Implementation of *CYP2C19* genotyping to guide proton pump inhibitor use at an academic health center

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Purpose: To describe the implementation of *CYP2C19* testing into clinical practice at University of Florida (UF) Health Gainesville hospital to guide proton pump inhibitor (PPI) dosing and the lessons learned from this experience.

Summary: Different *CYP2C19* genotypes are associated with variability in PPI plasma concentrations and intragastric pH, which may contribute to the risk of treatment failure due to subtherapeutic concentrations and adverse effects (eg, infection, bone fracture, renal dysfunction) with sustained supratherapeutic concentrations. Based on evidence available prior to the availability of pertinent Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines, the UF Health Precision Medicine Program (PMP) developed clinical recommendations, provided through automated alerts at the time of a PPI order, to (1) increase the PPI dose for individuals with genotypes linked to increased CYP2C19 enzyme activity (ie, rapid and ultrarapid metabolizers) to improve the likelihood of drug effectiveness and (2) decrease the dose for individuals with decreased CYP2C19 activity (ie, intermediate and poor metabolizers) to reduce the risk of harm. The *CYP2C19*-PPI implementation was an iterative process that taught us key implementation lessons. Most notably, physician engagement is essential, problem lists in the medical record are unreliable, and special populations (eg, pediatric patients) need to be considered.

Conclusion: Guiding PPI prescribing based on *CYP2C19* genotype is a practical approach to potentially improve the benefit-risk ratio with PPI therapy. Physician engagement is key for successful implementation. A CPIC guideline on *CYP2C19* genotype–guided PPI dosing is now available, and automated alerts may be instituted to facilitate implementation.

Keywords: clinical decision support, CYP2C19, pharmacogenetics, proton pump inhibitor

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Proton pump inhibitors (PPIs) are commonly prescribed for the treatment of gastroesophageal reflux disease (GERD), duodenal and gastric ulcers, and other gastrointestinal-related disorders. Reports of associations between PPI use and increased risks of bone fracture, renal disease, and infections, particularly with prolonged use, have emerged in recent years and have raised safety concerns about PPIs.[1-3] There are also reports of poor therapeutic response to PPIs, especially in the treatment of *Helicobacter pylori* infection and refractory GERD.[4,5] The gene encoding cytochrome P450 (CYP) isozyme 2C19, which metabolizes PPIs, is highly polymorphic. *CYP2C19* genotype is associated with variability in PPI plasma concentrations and pharmacodynamics parameters (eg, intragastric pH), which may contribute to the risks of treatment failure and PPI-related adverse effects.[6-8] Herein we describe the implementation of *CYP2C19* testing into clinical practice at University of Florida (UF) Health, Gainesville to guide PPI dosing to improve the likelihood of treatment success

and reduce the risk of adverse sequelae, especially with long-term use, and the lessons learned from this experience.

Initial implementation of *CYP2C19* testing to guide PPI dosing

UF Health precision medicine program. The UF Health precision medicine program (PMP) was established in 2011 as part of the UF Clinical and Translational Sciences Institute. The multidisciplinary PMP team is led by clinical pharmacists and includes physicians, clinical pathologists, informaticians, and genetics experts (Figure 1). With implementation of each gene-drug pair, including *CYP2C19* and PPIs, the UF Health PMP follows several key best practices, including the requirement of strong evidence for genetic associations with drug response, the testing for genetic variants recognized as essential across ancestry groups, and the entry of pharmacogenetic results into the electronic health record (EHR) as discrete data to allow for building clinical decision support (CDS).[9]

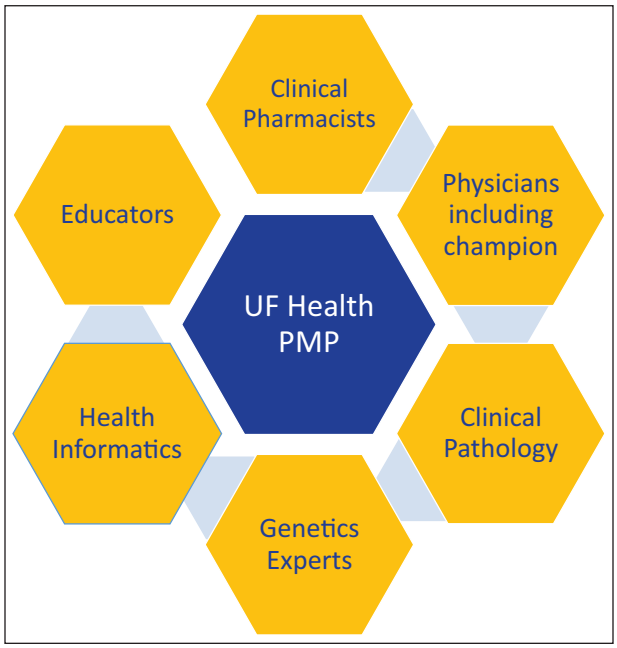
***CYP2C19* testing.** The majority of genotyping at UF Health is performed by UF Health pathology laboratories and ordered reactively. The UF Health PMP ensures the internal genotyping platform(s) includes tests for key genetic variants. Specifically, we require that tier 1, or "must test," single nucleotide polymorphisms (SNPs), as defined by the Association for Molecular Pathology (AMP), are included.[9,10] Tier 1 variants include those with known functional effects that are common in at least one population and for which reference material is available. For *CYP2C19*, AMP recommends designation of the *CYP2C19*2, *3,* and **17* alleles as tier 1 SNPs, whereby *CYP2C19**2 and *3 are no-function alleles and *CYP2C19**17 confers increased function. Our platform includes these alleles in addition to *CYP2C19*4, *6,* and **8* (no-function alleles) and *CYP2C19*10* (a decreased-function allele), which are tier 2 variants that are rare but meet other tier 1 criteria. *CYP2C19* testing is offered as both a single-gene test and as a part of a multigene panel, both performed with polymerase chain reaction (PCR) assays (TaqMan; Applied Biosciences). Currently, genotype and phenotype are both reported as discrete variables in the EHR. Phenotypes are derived from genotype combinations (eg, ultrarapid metabolizer [UM] is associated with the *CYP2C19* allele combination **17/*17*), consistent with Clinical Pharmacogenetics Implementation Consortium (CPIC) guidance.[11]

Within UF Health, clinical *CYP2C19* testing was initially launched in 2012 to

KEY POINTS

- Implementation of *CYP2C19* testing to guide proton pump inhibitor (PPI) dosing can be successful at an academic health center.
- Physician engagement is essential for pharmacogenetics implementations, and the selected physician champions should practice in the specialty area where the implementation will occur.
- Automatic clinical decision support alerts can support pharmacogenetics implementations and are a clear and timely mechanism to provide prescribers with pharmacogenetic recommendations.

Figure 1. UF Health precision medicine program (PMP) team.



guide antiplatelet prescribing decisions for patients undergoing percutaneous coronary intervention.[12] In 2016, inquiries from gastroenterologists regarding *CYP2C19* genotyping in the setting of PPI prescribing prompted program leaders to establish the infrastructure to provide clinical pharmacist support for *CYP2C19* testing to guide PPI dosing at UF Health Gainesville.

Evidence for *CYP2C19* allele impact on PPI response. The PMP evidence analysis process involves a review of existing pharmacogenetic and disease-specific guidelines, Food and Drug Administration (FDA) labeling and online recommendations (ie, Table of Pharmacogenetic Associations[13]), and an extensive review of the literature. The literature review includes an initial manual literature search and ongoing automated literature identification. A shared National Center for Biotechnology Information (NCBI) account was created to set up alerts for several PubMed search strings (eg, "omeprazole AND CYP2C19 AND pharmacogenetics"). Alert results are monitored by the PMP and subsequently evaluated as needed. At the time of our initial implementation, clinical pharmacogenetic guidelines from CPIC, which provide recommendations for how to integrate genotype results into prescribing recommendations, did not exist. Dutch Pharmacogenetics Working Group (DPWG) guidance existed for certain PPIs (ie, esomeprazole, lansoprazole, omeprazole, and pantoprazole), but the DPWG guidance pertained only to UMs, with a recommendation to increase the dose by 50% to 400%, depending on the medication.[14] FDA-approved product labeling stated that PPIs are CYP2C19 substrates and that pharmacokinetic changes have been observed with variations in CYP2C19, but the labeling provided no prescribing recommendations. FDA has since posted its Table of Pharmacogenetic Associations (first available in 2020), which lists gene-drug pairs for which there is sufficient evidence to suggest that patients with high-risk phenotypes are likely to have differential therapeutic effects.[13] The current table only provides PPI therapeutic recommendations for pantoprazole dosage reduction among children with the poor metabolizer (PM) phenotype. Clinical practice guidelines for GERD did not mention *CYP2C19* until 2022 and still do not include specific recommendations.[15,16] Notably, a lack of published guideline recommendations does not indicate a lack of clinical evidence supporting genotype-guided therapy. For example, CPIC prioritizes writing guidelines for gene-drug pairs based on several criteria (eg, prescribing actionability, clinical consequences, medication[s] usage).[17] At the time of the initial implementation at UF Health Gainesville, PPIs were assigned to CPIC level B, indicating that there was evidence to make at least one optional prescribing recommendation.[18]

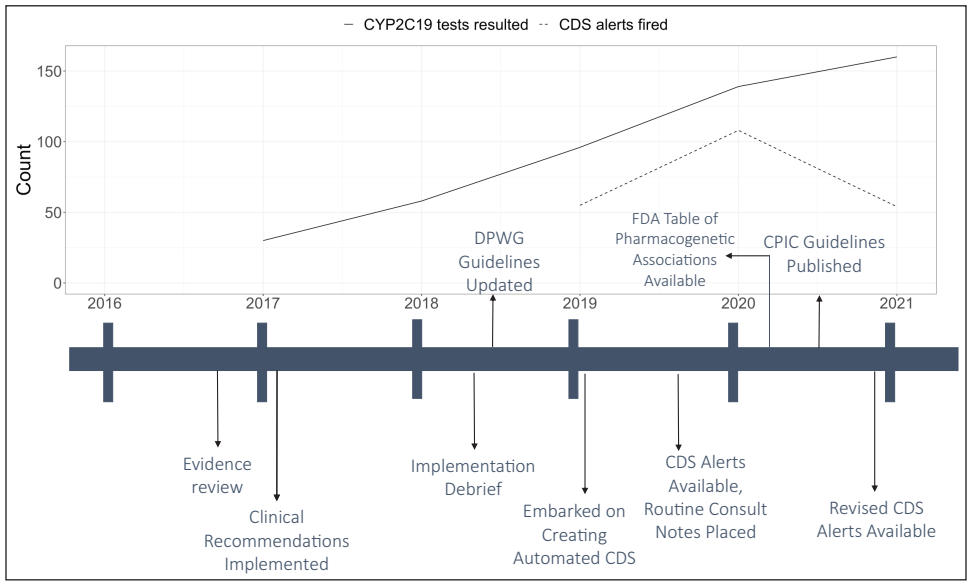
To develop clinical recommendations for *CYP2C19*-guided PPI therapy, we performed a comprehensive literature review. Once draft clinical recommendations were developed, they were presented to the clinical pharmacists within the UF Health PMP and gastroenterologist physician champions. While clinicians in other disciplines prescribe PPIs, our gastroenterologists were highly motivated to use pharmacogenetics and served as our physician champions for this implementation. The evidence review included analysis and synthesis of all published evidence of *CYP2C19* genotype and phenotype associations with PPI pharmacokinetics, pharmacodynamics, and clinical effects and was presented in combination with institution-specific metrics, such as prevalence of PPI use, population ancestries, frequency of specific diagnoses and procedures, and specialty settings in which PPIs were most commonly prescribed.

The evidence review demonstrated a large body of evidence linking *CYP2C19* genotype with variability in PPI pharmacokinetics and pharmacodynamics, most notably with regard to first-generation PPIs.[19] *CYP2C19* genotype was also associated with variability in therapeutic effectiveness, particularly with regard to eradication of *H. pylori* infection and healing rates for erosive esophagitis, whereby CYP2C19 phenotypes associated with increased PPI exposure were associated with improved treatment responses.[19-21] At that time, emerging evidence also suggested PPI exposure was associated with adverse events.[22,23] Ahead of the CPIC guidelines, Lima et al[24] published clinical recommendations for PPI dosage adjustment in children. Based on available literature, clinical recommendations were developed, as follows: (1) In CYP2C19 rapid metabolizers (RMs) and UMs, clinicians should increase the PPI dose by 50% to 100% to optimize effectiveness; and (2) in CYP2C19 intermediate metabolizers (IMs) and PMs, clinicians should decrease the dose by 50% to avoid adverse effects. In-person grand rounds education was conducted, and a 1-page quick reference sheet was disseminated to gastroenterologists both electronically and in person to supplement oral presentations.[9] Pharmacists were available to answer questions or place patient-specific consult notes with genotype-guided recommendations upon request. Prescribers preferred to not have automated alerts within the medical record at that time. The initial PPI implementation launched in early 2017 (Figure 2).

In October 2018, an implementation debriefing was conducted with prescribers. This one-time debriefing session was led by a PMP pharmacist and conducted to learn about challenges encountered directly from prescribers. At that time, gastroenterologists expressed that having more clinical support to help guide PPI prescribing based on *CYP2C19* genotype would be helpful.[25] Specifically, they requested that clinical recommendations on exactly what to do with *CYP2C19* results when prescribing PPIs be readily available.

CDS alerts. As a result of this feedback, the UF Health PMP determined that automatic CDS alerts would be most appropriate. The automated alerts

Figure 2. Timeline of implementation of *CYP2C19* testing to guide proton pump inhibitor use and number of clinical *CYP2C19* tests ordered by gastroenterologists that resulted at UF Health Gainesville. CDS indicates clinical decision support; CPIC, Clinical Pharmacogenetics Implementation Consortium; DPWG, Dutch Pharmacogenetics Working Group.



provided recommendations when a PPI order was placed if the patient had an actionable *CYP2C19* genotype result available in the EHR. UF Health utilizes an Epic EHR system (Epic Systems Corporation, Verona, WI) in which alerts for pharmacogenetic implementations range from real-time active CDS alerts (eg, disruptive pop-up alerts) or passive alerts (eg, background alerts) to static clinical consultation notes available within the chart and/or delivered to clinicians upon return of a *CYP2C19* genotype result (Figure 3).[26] In addition to real-time active alerts, static recommendations were placed via a consultation note in the medical record that could be accessed prior to prescribing of a PPI.

In early 2019, the PMP embarked on creating automated CDS for PPIs. As the CPIC guidelines were not yet published and evidence on adverse effects was less robust for IMs and PMs (as compared to the evidence on therapeutic failure in RMs and UMs), the PMP opted to pursue alerts only for the RM and UM phenotypes. The clinical recommendations were consistent with those set in place at the time of the initial implementation, as there was no compelling new evidence that warranted a change. The automated CDS alerts recommended that clinicians "consider increasing the PPI dose by 1.5-2 times the recommended starting dose, as clinically appropriate" in CYP2C19 RMs and UMs. The proposed tool was a disruptive pop-up alert triggered by any PPI prescription for a patient with available test results indicating the CYP2C19 UM or RM phenotype. The CDS language and recommendations were endorsed by the gastroenterology service, then presented to the UF Health CDS governance committee. This committee oversees and approves all CDS for the health system and is made up of the chief medical informatics officer and clinical informatics, pharmacy informatics, and nursing informatics personnel. Given that hospitalized patients commonly receive PPI therapy for short-term prophylaxis indications, the CDS governance committee raised concerns of the potential for alert fatigue if the automated CDS alert were implemented across the institution. Ultimately, the alert was approved exclusively for use in outpatient settings. Use of the alert can be reviewed in the future for an expansion to inpatient settings.

Once the automated CDS language and parameters were approved, the PMP's informatics pharmacist was able to build the alert. During the build, however, it was identified that the standard clinical action button embedded in all other pharmacogenetics alerts (eg, "avoid medication, choose alternative therapy") would not be adequate for dose adjustment recommendations required for PPI automatic CDS. Although it was not an ideal solution, we opted to have no direct link to the order to adjust the dose within the alert. Instead, the alert would recommend the appropriate dose adjustment, and upon clinician acknowledgment, the clinician was then brought to the dose adjustment screen where they could implement the recommendation, if applicable.

The alert moved into production in July of 2019, and CDS monitoring was initiated for the alert. Quality assurance through alert monitoring included evaluating the frequency of alert firing on a monthly basis and subsequently using Epic Clinical Validation (a validated Epic tool that allows for testing and validation without impacting patient care) on an ad hoc basis to test the alert on test patients. At unspecified

Figure 3. Example of a consult note written for a gastroenterologist upon ordering of *CYP2C19* testing.

Pharmacogenetics Consultation
UF Health Precision Medicine Program

Subjective/Objective

HPI: Jane Doe is a 77 y.o. female with a PMH significant for GERD with esophageal stricture who was last seen by Med GI on XX/XX/XX and reported inadequate relief with her current PPI regimen of omeprazole 20 mg daily. She is scheduled for an EGD on XX/XX/XX to evaluate for eosinophilic esophagitis.

CYP2C19 testing was ordered outpatient to guide current PPI therapy.

Assessment/Plan

Pharmacogenetic Test Results and Interpretation:
*CYP2C19 *17 / *17* (Ultrarapid metabolizer (UM) phenotype; increased CYP2C19 activity) This genotype is associated with decreased PPI levels and increased risk of pharmacotherapy failure.

Recommendation:
1. **Increase omeprazole frequency to 20 mg by mouth twice daily**
2. **Alternatively, switch omeprazole to rabeprazole 20 mg by mouth once daily**

Reference: Lima JJ, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C19 and Proton Pump Inhibitor Dosing. *Clin Pharmacol Ther*. 2021 Jun;109(6):1417-1423.

Potential implications for future medications affected by CYP2C19:

Indication	Relevant Medications	CYP2C19 UM Phenotype Interpretation	Recommendation(s)
GERD/ *H. Pylori*/ Ulcers	PPIs Dexlansoprazole Lansoprazole Omeprazole Pantoprazole Possibly Esomeprazole	Increased risk of treatment failure.	Increase the PPI dose by 2 times the standard dose.
Depression/ Anxiety	SSRIs Escitalopram Citalopram Sertraline	Increased risk of treatment failure.	Avoid escitalopram, citalopram, and potentially sertraline; AND Consider non-CYP2C19 SSRI (i.e., paroxetine, fluoxetine, or fluvoxamine) as an alternative; OR Consider non-SSRI antidepressant (e.g., duloxetine, bupropion, venlafaxine).
Fungal Infection	Voriconazole	Increased risk of subtherapeutic concentrations and treatment failure in TREATMENT of invasive fungal infections.	Choose alternative agent that is not dependent on CYP2C19 metabolism (e.g., isavuconazole, liposomal amphotericin B, and posaconazole). Please contact Infectious Diseases, Bone Marrow Transplant, or Antimicrobial Stewardship Program (258-5944) for recommendations and/or approval of other antifungal therapy not affected by CYP2C19.
Cardiology	Clopidogrel	Higher platelet inhibition, though an association with increased risk of bleeding following PCI has not been observed.	Use standard dose of clopidogrel.

These recommendations are based upon current guidelines by the Clinical Pharmacogenetics Implementation Consortium (CPIC), which can be found at cpicpgx.org/guidelines.

For questions regarding these results, please contact the UF Health Precision Medicine Program:
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time points, responses to alerts and recommendation acceptance frequencies were also monitored. Overall, the alert fired a total of 160 times from July 2019 to December 2020.

Post–CPIC guideline changes to *CYP2C19*-PPI implementation

In September 2020, CPIC published guidelines for PPIs.[19] CPIC guidelines and recommendations were developed by clinicians and researchers with expertise on the subject matter, including several members of the UF team given their experience with the initial implementation. A rigorous review of the literature was completed as a part of the writing process, with the evidence of *CYP2C19* allele associations with each PPI phenotype rated as strong, moderate, or weak.[27] These ratings served as the basis for the strength of CPIC recommendations.

In addition to the evidence review steps previously mentioned, when CPIC guidelines are available prior to implementation at UF Health Gainesville, the evidence review process includes evaluation of the recommendations proposed by CPIC and an overview of the accompanying supplemental literature to perform an internal appraisal of the data. In addition, we perform a supplementary literature search to screen for additional publications since the last CPIC review. In the case of the *CYP2C19*-PPI pair, for which CPIC guidelines became available after implementation, the UF Health PMP completed an internal assessment to see if clinical recommendations and automated CDS needed to be updated. Revisions for PPI automated CDS were deemed necessary once evaluated by the pharmacists within the PMP (Table 1).[19] Specifically, esomeprazole and rabeprazole were removed from the trigger criteria, as they were assigned to CPIC level C (ie, no recommendation because of inconsistent associations between *CYP2C19* and pharmacokinetics or therapeutic response).[19] In addition, the single alert for the RM and UM phenotypes was split into 2 alerts. For the UM alert, the dose increase recommendation was maintained but changed to specify an increase from 1.5 to 2 times the standard dose to 2 times the standard dose. The alert for RMs still recommended a 1.5- to 2-fold dose increase but clarified the recommendation applied only in treatment of *H. pylori* infection or erosive esophagitis. It was also decided to create alerts for the normal metabolizer (NM), IM, and PM phenotypes. This was the first time an alert for an NM phenotype was considered within the UF Health Gainesville system, which warranted special consideration to prevent alert fatigue and obtain approval from the CDS governance committee. Given the indication-specific recommendation by CPIC for NMs and RMs (ie, increase the PPI dose to 1.5 to 2 times the standard dose when treating *H. pylori* infection or erosive esophagitis), we explored the feasibility of incorporating those indications into the trigger criteria. Ideally, we wanted the alert to fire only if either indication was present on the patient's problem list.

Due to the complexity of the alerts and potential changes, we consulted with the gastroenterology service for feedback. First, we inquired if prescribers would be comfortable having an alert fire for NMs, who make up approximately 50% of the patient population. The gastroenterologists indicated that they would be comfortable with this alert but clinicians in other specialties might not be. Next, we inquired about the reliability of documenting *H. pylori* infection and erosive esophagitis in the problem list within the EHR. The gastroenterologists reported that because those indications were not documented consistently or reliably and patient problem lists were not systematically updated, an alert for NMs could lead to inappropriate indication-specific CDS alerts or the absence of appropriate alerts; for example, an alert suggesting PPI dose increases could be fired if a patient had a history of erosive esophagitis but was currently in remission, or an alert might not fire if a patient had active erosive esophagitis if the problem list contained incorrect or missing information. Lastly, we obtained clinician preferences on use of disruptive versus passive alerts to provide CDS information.

Although NM status and RM status prompt the same indication-specific clinical recommendation, based on clinician preferences it was decided to create an active nondisruptive (background) alert for NMs that only fired for gastroenterology prescribers. The alert was designated as active (as opposed to passive) because an acknowledgment reason was required. The PMP requires the selection of an acknowledgment for all automated CDS alerts, as evaluating the clinician's rationale is a part of the PMPs quality assurance plan for CDS monitoring. Filtering posttest CDS drug-gene alerts by provider type represents one approach to overcome limitations surrounding the problem list and helps decrease the overall quantity of CDS alerts by displaying indication-specific information to the correct provider. The alert for RMs remained an active disruptive alert, with language added to indicate that it was reasonable to increase the PPI dose in the context of nonresponse based on the clinical experience and preference of the gastroenterology prescriber.

The IM/PM recommendations were specific to prolonged PPI therapy (ie, use for greater than 12 weeks) and specified that at the 12-week time point a 50% dose reduction can be considered. Three options for IM/PM alerts were presented to gastroenterology prescribers: (1) active disruptive alerts for all PPI prescriptions, (2) active nondisruptive alerts for all PPI prescriptions, and (3) 2 "checkpoint" alerts, with a nondisruptive alert with the first PPI prescription followed by a disruptive alert if the prescription remained active for more than 12 weeks. The gastroenterologists unanimously favored the third option (Table 1). Like problem lists, medication lists suffer from inconsistencies, and firing a CDS alert solely on the basis of a PPI appearing on the medication list might have led to alert fatigue. Since the outcome-related

Table 1. Automatic Clinical Decision Support Alerts for Proton Pump Inhibitors Built at University of Florida Health

Alert	Type of alert	Triggers	Recommendations[a]	Lesson learned
CYP2C19 UM Single alert	Active disruptive (pop-up) alert	Outpatient provider orders certain PPI medications[b]	Consider increasing PPI dose by 2 times the standard dose as clinically appropriate	Limiting use of alert to outpatient settings can decrease potential for alert fatigue in the inpatient setting, where patients typically receive PPIs for short-term prophylaxis indications
CYP2C19 RM Single alert	Active disruptive (pop-up) alert	Outpatient provider orders certain[a] PPI medications	•For *H. pylori* infection or erosive esophagitis, consider increasing PPI dose to 1.5 to 2 times the standard daily dose •For all others, monitor patients for inadequate response; reasonable to increase daily dose as clinically appropriate	
CYP2C19 NM Single alert	Active background alert	Outpatient gastroenterology clinic provider orders certain PPI medications[b]	If patient has active *H. pylori* infection or erosive esophagitis, consider increasing PPI dose to 1.5 to 2 times the standard dose	Limiting to gastroenterology locations can decrease likelihood of providers seeing an inappropriate recommendation, as they are unlikely to be using PPIs for *H. pylori* infection or erosive esophagitis
CYP2C19 IM/PM Sequential alerts	Alert 1: active background alert	Outpatient gastroenterology clinic provider orders certain PPI medications[b]	For prolonged therapy (ie, >12 weeks), consider 50% dose reduction once symptoms are controlled	Gastroenterologists value this information up front
	Alert 2: active disruptive (pop-up) alert	Outpatient gastroenterology clinic provider opens patient profile after 12 weeks of PPI use, and PPI order is still active	For prolonged therapy (ie, >12 weeks), consider 50% dose reduction once symptoms are controlled	More attention is given to a disruptive alert, and creating a sequential alert makes the message more meaningful, as it is more likely the patient is truly on prolonged PPI therapy

Abbreviations: IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; PPI, proton pump inhibitor; RM, rapid metabolizer; UM, ultrarapid metabolizer.
[a]Patient problem statements accompany all recommendations to provide context.
[b]Omeprazole, pantoprazole, lansoprazole, and dexlansoprazole. Prior to CPIC guidelines, esomeprazole and rabeprazole were also included as trigger medications.

evidence for CYP2C19 IM or PM status and adverse effects with long-term PPI usage was determined to be weaker than other evidence, and since such adverse effects occurred primarily in the pediatric setting, this alert was limited to gastroenterology adult patients and pediatric clinics.[22,28,29]

The alerts were modified as described and then brought to the UF Health PMP for final approval before going to the CDS governance committee, which subsequently approved the alerts. These alerts went live in December 2020, and 57 alerts fired through December 2021. Education was provided around the go-live date, including a remote presentation, educational pamphlets with examples, and designation of a point person in the PMP who could answer questions as they arose.

Lessons learned

The *CYP2C19*-PPI implementation at UF Health Gainesville was ultimately an iterative and multidisciplinary process. Although strategies changed over time, this process was typical of real-world pharmacogenetic implementations, given that evidence continually evolves. Although the *CYP2C19*-PPI implementation was the sixth gene-drug implementation at UF Health Gainesville, we still learned key lessons, which are described below.

Integrating CDS into the EHR is a key part of implementation. Shortly after the initial implementation, it became clear to both prescribers and the PMP that CDS was necessary to facilitate medication change. In order for a clinical recommendation to be utilized, it needs to be presented at an appropriate time.[30] After implementing CDS, clinical orders for *CYP2C19* testing by gastroenterologists increased steadily (Figure 2). CDS also serves as a reoccurring educational tool, and it appears that gastroenterologists became comfortable adjusting PPI dosages based on *CYP2C19* results and guidance within the alert without the need to consult our PMP team. Indeed, during the 2019-2022 period, we began placing routine consult notes for all of our pharmacogenetic implementations. The consult notes were specific to the authorizing prescriber's specialty (eg, a gastroenterologist received a note specific to PPI) and designed per the provider's preference (Figure 3). The PMP pharmacists received alerts when pharmacogenetic test results were returned, and these alerts served as notification to place a consult note, which was typically posted in the EHR within 48 hours. However, by 2022 we observed that genotype-guided changes to PPI dosing were occurring before the consult note was placed.

The format of CDS with dose adjustment recommendations placed responsibility for implementing the recommendation on the prescriber, but a written recommendation was no longer available in the EHR. When prescribing a PPI, the prescriber selected the drug, which prompted the alert. After reading the alert, the prescriber had to decide to act upon it by selecting an appropriate acknowledgment reason (eg, will adjust dose, patient stable on current regimen, dose already adjusted, disagree with recommendation, other) and was then brought to the screen for dose selection, where they could implement the CDS recommendation. (These alerts were provided in an Epic system without the Epic genomics module. It is possible that there are more optimal solutions that can be implemented elsewhere and in the future with the genomics module.) While this put more responsibility on the prescriber, the gastroenterologists expressed preference for this alert format and the acknowledgment reasons provided. Further evaluation to assess the success of this type of alert is warranted.

Indication-specific alerts were not feasible to implement in the existing EHR system because the problem list was not reliable and accurate. While it makes sense to integrate indications into alert trigger criteria, especially for PPI recommendations that are based on the presence of *H. pylori* infection or erosive esophagitis, it is not feasible in clinical practice. Our solution was to limit the alert to the gastroenterology setting. Our implementation highlighted the importance of including physician champions. Through this collaboration, we discovered that the problem lists of patients with *H. pylori* infection and/or erosive esophagitis were generally unreliable.

Provider engagement is essential to designing clinical recommendations and CDS. Engaging with providers is critical to create clinically meaningful recommendations. Gastroenterologists were able to inform us of their typical workflow so we could ensure the alerts were being created in a meaningful way. Preferences regarding alert language are also important, as providers need to interpret the recommendations correctly.

Because *CYP2C19*-PPI clinical recommendations apply to both adults and pediatric patients, alerts were implemented for both populations within the gastroenterology setting. The pediatric population comes with its own considerations in terms of *CYP2C19* genotyping. Specifically, CYP2C19 expression is not fully developed at birth, and an infant has about 20% to 30% of the expression of an adult.[31] A linear increase in expression occurs up to about 5 months of age, at which time infants have a variable increase in expression to about 10 years of age.[31,32] At 10 years of age, CYP2C19 expression is that of an adult, but genotype-phenotype concordance is seen much earlier and reported to occur by 15 weeks after birth.[31-33] We opted to implement the same recommendations as those for the adult population and included the possibility of genotype-phenotype discordance in pediatric patients younger than 10 years of age in our education. When implementing pharmacogenetics in pediatrics, it is important to provide recommendations relevant to the age group, acknowledge the limitations of pharmacogenetics, and discuss when the providers can expect to use pharmacogenetics to help guide therapy.

While phenoconversion (a change in clinical phenotype secondary to drug-gene interaction) is more established with CYP2D6, coadministration of PPIs with strong CYP2C19 inhibitors (ie, fluvoxamine, fluconazole, and fluoxetine) may cause markedly increased PPI plasma concentrations in non-PMs. Alternatively, strong CYP2C19 inducers (ie, rifampin and St. John's wort) can lead to decreased systemic exposure and treatment failure.[19,34] As with problem lists, medication lists are sometimes not reliable in our health system and therefore should not be used to integrate drug interactions into automated CDS. However, potential phenoconversion can be discussed in pharmacogenetic consult notes within the EHR. More evidence is needed to recommend avoiding CYP2C19 inhibitors and inducers when a PPI is prescribed, but potential phenoconversion is something that we can make prescribers aware of so, for example, they can monitor for ineffectiveness when an inducer is prescribed.

Conclusion

Implementation of *CYP2C19*-PPI pharmacogenetic guidance is a clinically relevant implementation for health systems; all phenotypes are actionable, PPI utilization is common, CPIC guidelines are available, and there is robust evidence that prescribing based on *CYP2C19* genotype may improve the benefit-risk ratio with PPI therapy. Key factors for success are engaging with physician champions during the entire implementation process and implementing the alerts in a way that will be most useful while minimizing alert fatigue. We believe we implemented a successful approach to *CYP2C19*-guided PPI dosing, but a formal evaluation is warranted.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Disclosures

The authors have declared no potential conflicts of interest.

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