Colleen Sakon   ORCID iD: 0000-0001-7795-9939
Emma Tillman   ORCID iD: 0000-0001-8019-9811
Title: Opportunity for pharmacogenomic testing in patients with cystic fibrosis

Authors: Colleen Sakon, Pharm.D.,[1] Leah A. Alicea [2], Heather Patacca [2], Cynthia D. Brown, M.D., [3] Todd C. Skaar, Ph.D.[2] Emma M. Tillman, Pharm.D., Ph.D.[2]
Affiliations:
1. Pharmacy Department, Indiana University Health, Indianapolis, IN
2. Division of Clinical Pharmacology, Indiana University School of Medicine, Indianapolis, IN
3. Division of Pulmonary and Critical Care Medicine, Indiana University School of Medicine, Indianapolis, IN

Corresponding author:
Emma M. Tillman, Pharm.D., Ph.D.,
Associate Research Professor, Division of Clinical Pharmacology
Indiana University School of Medicine
950 West Walnut Street, Room 478, Indianapolis, IN 46202
317.274.2797
emtillma@iu.edu

Abstract:

Patients with cystic fibrosis (CF) are exposed to many drugs in their lifetime and many of these drugs have Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines that are available to guide dosing. Contemporary CF treatments are targeted to specific mutations in the CF transmembrane conductance regulator (CFTR) gene, and thus, require patients to have genetic testing prior to initiation of modulator therapy. However, aside from CFTR genetic testing, pharmacogenomic testing is not standard of care for

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CF patients. The aim of this study was to determine the number of non-CFTR modulator medications with CPIC guidelines that are prescribed to patient with CF. We identified all patients with a diagnosis of CF and queried our hospital electronic medical records (EMR) for all orders, including inpatient and prescriptions, for all drugs or drug classes that have CPIC actionable guidelines for drug-gene pairs that can be used to guide therapy. We identified 576 patients with a diagnosis of CF that were treated at our institution during this 16-year period between June 2005 – May 2021. Of these patients, 504 patients (87.5%) received at least one drug that could have been dosed according to CPIC guidelines if pharmacogenomic results would have been available. Patients with CF have a high utilization of drugs with CPIC guidelines, therefore preemptive pharmacogenomic testing should be considered in CF patients at the time of CFTR genetic testing.

Introduction:

Patients with cystic fibrosis (CF) have multi-organ system sequelae and therefore are exposed to many drugs in their lifetime,[1] many of which have Clinical Pharmacogenetics Implementation Consortium (CPIC) published evidence-based guidelines for pharmacogenetics (PGx) that are available to guide dosing.[2] Contemporary CF treatments are targeted to specific mutations in the CF transmembrane conductance regulator (CFTR) gene,[3-6] therefore patients are required to have genetic testing prior to initiation of modulator therapy. The aim of this study was to determine the number of non-CFTR modulator medications with CPIC guidelines that are prescribed to patients with CF. We

hypothesized that patients with CF will be prescribed multiple medications that have PGx dosing guidelines, and the number of these medications per patient increases with age. Therefore, early preemptive PGx testing may be cost effective in optimizing therapy and preventing adverse drug reactions in patients with CF.

Methods:

After obtaining institutional review board approval, we identified all patients with a diagnosis of CF by International Classification of Diseases (ICD) 9 and 10 codes 277 and E84, respectively within our hospital electronic medical records (EMR). All orders, including outpatient prescriptions, inpatient scheduled orders, and inpatient as needed orders for these patients were searched for all drugs or drug classes that have CPIC evidence for drug-gene pairs that can be used to guide therapies. These included: opioids (codeine, hydrocodone, tramadol), non-steroidal anti-inflammatory agents (ibuprofen, meloxicam), selective-serotonin reuptake inhibitors (citalopram, escitalopram, fluvoxamine, paroxetine, sertraline), tricyclic antidepressants (amitriptyline, clomipramine, doxepin, imipramine, trimipramine), proton pump inhibitors (dexlansoprazole, lansoprazole, omeprazole, pantoprazole), warfarin, tacrolimus, and serotonin 5-HT_3 receptor antagonists (ondansetron). The EMR was implemented June 2005 and this data report was generated May 2021, so all inpatient or outpatient drug orders from June 2005 – May 2021 within our hospital EMR system were included in this analysis. Some patients had as few as 1 year of EMR data and

some patients had data for 16 years. Additionally, this included patients across the healthcare system from birth through adulthood.

Detailed drug classification and drugs can be found in Table 1. Some drugs included within a class do not have CPIC guidelines, but they have been included because they are therapeutic alternatives to drugs that do have CPIC guidelines and PGx results could be used when deciding to use those alternatively to the drugs with CPIC guidelines. This could be especially useful in pediatrics where codeine is often avoided due to variability and risk for toxicity and inefficacy, and more potent opioids are prescribed. If a patient had multiple drugs within the same drug class, it was only counted once. Data are presented with descriptive statistics and difference between groups were evaluated using Kruskal-Wallis with Bonferroni correction and an a=0.05. All descriptive statistics were calculated using Microsoft Excel and Kruskal-Wallis was performed using Statistics Kingdom.[7]

Results:

We identified 576 patients with a diagnosis of CF that were treated at our institution during this 16-year period between June 2005 – May 2021. Of these patients, 504 patients (87.5%) received at least one drug that could have been dosed according to CPIC guidelines if PGx results would have been available. The median (range) age of patients with at least one medication was 20 years-old (0 – 76) compared to 9 years-old (0 – 60) for patients without any EMR data for the CPIC drugs. Patients had a mean ± standard deviation of 3.5 ± 4.8 CPIC drugs per person with 7.1 ± 4.8 years of EMR data within our healthcare system.

Patients with more CPIC drugs were older *(p<0.01)* (Figure 1) and patients with more CPIC drugs also had more years of EMR data available *(p<0.01)* (Figure 2).

The most utilized drug class among the CF population was serotonin 5-HT_3 receptor antagonist with 73% of the patients receiving one or more of these drugs. This was closely followed by opioids which was the next most common drug class with 71% of patients receiving one or more of these medications. Both serotonin 5-HT_3 receptor antagonist and opioids had a median age of initiation of 9 years-old. Non-steroidal anti-inflammatory and proton pump inhibitors were highly utilized with over half of the CF patients at our institution receiving one or more of these drugs. The median age of initiation of non-steroidal anti-inflammatory was 11 years-old and proton pump inhibitors were initiated at a median age of 13 years. Voriconazole and tacrolimus were less utilized at 7.5% and 5% respectively, and their median ages of initiation were 28 and 29 years respectively. Complete details of utilization by drug class are shown in Table 1.

Discussion:

We report a high utilization of drugs with CPIC guidelines in patients with CF. Specifically, our results highlight three key findings: 1) CF patients received an average of 3.5 unique CPIC drugs per person, 2) serotonin 5-HT_3 receptor antagonist and opioids were the most utilized CPIC drugs, and 3) exposure to CPIC drugs increased with patient age.

To our knowledge, this is the first study to evaluate the overall utilization of drugs with CPIC guidelines in a CF population. The use of PGx to guide drug

selection for the CFTR modulator therapy,[3-5] is now widely used; however, preemptive PGx to guide supportive care medications CF patients is rare. As CFTR modulator therapy has expanded to impact 90% of all patients with CF, including children as young as 4 months, genetic testing is now recommended at the time of diagnosis of CF.[1,8] Along with that testing, PGx testing could easily be incorporated into the workflow and done for a minimal cost. The results could then be used across their lifetime to guide medication selection and dosing for the treatment of the multiple disease sequelae that affect CF patients and require drugs with CPIC guidelines.

Several of the commonly used drugs used by these patients have serious implications if they are not used optimally. Additionally, variations in CYP enzymes are not uncommon. For example, in an American or European population consistent with the genetic ancestry of a CF population, ~20-25% of patients will be CYP2C19 intermediate metabolizers, 13-30% will be rapid or ultrarapid metabolizers, and 1-2% will be poor metallizers.[2] Serotonin 5-HT$_3$ receptor antagonist and opioids were the most utilized drug classes in the population; many patients receive these drugs as children. It is possible that poor pain control from the wrong opioids can lead to the use of illicit drugs, drug addictions, and consequently further healthcare problems.[9] Inadequate antiemetic therapy can lead to dehydration, emergency department visits, and hospitalization. Voriconazole and tacrolimus were less utilized and were initiated at an older age; this reflects the disease progression and need for anti-fungal treatment and immunosuppression. Inadequate voriconazole dosing can lead to

fungal resistance and eventual fungal complications.[10] Inadequate

immunosuppression can lead to immune disorders and serious complications

with organ rejection.[11] Not only has PGx been shown to decrease risk of adverse

outcomes, implementation of PGx can optimize care by determining if first-line

agents are most appropriate in a specific patient or if an alternative agent is

warranted.[12]

Our results also showed that as patient age increases, so does utilization

of CPIC drugs and potential cost savings. This is perhaps even more important

now that CFTR modulators are extending lifespan and CF patients are living

longer yet still managing some sequelae of CF. By completing an 8-10 gene PGx

panel at the time of CFTR genotyping, clinicians could gain valuable PGx

information to guide medication selection and dosing of a variety of drugs over

their lifetime. The genes most relevant to this population would be CYP2D6,

CYP2C19, and CYP2C9 and can be used to guide dosing of opioids, non-

steroidal anti-inflammatory, selective-serotonin reuptake inhibitors, tricyclic

antidepressants, proton pump inhibitors, and serotonin 5-HT$_3$ receptor

antagonist. Depending on the testing lab, it may be more cost effective to

perform a standardized clinical PGx panel with a cost of ~$200-300.

Reimbursement and coverage for PGx testing is variable from insurance

providers and may be dependent on indication. The cost of outpatient

appointments, laboratory monitoring, emergency room visits, or hospital

admissions for an ADR can be orders of magnitude more than the cost of PGx

testing depending on the type and severity of event.[13] Because CF patients are

known to be high health care utilizers, they have many incidents that are opportunities to minimize these costs by optimizing drug therapy and minimizing potential adverse drug reactions. Also, their costs continue to increase since life expectancy is also increasing and more expensive therapeutics are utilized; these provide even more opportunities for cost saving and better health care from optimized supportive care therapies[5,14] While the cost effectiveness of preemptive PGx testing has not been studied in the CF population, preemptive PGx testing has shown to be highly cost effective in other therapeutic disciplines[15,16] Due to the high level of healthcare utilization and the large number of medications used by CF patients with PGx labeling in the FDA package insert and CPIC guidelines, testing the utility preemptive PGx in this population would be warranted. This could be done at the time of CFTR genotyping but could also be done at any time during a patient's lifetime and timed with a clinical necessary blood test. The advantage to doing PGx genotyping early is that the results can be used for their lifetime.

It is important to acknowledge that PGx can be a valuable tool to use when making dosing decisions, but this should be used within context of other dosing considerations in the CF population such as weight, pharmacokinetic parameters, and drug interactions. Although genotype guided dosing has been shown to be effective in many patient populations, it has not been specifically studied and validated in a CF population. It is possible due to CF specific pharmacokinetic parameters or effects of acute inflammation on CYP enzymes that applying PGx recommendations in CF patients may be different than in a

general population.[17] Provider education, EMR decision support, and ability for specialized PGx consults should also be considered prior to implementing PGx.[18]

Due to the retrospective nature of this report, a limitation of our study is the number of years of EMR data. Since it was a cross sectional study over a 16-year period, the length of follow up was not the same for all patients. Also, the EMR in place has been used at this site for only 16 years and patients may not spend their entire lives within one healthcare system; thus, for some patients we have multiple years of EMR data, while others have only a few encounters. However, even though this is a snapshot of the available data, it still showed a high utilization of drugs with CPIC guideline recommendations that increased with age.

In conclusion, our data illustrates that the CF patients could likely benefit from preemptive PGx testing. The results would likely be useful to optimize their supportive care drugs. Since these patients utilize large amounts of health care resources, and they are vulnerable to CF associated illnesses, the PGx testing could likely help maximize the efficacy and decreased adverse events in many patients by ensuring that the most appropriate drugs and doses are chosen. Thus, PGx testing could reasonably be considered to benefit many patients and the health care systems if it was done at the time of CFTR genotyping.

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Table 1: Drug Utilization

Drug Category	Number of Patients (n, %)	Age when initiated (median, range)
Serotonin 5-HT$_3$ receptor antagonist Ondansetron*, granisetron, dolasetron, palonosetron)	421 (73)	9 (0 – 76)
Opioids Buprenorphine, codeine*, fentanyl, hydrocodone*, hydromorphone, morphine, naltrexone, oxycodone, tramadol*	411 (71)	9 (0 – 72)
Proton pump inhibitors Dexlansoprazole*, esomeprazole, lansoprazole*, omeprazole*, pantoprazole*, rabeprazole	372 (64.5)	13 (0 – 76)
Non-steroidal anti-inflammatory Aspirin, ibuprofen*, meloxicam*, naproxen	334 (58)	11 (0 – 72)
Selective serotonin reuptake inhibitor Citalopram*, escitalopram*, fluvoxamine*, paroxetine*, sertraline*	127 (22)	21 (6 – 62)
Voriconazole*	43 (7.5)	28 (8 – 53)
Tacrolimus*	30 (5.2)	29 (5 – 53)

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Tricyclic antidepressants Amitriptyline*, clomipramine*, desipramine, doxepin*, imipramine*, nortriptyline, trimipramine*	24 (4.2)	24.5 (7 – 45)
Warfarin*	12 (2.1)	30 (19 – 72)
Anticonvulsants Phenytoin*, fosphenytoin*, carbamazepine*, oxcarbazepine*	9 (1.6)	26 (1 – 44)
Allopurinol*	7 (1.2)	40 (28 – 43)
Clopidogrel*	2 (<1)	38 (34 – 42)

* Drugs with CPIC guidelines recommendation for dosing adjustment based on

genotype.

Figure legend:
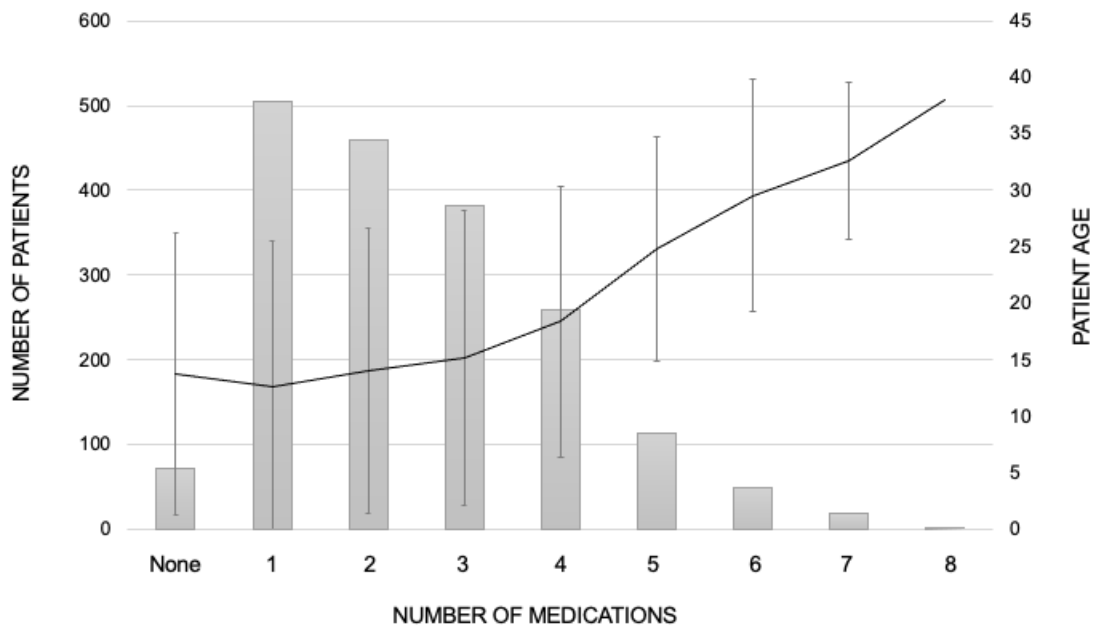
Figure 1: Medications with CPIC Guidelines by patient age. The x-axis

displays the number of medications with CPIC guidelines. The primary y-axis

(left) displays the number of patients shown 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.
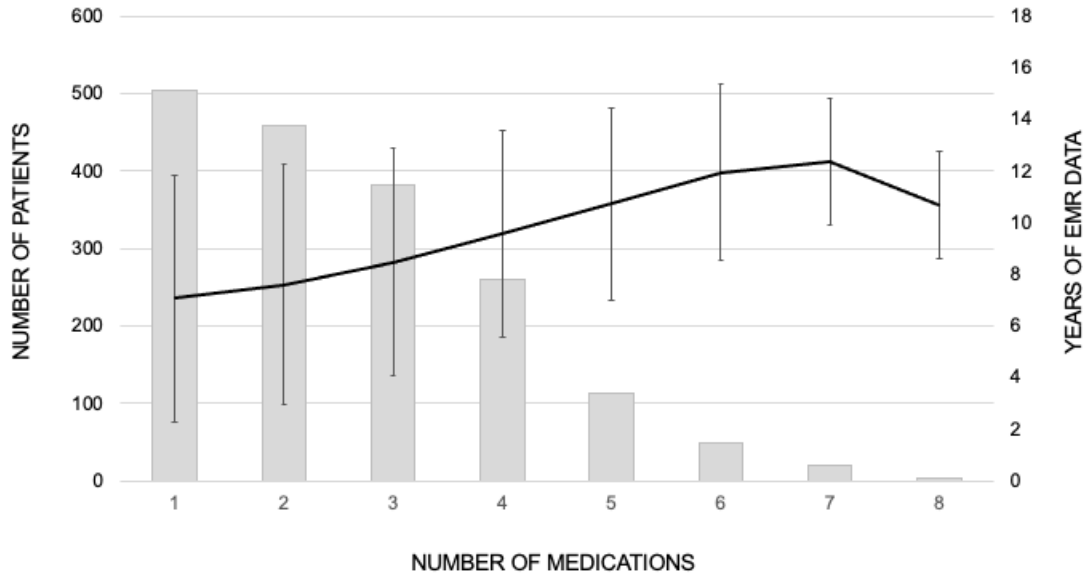
Figure 2: Medications with CPIC Guidelines by years of available EMR data.

The x-axis displays the number of medications with CPIC guidelines. The primary y-axis (left) displays the number of patients shown 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.