nortriptyline)	N/A	UM	Avoid use. Consider alternative drug not metabolized by CYP2D6
		NM	Standard therapy
		IM	Consider a 25% reduction of recommended starting dose and therapeutic drug monitoring to guide dose adjustments
		PM	Avoid use. Consider alternative drug not metabolized by CYP2D6
TCAs – tertiary amines (e.g., amitriptyline)	UM or RM	UM	Avoid use
		NM	Consider use of alternative drug not metabolized by CYP2C19
		IM	Consider use of alternative drug not metabolized by CYP2C19
		PM	Avoid use
	NM	UM	Avoid use. If use is warranted, consider titrating to a higher target dose
		NM	Standard therapy
		IM	Consider a 25% reduction in recommended starting dose
		PM	Avoid amitriptyline use and consider a 50% dose reduction
	IM	UM	Avoid use
		NM	Standard therapy
		IM	Consider a 25% reduction in recommended starting dose
		PM	Avoid amitriptyline use and consider a 50% dose reduction
	PM	UM	Avoid use
		NM	Avoid use. If use is warranted, consider a 50% reduction of recommended starting dose
		IM	Avoid use
		PM	Avoid use

Data taken from [23,24].

IM: Intermediate metabolizer; N/A: Not applicable; NM: Normal metabolizer; PM: Poor metabolizer; RM: Rapid metabolizer; TCA: Tricyclic antidepressant; UM: Ultra-rapid metabolizer.

Table 2.

Clinical Pharmacogenetics Implementation Consortium level for opioids.

Medication	Drug class	Gene(s) involved	CPIC level [†]
Amitriptyline [‡]	TCA	<i>CYP2C19</i>	A
		<i>CYP2D6</i>	A
Celecoxib	NSAID	<i>CYP2C9</i>	B
Codeine	Weak opioid	<i>CYP2D6</i>	A
Methadone	Strong opioid	<i>CYP2B6</i>	B
Nortriptyline [‡]	TCA	<i>CYP2D6</i>	A
Oxycodone	Strong opioid	<i>CYP2D6</i>	A
Tramadol	Weak opioid SNRI	<i>CYP2D6</i>	A
Venlafaxine	SNRI	<i>CYP2D6</i>	B

[†]Level A: genetic information should be used to change prescribing of affected drug; Level B: genetic information could be used to change prescribing of the affected drug because alternative therapies/dosing are extremely likely to be as effective and as safe as nongenetically based dosing. Level C or D: there are published studies at varying levels of evidence and no prescribing actions are recommended. Additional information can be found via [22].

[‡]Evidence for other TCAs is based on amitriptyline and nortriptyline, therefore CPIC has assigned a Level B for *CYP2D6* and *CYP2C19* for tertiary amines (e.g., clomipramine) and a Level

B for *CYP2D6* and secondary amines (e.g., desipramine) [24].

CPIC: Clinical Pharmacogenetics Implementation Consortium; SNRI: Serotonin–norepinephrine reuptake inhibitor; TCA: Tricyclic antidepressant.

Table 3.CYP2D6 inhibitors [†].

Strong inhibitors	Moderate inhibitors	Weak inhibitors
Bupropion, fluoxetine, paroxetine	Cimetidine, cinacalcet, duloxetine, fluvoxamine	Amiodarone, celecoxib, cimetidine, clobazam, cobicistat, desvenlafaxine, escitalopram, labetalol, ritonavir, sertraline

[†]Strong CYP2D6 inhibitors reduce enzyme activity to the point of equivalence with poor metabolism while moderate inhibitors (e.g., duloxetine) reduce enzyme activity by approximately 50% [65].

Data taken from [69].