Research Article

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Pharmacogenomics

Opportunity for pharmacogenetics testing in patients with sickle cell anemia

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Background: Patients with sickle cell disease (SCD) are exposed to numerous drugs over their lifespan, and many of these drugs have Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for personalized dosing. The authors' aim was to ascertain the number of drugs with CPIC guidelines prescribed to SCD patients. **Materials & methods:** A search of Indiana University Health affiliated hospitals' electronic medical record identified 957 patients with a diagnosis of SCD. Drugs or drug classes with CPIC actionable guidelines ordered as inpatient and outpatient prescriptions were collected from SCD patients. **Results:** During the 16-year period, 892 (93%) patients received at least one drug that could have been dosed according to CPIC guidelines. **Conclusion:** Preemptive pharmacogenetics testing should be considered in SCD patients in order to utilize these data throughout the patient's life.

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Keywords: genomics • pharmacogenetics • precision medicine • sickle cell anemia

Personalized medicine using pharmacogenetics (PGx) is emerging as a useful tool for improving therapeutic outcomes and avoiding adverse drug reactions (ADRs) [1]. Data are emerging with PGx associations for therapeutics for patients with sickle cell disease (SCD), specifically with regard to hydroxyurea [2–4]. Although early data suggest PGx associations with hydroxyurea, these have not yet resulted in clinical guidelines for use in guided therapy. Aside from disease-modifying therapy, patients with SCD receive many drugs for supportive care to manage symptoms such as pain, anticoagulation and iron chelation. Mental health issues are also very common, with the prevalence of depression estimated to be between 25% and 40% [5,6]. The nature of SCD as a chronic disease results in high healthcare utilization and exposure to multiple drugs and drug classes over a patient's lifespan. Many of the drugs used to manage symptoms associated with SCD have Clinical Pharmacogenetics Implementation Consortium (CPIC) evidence-based guidelines when PGx is available to guide dosing [7]. The aim of this study was to ascertain the number of drugs with available CPIC guidelines prescribed to SCD patients. The authors hypothesized that patients with SCD would be prescribed numerous medications for which PGx dosing guidelines are available and the patient's age would be directly related to the number of these medications..

Materials & methods

This study was approved by Indiana University's institutional review board. To identify all patients with a diagnosis of SCD, the authors used *International Classification of Diseases, Ninth Revision* code 282.60 sickle cell anemia (prior to October 2015) and *International Classification of Diseases, Tenth Revision* code D57.1 sickle cell anemia without crisis (October 2015 to 2021) to generate a report within Indiana University Health affiliated hospitals' electronic medical record (EMR). All orders (outpatient prescriptions and inpatient orders) were included. The methods used are the same as those used in a previous study by the authors' group evaluating the opportunity of PGx to guide therapy in patients with cystic fibrosis [8]. The authors identified any drugs or drug classes with CPIC evidence for drug–gene pairs that can be used to guide therapy. Throughout this article, when the authors

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Table 1. Drug utilization.

Drug category	Patients, n (%)	Age when initiated, median (range)	Genes (drugs) with CPIC guidelines
Serotonin 5-HT_3 receptor antagonists: ondansetron†, granisetron‡, palonosetron‡, dolasetron‡	693 (72.4)	18 (0–86)	*CYP2D6* (ondansetron)
Opioids: codeine†, hydrocodone†, tramadol†, hydromorphone‡, morphine‡, oxycodone‡, fentanyl‡	814 (85.1)	14 (0–86)	*CYP2D6* (codeine, hydrocodone, tramadol)
Proton pump inhibitors: dexlansoprazole†, esomeprazole†, lansoprazole†, omeprazole†, pantoprazole†, rabeprazole†	324 (33.9)	25 (0–85)	*CYP2C19* (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole)
NSAIDs: aspirin‡, ibuprofen†, meloxicam†, naproxen‡	774 (80.9)	13 (0–85)	*CYP2C9* (ibuprofen, naproxen)
Selective serotonin reuptake inhibitors: citalopram†, escitalopram†, fluvoxamine†, paroxetine†, sertraline†	121 (12.6)	28 (8–93)	*CYP2C19* (citalopram, escitalopram, sertraline), *CYP2D6* (fluvoxamine, paroxetine)
Tricyclic antidepressants: amitriptyline†, clomipramine†, desipramine†, doxepin†, imipramine†, nortriptyline†, trimipramine†	71 (7.4)	27 (4–78)	*CYP2D6* (amitriptyline, nortriptyline, desipramine, trimipramine), *CYP2C19* (amitriptyline, clomipramine, doxepin, imipramine, trimipramine)
Anticonvulsants: carbamazepine†, oxcarbazepine†	20 (2.1)	23 (2–69)	*HLA-A* (carbamazepine), *HLA-B* (oxcarbazepine)
Allopurinol†	17 (1.8)	56 (11–74)	*HLA-B*
Clopidogrel†	25 (2.6)	65 (21–77)	*CYP2C19*
Voriconazole†	10 (1.0)	8 (1–72)	*CYP2C19*
Tacrolimus†	13 (1.4)	36 (7–71)	*CYP3A5*
Warfarin†	60 (6.3)	38.5 (3–85)	*CYP2C9*
Phenytoin†	11 (1.1)	8 (0–33)	*CYP2C9*

†Drugs with CPIC guideline recommendations for dosing adjustment based on genotype.
‡Alternative therapeutics to drugs with CPIC guidelines.
CPIC: Clinical Pharmacogenetics Implementation Consortium; Non-steroidal anti-inflammatory drugs.

refer to the number of CPIC drugs, these references are to the class of drugs, not each individual drug within a given class. Both actionable gene–drug pairs and therapeutic alternative therapies listed in CPIC guidelines were included in this analysis. For example, in cases of opioid prescribing when genotype is unknown, extensively *CYP2D6*-metabolized drugs (i.e., tramadol or codeine) are often avoided because of risk of toxicity or inefficacy and alternative drugs may be prescribed. Drugs included in analysis were serotonin 5-HT_3 receptor antagonists (ondansetron, granisetron, palonosetron, dolasetron), opioids (codeine, hydrocodone, tramadol, hydromorphone, morphine, oxycodone, fentanyl), proton pump inhibitors (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole), NSAIDs (aspirin, ibuprofen, meloxicam, naproxen), selective serotonin reuptake inhibitors (citalopram, escitalopram, fluvoxamine, paroxetine, sertraline), tricyclic antidepressants (amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, trimipramine), anticonvulsants (carbamazepine, oxcarbazepine), allopurinol, clopidogrel, voriconazole, tacrolimus, warfarin and phenytoin. The authors included data from June 2005 (when the EMR was implemented) and May 2021 (the date the data report was generated). The authors included all inpatient or outpatient drug orders from June 2005 to September 2021 within the Indiana University Health affiliated hospitals' EMR system in the analysis.

Table 1 displays drugs and drug classes. Some of the drugs included within a class do not have CPIC guidelines, but they have been included because they are therapeutic alternatives to drugs with CPIC guidelines. These PGx results could be interpreted with CPIC guidelines when deciding the most appropriate drug within a given class. This could be especially useful in pediatrics, where codeine is often avoided because of variability and risk of toxicity and inefficacy and more potent opioids are prescribed. If a patient had multiple drugs within the same drug class, the class was counted only once. As the data followed non-normal distribution, nonparametric tests were used to determine significant correlations using SAS 9.4 (SAS Institute Inc., NC, USA), and data are presented with descriptive statistics. Kruskal–Wallis test was used to determine the relationship between patient age and number of CPIC drugs received and years of EMR data, with a significance of $p = 0.05$.

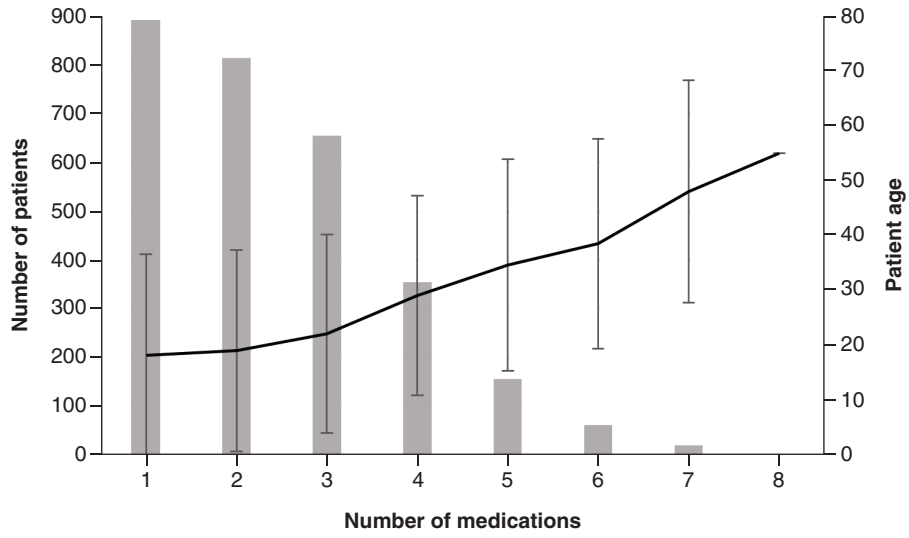

Figure 1. Drugs with Clinical Pharmacogenetics Implementation Consortium Guidelines by patient age. The x-axis shows the number of drugs with CPIC guidelines. The primary y-axis (left) shows the number of patients with grey bars and the secondary y-axis (right) displays a black line with the mean ± SD for age of patients the correspond number of CPIC medications.
CPIC: Clinical Pharmacogenetics Implementation Consortium.

Results

During the 16-year study period, the authors identified 957 patients with a diagnosis of SCD who were treated across the Indiana University Health healthcare system, ranging from birth to adulthood; however, few patients had a lifetime of data. The median duration of EMR data available in the authors' healthcare system was 5 years (range: 0–16). A total of 93% (892) of patients received at least one drug that could have been dosed based on CPIC guidelines had PGx results been available at the time of prescribing. A total of 814 (85.1%) patients received two drugs with CPIC guidelines, 654 (68.3%) received three drugs, 355 (37.1%) received four drugs, 157 (16.4%) received five drugs, 63 (6.6%) received six drugs, 21 (2.2%) received seven drugs and one (0.1%) received eight drugs. 65 (6.8%) patients received no drugs with CPIC guidelines. Patients were prescribed an average of 3.32 (± 1.37) drugs with CPIC guidelines over the course of this cohort study. The median age of patients with one or more drugs was 13 years (range: 0–86 years), median age of 14 years (range: 0–85 years) for two drugs, 18 years (range: 0–85 years) for three drugs, 25 years (range: 0–86 years) for four drugs, 28 years (range: 3–86 years) for five drugs, 32 years (range: 3–93 years) for six drugs and 42 years (range: 21–77 years) for seven drugs prescribed. Older patients had more medications with CPIC guidelines ($p < 0.001$) (Figure 1). Additionally, patients with more available EMR data had more CPIC drugs ($p < 0.01$) (Figure 2).

Opioids, which are prescribed to treat moderate to severe pain, were the most utilized drug class in the authors' SCD population, with 85% of patients receiving one or more drugs in this class. This was closely followed by NSAIDs, which are commonly used to relieve pain, decrease inflammation and reduce fevers, with 80.1% of patients receiving one or more of these medications. Opioids and NSAIDs had a median age initiation of 14 and 13 years, respectively. Serotonin 5-HT_3 antagonists were highly utilized, with over half (72.4%) of patients with SCD within Indiana University Health's healthcare system receiving one or more of these drugs to prevent nausea and vomiting. Over one-third (33.9%) of patients received proton pump inhibitors, which are commonly used in acid-related disorders and as a preventative measure against NSAID-induced ulcers. The median age of initiation of 5-HT_3 antagonists was 18 years, and proton pump inhibitors were initiated at a median age of 25 years. Selective serotonin reuptake inhibitors were less utilized (12.6%), and the median age of initiation was 28 years. Detailed utilization data by drug class are shown in Table 1.

Discussion

In this article, the authors have shown that patients with SCD have a high utilization of drugs with CPIC guidelines. Specifically, the authors' results highlight three key findings: patients with SCD received an average of three unique

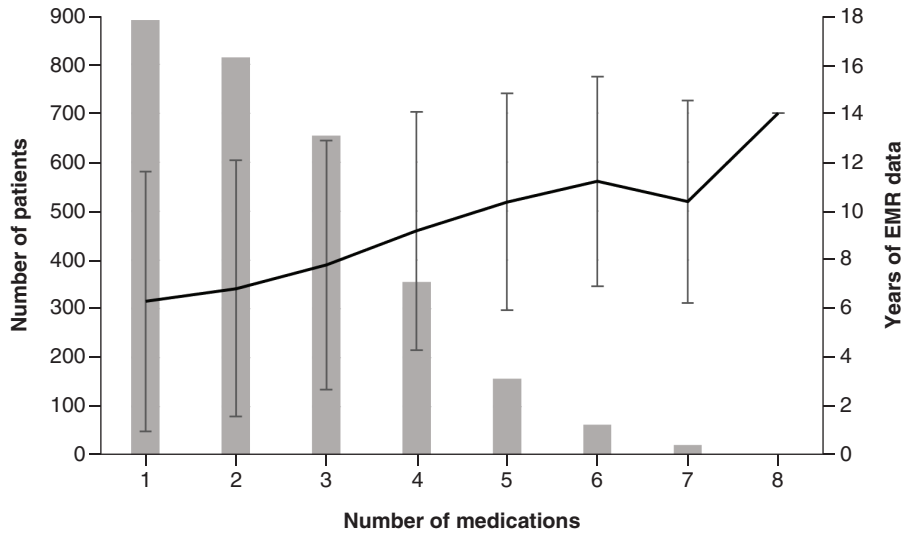

Figure 2. Drugs with Clinical Pharmacogenetics Implementation Consortium Guidelines by years of available electronic medical record data. The x-axis shows the number of drugs with CPIC guidelines. The primary y-axis (left) displays the number of patients with grey bars and the secondary y-axis (right) displays a black line with the mean ± SD for number of years of available EMR data.
CPIC: Clinical Pharmacogenetics Implementation Consortium; EMR: Electronic medical record.

CPIC drugs/drug classes per person, the most utilized drug classes by SCD patients were opioids and NSAIDs and exposure to CPIC drugs was directly related to patient age.

To the authors' knowledge, this is the first study to evaluate the overall utilization of drugs with CPIC guidelines in an SCD population. Because PGx results can be used to guide medication therapy throughout a patient's lifetime, the authors aimed to determine the potential impact of early preemptive PGx testing. Many commonly used medications can be associated with serious ADRs if they are not dosed correctly. Variations in CYP450 enzymes are common; for example, in a population with African ancestry, such as the SCD population, approximately 20% of patients will have variations in *CYP2D6*, which impacts opioid metabolism and approximately 10% of patients will have variations in *CYP2C9* that can impact NSAID dosing [7].

Patients with SCD require pain medication for acute and chronic pain related to the disease; therefore, it was expected that opioids and NSAIDs would be the most utilized drugs with CPIC guidelines in this population. Because of US FDA black box warnings and reported ADRs, codeine is often avoided in young children [9,10]. Unexpected ADRs with codeine and tramadol could be avoided with preemptive PGx testing, providing prescribers with a larger repertoire of less potent opioids for use in the management of pain in children and adolescents [11].

In consideration of the opioid crisis, prescribers have implemented prescribing protocols to minimize opioid prescribing and maximize non-opioid analgesics [12]. Introducing opioids for acute and chronic pain can lead to tolerance, escalation of doses to control pain and dependence. This trend has increased prescribing of NSAIDs, which is reflected in the authors' cohort. Although NSAIDs provide a suitable alternative and/or adjunct to opioids, they are not without risk of ADRs. Chronic use of NSAIDs can have deleterious effects on the gastrointestinal system and kidneys. Additionally, the use of NSAIDs can exacerbate underlying chronic kidney disease (CKD) and shorten the time to end-stage renal disease (ESRD) and men and women of African ancestry are 1.9-times more likely to develop ESRD compared with white women [13]. This is apparent in the SCD population (nearly all of whom have African ancestry), in whom ESRD is responsible for high morbidity and mortality [14]. Two genes, *MYH9* and *APOL1*, have been associated with the risk of ESRD in patients with African ancestry, specifically those in the SCD population [15–18]. Knowing the genetic risk of ESRD may also help guide medication therapy to avoid nephrotoxic drugs. This was illustrated in the case report of a patient with CKD who progressed with high-dose NSAIDs and was later found to be *APOL1*-positive [19].

Patients who are poor or intermediate *CPY2C9* metabolizers should be started on lower than normal starting doses of NSAIDs to avoid potential ADRs, whereas patients who are normal *CYP2C9* metabolizers may require higher doses of NSAIDs to achieve effective pain relief [20]. Inadequate antiemetic therapy can lead to ADRs of

inefficacy, causing dehydration, which may result in emergency department visits and hospitalization [21]. Although using PGx to prevent ADRs is paramount, PGx can also be used to optimize care by determining the most appropriate first-line agent for a specific patient and/or whether use of an alternative agent is warranted [22].

The authors' results show a direct relationship between patient age and number of drugs with CPIC guidelines prescribed; therefore, early pre-emptive PGx testing could result in potential cost savings by preventing ADRs throughout a patient's lifetime. By ordering a multigene PGx panel of eight to ten genes in pediatric patients with SCD, clinicians could gain valuable PGx information that could be used to guide drug selection and dosing of a variety of drugs throughout a patient's lifetime. The genes most relevant to this population are *CYP2D6*, *CYP2C19,* and *CYP2C9*. These can be used to guide dosing of opioids, NSAIDs, selective serotonin reuptake inhibitors, tricyclic antidepressants, proton pump inhibitors and serotonin 5-HT_3 receptor antagonists. Additionally, disease-specific genotypes such as *APOL1* and *MYH9* may provide valuable information for drug selection. For example, if treating a patient who is *APOL1*-positive, a poor *CYP2C9* metabolizer and a normal *CYP2D6* metabolizer, a provider may consider low-dose or no NSAIDs so as to not further increase the risk of CKD and choose tramadol or codeine for pain control. In recent years, three new SCD disease-modifying agents (L-glutamine, voxelotor and crizanlizumab) have been approved, but these drugs currently do not have CPIC PGx recommendations [23]. Although these treatments have shown benefit in SCD patients, they have not been shown to significantly alter the disease course; therefore, patients are likely to be exposed to all the supportive care medications reviewed here. To the authors' knowledge, efforts to establish pharmacogenetics testing in SCD patients have been limited. Several groups have examined genetic variability associations in patients receiving hydroxyurea [4,24,25]; however, this drug does not currently have CPIC guidelines and was not included in the present study.

Cost of PGx testing can vary depending on the laboratory. A standardized PGx panel can cost anywhere from US$200 to $2000; reimbursement and insurance coverage for PGx testing are variable based on the provider, health system and indication for the test. Although the upfront cost for PGx testing may seem high, the consequences of an ADR, such as an outpatient visit, laboratory monitoring, emergency room visit, or hospital admission for treatment, could cost substantially more [26]. Because patients with SCD can be high healthcare utilizers, PGx offers an appealing tool for minimizing healthcare costs by optimizing drug therapy and decreasing the risk of ADRs. Although the cost–effectiveness of pre-emptive PGx testing has not been studied in the SCD population, pre-emptive PGx testing has been shown to be highly cost-effective in other therapeutic disciplines [27,28]. Due to the high level of healthcare utilization and the large number of medications prescribed with PGx labeling in the FDA package insert and/or CPIC guidelines, testing the utility of pre-emptive PGx in the SCD population would be warranted. To be of most benefit, the timing of PGx testing should be considered early, such as at the time of diagnosis to decrease ADR risk and optimize drug therapies.

Although PGx results can be used to make drug and dosing decisions, it is important to acknowledge that PGx should be used in the SCD population as a tool within the context of other dosing considerations, such as weight, pharmacokinetic parameters, drug interactions and disease risk (e.g., CKD or ESRD). Genotype-guided dosing has been shown to be effective in many patient populations but has not been specifically studied and validated in an SCD population. Because of this, providers may be unfamiliar with how to use PGx results; therefore, provider education, EMR decision support, and ability for PGx consults should also be considered prior to implementing PGx as standard care in a health system [29].

This study is limited by its retrospective nature and the number of years of EMR data. Because this was a cross-sectional study over a 16-year period, the length of follow-up varied greatly among patients. Additionally, patients came in and out of the authors' system and may not have received all of their care within the one healthcare system. The authors also had multiple years of EMR data for some patients, whereas other patients had only a few encounters. However, despite being only a snapshot of the available data, the authors' study clearly showed a high utilization of medications with CPIC guideline recommendations that increased with patient age.

Conclusion

The authors' data demonstrate that patients with SCD can benefit from pre-emptive PGx testing. Pre-emptive PGx results could be useful for optimizing many drugs used as supportive care in SCD. Patients with SCD are high consumers of healthcare resources and are vulnerable to SCD-associated illnesses. Early pre-emptive PGx testing could improve efficacy and decrease ADRs in SCD patients by offering another tool to ensure that the most appropriate drugs and/or doses are chosen.

Summary points

- Sickle cell disease patients are exposed to numerous drugs with Clinical Pharmacogenetics Implementation Consortium guidelines for personalized dosing throughout their lifetime.
- A total of 957 sickle cell disease patients were identified in the authors' academic healthcare system during a 16-year period, 93% of whom received one or more drugs with Clinical Pharmacogenetics Implementation Consortium actionable guidelines.
- Pre-emptive pharmacogenetics testing in sickle cell disease patients could be beneficial for optimizing drug selection, decreasing adverse drug reactions and improving the efficacy of medications given as supportive care.

Financial & competing interests disclosure

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