ARTICLE

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Clinical impact of preemptive pharmacogenomic testing on antiplatelet therapy in a real-world setting

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CYP2C19 genotyping to guide antiplatelet therapy after patients develop acute coronary syndromes (ACS) or require percutaneous coronary interventions (PCIs) reduces the likelihood of major adverse cardiovascular events (MACE). Evidence about the impact of preemptive testing, where genotyping occurs while patients are healthy, is lacking. In patients initiating antiplatelet therapy for ACS or PCI, we compared medical records data from 67 patients who received *CYP2C19* genotyping preemptively (results >7 days before need), against medical records data from 67 propensity score-matched patients who received early genotyping (results within 7 days of need). We also examined data from 140 patients who received late genotyping (results >7 days after need). We compared the impact of genotyping approaches on medication selections, specialty visits, MACE and bleeding events over 1 year. Patients with *CYP2C19* loss-of-function alleles were less likely to be initiated on clopidogrel if they received preemptive rather than early or late genotyping (18.2%, 66.7%, and 73.2% respectively, $p = 0.001$). No differences were observed by genotyping approach in the number of specialty visits or likelihood of MACE or bleeding events (all $p > 0.21$). Preemptive genotyping had a strong impact on initial antiplatelet selection and a comparable impact on patient outcomes and healthcare utilization, compared to genotyping ordered after a need for antiplatelet therapy had been identified.

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INTRODUCTION

Pharmacogenomic (PGx) testing is transforming the use of $P2Y_{12}$ inhibitors, a class of antiplatelet medications used for the treatment of acute coronary syndromes (ACS), neurovascular indications, and vascular disorders [1–3]. The most commonly ordered $P2Y_{12}$ inhibitor is clopidogrel [4], a prodrug that undergoes conversion to an active metabolite via multiple pathways, of which the cytochrome P450 2C19 enzyme is dominant. In individuals with loss-of-function (LOF) alleles in the *CYP2C19* gene that codes for the enzyme, the efficacy of clopidogrel is reduced [5–9], which increases risks for major adverse cardiovascular events (MACE) in certain patients [10, 11]. Genotyping of *CYP2C19* can identify patients with LOF alleles who will benefit from switching from clopidogrel to ticagrelor or prasugrel, $P2Y_{12}$ inhibitors which do not require activation via the *CYP2C19* pathway [12, 13]. A recent meta-analysis of clinical trials in patients with ACS concluded that *CYP2C19*-guided $P2Y_{12}$ inhibitor selection provided a better balance of efficacy and bleeding events compared to use of any single $P2Y_{12}$ inhibitor [14]. The United States Food and Drug Administration has developed a black boxed warning for clopidogrel regarding the association between *CYP2C19* poor metabolizer (PM) phenotypes (two LOF alleles) and diminished antiplatelet activity [15]. Similarly, the Clinical Pharmacogenetics Implementation Consortium (CPIC) published "strong" recommendations for alternative therapy over clopidogrel, if no contraindications present, for individuals utilizing antiplatelet therapy for ACS or percutaneous coronary intervention (PCI) who have either 1 or 2 LOF *CYP2C19* alleles [1].

Notably, most of the evidence to date about the benefits and risks of *CYP2C19* genotyping to inform antiplatelet medication management has been derived from studies where genotyping is ordered after a need for $P2Y_{12}$ inhibitor therapy has been identified. The successes of reactive genotype-guided therapy have raised excitement about preemptive PGx testing, where patients' genetic profiles are characterized prior to a medication need, thereby avoiding potentially devastating delays waiting for test results [16–18]. An increasing number of pharmacy programs and health systems have developed medication management systems that integrate PGx profiles into patients' medical records and utilize this genetic data to identify drug-gene interactions at the time of medication ordering [19–23]. These systems have been applied to support PGx panel testing, where numerous PGx genes,

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including *CYP2C19*, are profiled simultaneously in anticipation of future needs [18, 24]. Early data are favorable about its impact. Recently, an analysis across multiple European countries compared preemptive PGx testing to usual care in patients receiving a new medication with PGx guidance available. Participants were followed for a 12-week period with occurrence of adverse events within this time frame being recorded. PGx guided care was shown to reduce occurrence of adverse events by 30% with clopidogrel being the second most prescribed medication with PGx guidance in this cohort [25].

Comparisons against universal reactive PGx testing were not conducted, however, and questions remain about whether preemptive strategies outperform reactive strategies where healthcare providers and patients may be better prepared to respond to test findings [26].

The objective of this study is to compare medication selections and health outcomes following preemptive PGx testing and *CYP2C19* genotyping ordered after a need for $P2Y_{12}$ inhibitor therapy was identified. The real-world data summarized here provides novel evidence to inform policymakers and health systems about the benefits and risks of preemptive PGx testing.

MATERIALS AND METHODS

A retrospective cohort study was conducted of patients with *CYP2C19* results who received $P2Y_{12}$ inhibitor therapy following ACS or PCI at Sanford Health, a single healthcare system primarily spanning the states of South Dakota, North Dakota, Minnesota and Iowa in the United States. Sanford Imagenetics is Sanford Health's genetic medicine initiative [27, 28]. Data was extracted from the electronic medical record (EMR) during the time period of January 2018 to September 2021.The research protocol was approved by the Sanford Health Institutional Review Board (STUDY #00001862) and informed consent was not required.

Overview of PGx testing for antiplatelet therapy at Sanford Health

Single gene *CYP2C19* testing was first implemented within Sanford Health in 2014 in effort to guide antiplatelet therapy [28]. *CYP2C19* testing was conducted by the Sanford Medical Genetics Laboratory using various molecular diagnostic assays over the years to identify eight alleles (*2, *3, *4, *5, *6, *7, *8, and *17). Turnaround times for reactive *CYP2C19* testing, when testing is ordered to inform an immediate need for antiplatelet therapy, average 4.1 days [29]. Discrete results are available within the EMR to generate automated clinical decision support (CDS) to further guide clinicians' prescribing [27]. An alert is triggered upon ordering of clopidogrel for those that would be impacted by their genetic results, either *CYP2C19* intermediate metabolizer (IM) or PM status. In 2017, the ability to order single-gene *CYP2C19* was placed on select cardiac catheterization order sets utilized by interventional cardiologists in the setting of PCI. Preemptive testing called the Sanford Chip which included PGx testing and medically actionable disease predispositions was implemented in 2018, as another aspect to Sanford Health's genetic medicine initiative [28].

Study population

Patients were included in analyses if they had a new antiplatelet agent order within the Sanford Health system following ACS or PCI between January 2018 and September 2020, received PGx testing at any time, and had been invited to participate in the Sanford Chip program [28]. Antiplatelet agents of interest were clopidogrel, ticagrelor, and prasugrel. New antiplatelet agent orders were defined as instances where the medication start date was (a) at least 1 year after the end date of any prior $P2Y_{12}$ inhibitor orders, and (b) at least 2 years after the start date for any prior $P2Y_{12}$ inhibitor orders. These criteria were utilized to prevent classification of antiplatelet refills as new starts.

Classification of indications and PGx testing

PCIs were identified based on stent placement that occurred within 3 days of initiation of antiplatelet therapy. Patients were classified as receiving antiplatelet therapy for ACS when relevant diagnoses were identified in patient problem lists no more than 3 days prior to antiplatelet therapy initiation (Supplementary Table 1). Index dates represent the date that stents were placed or the date of ACS.

The PGx testing approach was defined as preemptive, early genotyping, or late genotyping depending on the amount of time between the index date and the availability of PGx results. PGx testing approach was classified as preemptive when PGx test results were available at least 8 days prior to the index date, early genotyping when PGx test results were available within 7 days of the index date, and late genotyping if PGx test results were available at least 8 days after the index date. Patients with PGx results within 7 days of the index date were classified as early genotyping. The majority of patients in this group had likely received reactive PGx testing, where *CYP2C19* genotyping is ordered as soon as a need for antiplatelet therapy is identified, given that the expected test turnaround time at Sanford Health is 5–7 days. Patients in the early genotyping group who received PGx results before and after the index date were combined for analyses because only three patients had received PGx results 7 days or less before the index date. The late genotyping testing group was included to provide insight about medication selections and patient outcomes in patients who initiate antiplatelet therapy without consideration of potential drug-gene interactions.

Patient characteristics and outcomes

The primary outcome was the initial $P2Y_{12}$ selections and whether they were consistent with patients' *CYP2C19* genotypes per CPIC guidelines. Secondary outcomes included escalation and de-escalation of antiplatelet therapy after it had been initiated and healthcare visits that may be associated with management of cardiovascular care or related adverse patient outcomes (i.e., visits to cardiology, neurology, or emergency departments). Exploratory outcomes included MACE, including myocardial infarctions (MI), stent thromboses or re-thromboses, strokes, transient ischemic attacks, or deaths from any cause; and bleeding events, including intracranial bleeding and gastrointestinal bleeding.

Data were collected through 1 year after the index date. Medication data were abstracted from the EMR, and included order dates, start dates, and end dates for loading and maintenance doses of selected $P2Y_{12}$ inhibitors, interacting medications that increase bleeding risks when taken concurrently with $P2Y_{12}$ inhibitors (Supplementary Table 2), and aspirin. Data represent signed medication orders/prescriptions within the EMR. MACE and bleeding events were identified with International Classification of Disease-10th edition codes, laboratory values within the EMR (Supplementary Tables 3, 4), and by examining changes to hematocrit and hemoglobin scores using thrombolysis in MI criteria [30]. All outcomes were manually reviewed to minimize duplicative reporting. All-cause mortality was identified from EMR records from inpatient deaths or external sources (staff searching obituaries or family notifying the healthcare team). Additional data elements were collected from the EMR and validated through manual review by a member of the Sanford Imagenetics PGx team.

Data analyses

We used R version 4.3.2 to analyze data. Given that the risk for MACE is highest closest to the date of an ACS or PCI, analyses included data from all patients regardless of the amount of time they received antiplatelet therapy. Analyses that examined changes in antiplatelet therapy over time, patient outcomes, and the likelihood of clinical visits used logistic regression to compare whether likelihoods of choices or events varied between the preemptive and early genotyping PGx testing strategies. Analyses that examined initial $P2Y_{12}$ inhibitor selections included an additional term for interaction between genotype and PGx testing strategy. Propensity score matching was used to address confounding and selection bias in comparisons of the preemptive and early genotyping PGx testing groups. The variables we used for matching were characteristics where differences between the preemptive and early genotyping PGx testing strategies were observed at $p < 0.05$: setting of $P2Y_{12}$ inhibitor initiation (inpatient vs outpatient), indication for antiplatelet therapy, date of antiplatelet agent start, number of medications being taken at antiplatelet agent start, prior diagnosis of a stroke or transient ischemic attacks, prior PCI, and use of interacting medications that increase risks for bleeding events. Cluster-robust variance was used to estimate standard errors in statistical models. All patients who received late genotyping PGx testing were included in descriptive summaries of outcomes to contextualize findings of analyses of the preemptive and early genotyping PGx testing groups. Statistical comparisons of these patients were not conducted, however, due to likely differences on unobserved factors such

Table 1. Characteristics of analyzed patients, by pharmacogenomic testing strategy.

	Preemptive ($n = 67$)	Early genotyping ($n = 67$)	Late genotyping ($n = 140$)
Mean Age	67.1 (9.7)	66.8 (10.9)	63.3 (11.4)
Legal Sex			
Female	16 (23.9%)	26 (38.8%)	42 (30.0%)
Male	51 (76.1%)	41 (61.2%)	98 (70.0%)
Self-Identified Race: White	65 (97.0%)	67 (100.0%)	135 (96.4%)
Average Body Mass Index (kg/m^2)	31.7	31.6	31.2
Tobacco Use			
Current smoker	6 (9.0%)	10 (14.9%)	10 (7.1%)
Former smoker	25 (37.3%)	24 (35.8%)	69 (49.3%)
Nonsmoker	35 (52.2%)	30 (44.8%)	57 (40.7%)
Undocumented smoking status	1 (1.5%)	3 (4.5%)	4 (2.9%)
Comorbidities			
Diabetes	20 (29.9%)	25 (37.3%)	33 (23.6%)
Hyperlipidemia	41 (61.2%)	38 (56.7%)	64 (45.7%)
Hypertension	39 (58.2%)	51 (76.1%)	76 (54.3%)
Stroke	10 (14.9%)	8 (11.9%)	12 (8.6%)
Transient ischemic attack	4 (6.0%)	4 (6.0%)	2 (1.4%)
Myocardial infarction (MI)	17 (25.4%)	19 (28.4%)	40 (28.6%)
Peripheral artery disease	6 (9%)	4 (6.0%)	5 (3.6%)
Previous percutaneous coronary intervention (PCI)	10 (14.9%)	8 (11.9%)	17 (12.1%)
Previous coronary artery bypass graft (CABG)	0 (0%)	2 (3.0%)	3 (2.1%)
Setting			
Inpatient	63 (94.0%)	65 (97.0%)	122 (87.1%)
Outpatient	4 (6.0%)	2 (3.0%)	18 (12.9%)
Antiplatelet Indication			
Percutaneous intervention (PCI)	54 (80.6%)	57 (85.1%)	82 (58.6%)
Acute coronary syndrome (ACS)	33 (49.3%)	36 (53.7%)	103 (73.6%)
Year Antiplatelet Agent Was Ordered			
2018	6 (9.0%)	5 (7.5%)	73 (52.1%)
2019	31 (46.3%)	34 (50.7%)	49 (35.0%)
2020	30 (44.8%)	28 (41.8%)	18 (12.9%)
Year Genotyped			
Before 2018	14 (20.9%)	0 (0.0%)	0 (0.0%)
2018	17 (25.4%)	5 (7.5%)	24 (17.1%)
2019	30 (44.8%)	33 (49.3%)	51 (36.4%)
2020	6 (9.0%)	29 (43.3%)	49 (35.0%)
2021	0 (0.0%)	0 (0.0%)	16 (11.4%)
CYP2C19 Phenotype			
Poor Metabolizer	3 (4.5%)	1 (1.5%)	6 (4.3%)
Intermediate Metabolizer	19 (28.4%)	17 (25.4%)	35 (25.0%)
Normal Metabolizer	21 (31.3%)	27 (40.3%)	55 (39.3%)
Rapid Metabolizer	19 (28.4%)	20 (29.9%)	38 (27.1%)
Ultra-rapid Metabolizer	5 (7.5%)	2 (3.0%)	6 (4.3%)
Mean Length of Med List (SD)	15.6 (7.9)	16.9 (9.5)	12.6 (8.0)
Taking Interacting Medications at Time of Order			
Increases bleeding risks	52 (77.6%)	57 (85.1%)	100 (71.4%)
Aspirin	57 (85.1%)	61 (91.0%)	126 (90%)

Data represent patient characteristics at the time the $P2Y_{12}$ inhibitor was initiated. Patients in the early genotyping pharmacogenomic testing cohort were propensity-score matched to patients in the preemptive pharmacogenomic testing cohort using near-neighbor approaches. Patients in the late genotyping pharmacogenomic testing cohort were all patients whose *CYP2C19* genotypes were available at least 8 days after initiation of a $P2Y_{12}$ inhibitor.

as the ordering of PGx testing because initial antiplatelet agent selections were ineffective or because patients had experienced bleeding events.

Analyses of high-dose clopidogrel orders, defined as maintenance doses of 150 mg/day or higher, were considered but omitted from analyses because only three patients were initiated on such doses. Results were reported if differences were observed at $p < 0.05$. To provide insight about potential effects of censoring for loss to follow-up due to patients receiving care at other health systems, we repeated analyses on only patients who had evidence of engagement with Sanford Health beyond 11 months of the index date. Given the high percentage of patients with evidence of continuing care in the Sanford Health system (92.2%) and no differences in findings, these analyses are omitted from the manuscript.

RESULTS

Data were analyzed from 274 patients, including 67 of 694 classified as receiving early genotyping testing who were propensity-score matched to 67 patients classified as receiving preemptive PGx testing, and 140 patients classified as receiving late genotyping testing (Supplementary Table 5). Characteristics of patients included in statistical analyses are summarized in Table 1.

Table 2. $P2Y_{12}$ inhibitor initiated, stratified by metabolizer phenotype and pharmacogenomic testing approach.

	Preemptive ($n = 67$)	Early genotyping ($n = 67$)	Late genotyping ($n = 140$)
Poor or Intermediate Metabolizer			
Clopidogrel	4 (18.2%)	12 (66.7%)	30 (73.2%)
Ticagrelor	18 (81.8%)	6 (33.3%)	10 (24.4%)
Prasugrel	0 (0.0%)	0 (0.0%)	1 (2.4%)
Normal Metabolizer			
Clopidogrel	17 (81.0%)	20 (74.1%)	34 (61.8%)
Ticagrelor	4 (19.0%)	7 (25.9%)	18 (32.7%)
Prasugrel	0 (0.0%)	0 (0.0%)	3 (5.5%)
Rapid or Ultra-Rapid Metabolizer			
Clopidogrel	18 (75.0%)	16 (72.7%)	28 (63.6%)
Ticagrelor	6 (25.0%)	6 (27.3%)	15 (34.1%)
Prasugrel	0 (0.0%)	0 (0.0%)	1 (2.3%)

Data summarize the number and percentage of patients initiated on each $P2Y_{12}$ inhibitor.

Before propensity-score matching, patients in the early genotyping testing group were more likely than patients in the preemptive testing group to initiate antiplatelet therapy during inpatient care and in response to a PCI, and more likely to have been taking interacting medications at time of the antiplatelet agent order that increased bleeding risks. They were also less likely to have had prior diagnoses of strokes and transient ischemic attacks, less likely to have had a prior PCI, and had been taking fewer medications. Differences identified before matching were more balanced between patients receiving preemptive and early genotyping testing after matching (Supplementary Table 6). Differences between patients receiving late genotyping testing and patients who received preemptive or early genotyping testing were observed on age, date of antiplatelet agent order, prior diagnoses of hypertension, number of concurrent medications, and indication for antiplatelet therapy (Table 1). On average, analyzed patients classified as receiving preemptive PGx testing had results available 398 days (sd = 418 days) prior to initiation on a $P2Y_{12}$ inhibitor, while patients classified as receiving early and late genotyping PGx testing had results available an average of 4 (sd = 2 days) and 288 days (sd = 306 days), respectively, after initiation on a $P2Y_{12}$ inhibitor. Analyzed patients in the preemptive and early genotyping PGx testing groups received antiplatelet therapy for 509 days on average, with no difference by PGx testing approach ($p = 0.20$). Patients in the late genotyping PGx testing group received antiplatelet therapy for 682 days on average.

Analyses showed that initial $P2Y_{12}$ inhibitor selections for patients with ACS or PCI differed by PGx testing approaches and *CYP2C19* phenotype. Patients with PM or IM phenotypes were less likely to be initiated on clopidogrel when they received preemptive PGx testing (18.2% initiated on clopidogrel) than when they received early genotyping PGx testing (66.7%; $p = 0.001$ for interaction between agent and PGx testing approach; Table 2). However, 9 of 12 patients (75.0%) with PM or IM phenotypes who were initiated on clopidogrel and received early genotyping PGx testing received an order for an alternative $P2Y_{12}$ inhibitor within 10 days, and 11 of these patients (91.7%) had received an order for alternative $P2Y_{12}$ inhibitor within 60 days (Fig. 1a). In the late genotyping PGx testing group, 30 of 41 patients with PM or IM phenotypes (73.2%) were initiated on clopidogrel, and only 7 of these patients (23.3%) had received an order for alternative $P2Y_{12}$ inhibitor within 60 days. No differences were observed between PGx testing groups when considering de-escalation of $P2Y_{12}$ inhibitor therapy among patients initiated on ticagrelor or prasugrel (Fig. 1b).

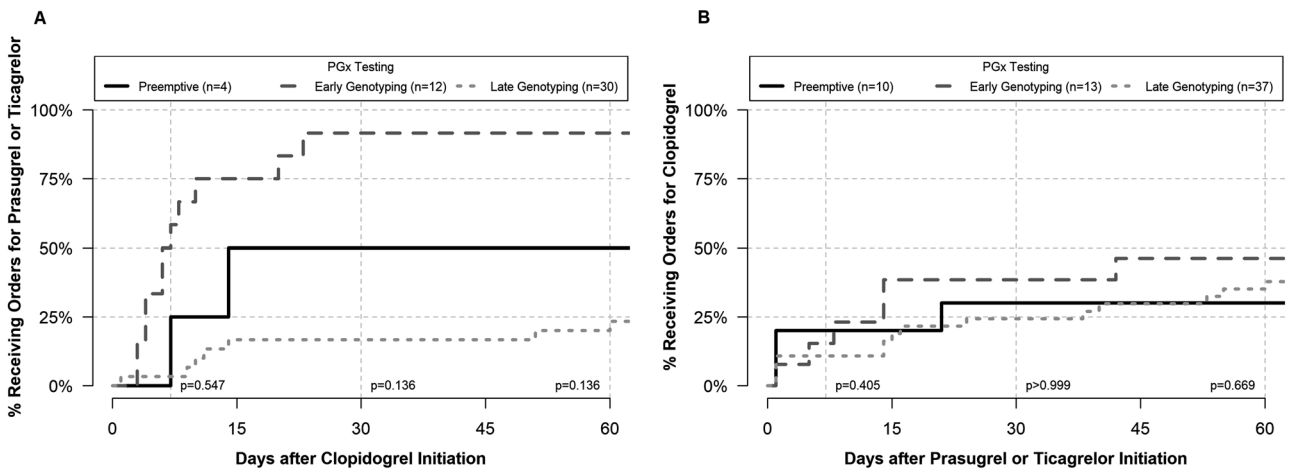

Fig. 1 Escalation and de-escalation of antiplatelet therapy. Lines represent the percentage of patients, stratified by pharmacogenetic testing approach, who initiated $P2Y_{12}$ inhibitor therapy in response to acute coronary syndrome or percutaneous coronary intervention (**A**) with poor or intermediate metabolizer phenotypes who were initiated on clopidogrel and received orders for ticagrelor or prasugrel and (**B**) with normal, rapid, or ultra-rapid metabolizer phenotypes who were initiated on ticagrelor or prasugrel and received orders for clopidogrel.

Table 3. Specific major adverse cardiovascular events (MACE) and bleeding events.

	Preemptive ($n = 67$)	Early genotyping ($n = 67$)	Late genotyping ($n = 140$)	p
14 Days After Index Date				
Death	1 (1.5%)	0 (0.0%)	0 (0.0%)	>0.999
Myocardial Infarction	2 (3.0%)	5 (7.5%)	6 (4.3%)	0.441
Stroke or Transient Ischemic Attack	0 (0.0%)	1 (1.5%)	1 (0.7%)	>0.999
Intracranial Bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	>0.999
Gastrointestinal Bleeding	1 (1.5%)	0 (0.0%)	3 (2.1%)	>0.999
30 Days After Index Date				
Death	1 (1.5%)	0 (0.0%)	0 (0.0%)	>0.999
Myocardial Infarction	2 (3.0%)	5 (7.5%)	7 (5.0%)	0.441
Stroke or Transient Ischemic Attack	0 (0.0%)	1 (1.5%)	1 (0.7%)	>0.999
Intracranial Bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	>0.999
Gastrointestinal Bleeding	1 (1.5%)	0 (0.0%)	3 (2.1%)	>0.999
1 Year After Index Date				
Death	1 (1.5%)	0 (0.0%)	0 (0.0%)	>0.999
Myocardial Infarction	3 (4.5%)	5 (7.5%)	10 (7.1%)	0.718
Stroke or Transient Ischemic Attack	0 (0.0%)	1 (1.5%)	2 (1.4%)	>0.999
Intracranial Bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	>0.999
Gastrointestinal Bleeding	6 (9.0%)	2 (3.0%)	5 (3.6%)	0.274

This table summarizes the cumulative number and percentage of patients experiencing any cause death, myocardial infarction, stroke or transient ischemic attack, intracranial bleeding, or gastrointestinal bleeding, stratified by pharmacogenomic testing strategy and time point. P-values represent comparisons between patients who received preemptive and early genotyping PGx testing.

Analyses of healthcare utilization showed no differences by PGx testing approach in the mean number of cardiology, neurology, or emergency department visits in the year following the index date (all $p > 0.30$; Supplementary Fig. 1 and Supplementary Table 7), nor likelihood of having a clinical encounter in any of those departments.

Among patients who initiated $P2Y_{12}$ inhibitor therapy in response to ACS or PCI, no differences were observed in the cumulative incidence of MACE when comparing preemptive and early genotyping PGx testing groups at 2 weeks and 30 days after the index date (4.4% vs 9.0% at both time points, respectively, $p = 0.27$), or 1 year after the index date (6.0% vs 9.0%, respectively, $p = 0.48$; Supplementary Fig. 2a and Supplementary Table 8). Analyses of propensity-score matched patients showed that the cumulative incidence of bleeding events also did not differ when the PGx testing approach was preemptive rather than early genotyping at 14 days or 30 days after the index date, (1.5% vs 0.0% at both time points, respectively, $p = 0.996$; Supplementary Fig. 2b), or 1 year after the index date (10.4% vs 4.5%, $p = 0.22$), although logistic regression models that included all patients suggested lower risks for bleeding at 14 days and 1 year after the index date among patients receiving early genotyping (Supplementary Table 9). Patient characteristics at the time of a bleed are summarized in Supplementary Table 10. Specific MACE and bleeding outcomes are summarized in Table 3. In the late genotyping PGx testing group, MACE were observed in 5.0%, 5.7%, and 8.6% of patients at 14 days, 30 days, and 1 year after the index date, respectively; and bleeding events were observed in 2.1%, 2.1%, and 3.6% of patients at 14 days, 30 days, and 1 year after the index date, respectively. Sub-analyses of patients with IM or PM phenotypes were consistent with analyses across phenotypes (Fig. 2).

DISCUSSION

In this study, we compared the impact of preemptive and likely reactive *CYP2C19* genotyping on $P2Y_{12}$ inhibitor selections, patient outcomes, and healthcare utilization in high-risk patients to provide insight about how preemptive PGx testing affects medication orders, healthcare utilization, and patient outcomes, compared to reactive PGx testing. Results provide mixed evidence about the benefits and challenges of preemptive PGx testing. Our study shows that initial $P2Y_{12}$ inhibitor selections were far more likely to be concordant with CPIC recommendations when patients received preemptive testing compared to early genotyping. However, providers quickly changed patients' $P2Y_{12}$ inhibitor orders from clopidogrel to ticagrelor or prasugrel when early genotyping PGx testing revealed that patients had *CYP2C19* IM or PM phenotypes. No differences were observed in the number or likelihood of healthcare visits in comparisons of preemptive and early genotyping. Lower risks of MACE and higher risks of bleeding events in patients who received preemptive rather than early genotyping PGx testing were not statistically significant in analyses of propensity score-matched patients.

The comparable effects of preemptive and early genotyping testing on the likelihood of MACE are encouraging given the robust support for both approaches at Sanford Health. Between 2017 and 2019, the health system mandated genomics education for all physicians and advanced practice providers [31]. Unlike many clinical programs, PGx testing in the Sanford Health system included a proactive review of results against patients' medication lists by a pharmacist with PGx expertize who alerted providers about active drug-gene interactions [27]. Automated CDS alerted providers about drug-gene interactions at the time of clopidogrel orders and allowed providers to easily order alternative medications (Supplementary Fig. 3) [19, 27]. Furthermore, genetic specialists were strategically placed system-wide to support healthcare providers [32]. These reasons may explain why the frequency of antiplatelet therapy escalation in patients identified as IM or PM during early genotyping testing was higher in our study than others [33]. It is possible that MACE frequencies did not differ among patients receiving preemptive and early genotyping testing in our study because providers were especially responsive to early genotyping.

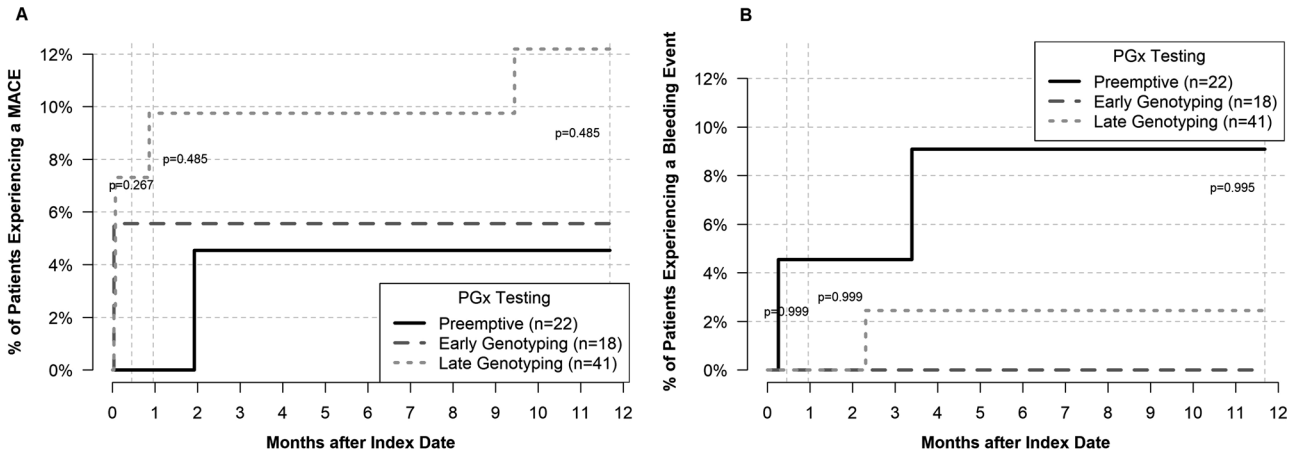

Fig. 2 Cumulative incidence of major adverse cardiovascular events and bleeding events in patients with *CYP2C19* loss of function alleles. Lines represent the percentage of patients whose $P2Y_{12}$ inhibitor therapy initiation was in response to ACS or PCI, stratified by PGx testing approach, who experienced (**A**) a major adverse cardiovascular event (MACE) or (**B**) bleeding in the 12 months after the index date for $P2Y_{12}$ inhibitor therapy initiation.

Our data also show that providers are less likely to use PGx test results to de-escalate antiplatelet therapy when patients were identified as having *CYP2C19* normal, rapid, or ultra-rapid metabolizer phenotypes. This finding may simply reflect providers' or patients' preferences about the balance of benefits to risks and costs of ticagrelor and/or prasugrel. The higher rates of escalation compared to de-escalation may also be influenced by the design of CDS alerts, which only trigger for drug-gene interactions when clopidogrel is ordered for patients with *CYP2C19* IM or PM phenotypes. While continuation of ticagrelor or prasugrel can maximize patient outcomes, some analyses suggest that de-escalation after an initial 30-day period may be a more cost-effective approach to patient care, given the high costs of those medications [6]. Importantly, patients and providers often favor clopidogrel therapy due to its once-daily dosing, generic formulation availability/cost, tolerability, and safety profile [34–36].

The strong response of providers to early genotyping PGx test results raises questions about whether expectations that preemptive PGx testing would improve patient outcomes are realistic. Ticagrelor and prasugrel, often preferred over the use of clopidogrel in the management of non-ST-elevation ACS and ST-elevation MI [37], were initiated on about 30% of patients in our early and late genotyping cohorts, regardless of genotype. In addition, early genotyping PGx testing results may have unexpected benefits by necessitating ongoing engagement between patients and clinical teams. However, preemptive testing may provide additional benefits such as time savings and resource allocations. Preemptive testing can enhance clinician workflow and minimize redundancy with regard to antiplatelet prescribing (i.e., escalation or de-escalation based on genetic results). Although the relative influence of genetics on patient response to clopidogrel is unknown, between 5% and 80% of variability in drug response is thought to be attributable to non-genetic factors [38, 39]. Patients with ACS and PCI may benefit from engagement that may be facilitated through discussion of results from PGx testing. We found that patients who were taking medications which increase the risk of bleeding concomitantly with $P2Y_{12}$ inhibitors had lower frequencies of bleeding events. This counterintuitive finding may suggest that those high-risk patients were being managed more carefully over time. Assuming providers act on reactive PGx test results in a timely manner, the argument for preemptive PGx testing may simply be that panel testing is a more efficient strategy for ensuring PGx information is considered in medication decision-making, an argument supported by model-based analyses of PGx testing in patients initiating statin therapy [40].

The higher frequency of bleeding in patients who received preemptive testing, although not statistically significant, merits some caution. Prasugrel and ticagrelor have higher bleeding risks compared to clopidogrel. Meta analyses show trends towards greater bleeding risks in patients who receive genotype-guided therapy compared to clopidogrel therapy, although the analyses also show trends towards lower bleeding risks of genotype-guided therapy compared to prasugrel and ticagrelor [14, 34, 35]. It is notable that among patients who are *CYP2C19* IM or PM, higher frequencies of bleeding events were observed immediately among patients receiving preemptive testing compared to early genotyping, likely reflecting how patients were initiated on prasugrel or ticagrelor sooner. The reason the frequency of bleeding events among patients receiving preemptive PGx testing continued to rise among patients with other metabolizer phenotypes is unclear, but may raise questions about how antiplatelet therapy is managed in the time frame after immediate risks for MACE are navigated.

Strengths of this study include it being one of the first studies to examine the impact of preemptive PGx testing on patient outcomes. Real world data were collected from a health system where panel PGx testing that included *CYP2C19* genotyping was offered as a clinical service system-wide to patients in primary care settings.

Limitations

Limitations to our study include analyses of a patient population that was primarily of European descent, which is reflective of Sanford Health's demographic profile. The small sample size of the preemptive cohort ($n = 67$) limited the statistical power of our analyses and ability to measure clinical outcomes. Clinical events for some patients may have been missed due to care received outside the Sanford Health system or due to censoring. Findings may understate the relative benefits of preemptive PGx testing because patients who received early genotyping and died prior to disclosure of results were omitted from analyses due to protocol limitations. Outpatient and inpatient medication orders could not be delineated reliably, nor could elective and emergent PCIs. The $P2Y_{12}$ inhibitor being taken at the time of clinical events or last follow-up were derived from medication order data and were not confirmed via manual chart reviews. Reasons for death or specialty visits (cardiology, neurology, and emergency department) were not ascertained. Patients may have received PGx testing due to prior medication experiences, particularly in the late genotyping testing group.

CONCLUSIONS

Early evidence from a health system with robust education and CDS support suggests that preemptive *CYP2C19* genotyping has a strong influence on initial $P2Y_{12}$ inhibitor selections, but does not improve or worsen patient outcomes compared to *CYP2C19* genotyping ordered at the time the medication need is identified. Results provide some of the earliest data about the clinical impact of preemptive *CYP2C19* genotyping to inform clopidogrel ordering in high-risk patients.

DATA AVAILABILITY

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study.

REFERENCES

1. Lee CR, Luzum JA, Sangkuhl K, Gammal RS, Sabatine MS, Stein CM, et al. Clinical pharmacogenetics implementation consortium guideline for CYP2C19 genotype and clopidogrel therapy: 2022 update. Clin Pharm Ther. 2022;112:959–67.
2. McDermott JH, Leach M, Sen D, Smith CJ, Newman WG, Bath PM. The role of CYP2C19 genotyping to guide antiplatelet therapy following ischemic stroke or transient ischemic attack. Expert Rev Clin Pharm. 2022;15:811–25.
3. Ellithi M, Baye J, Wilke RA. CYP2C19 genotype-guided antiplatelet therapy: promises and pitfalls. Pharmacogenomics. 2020;21:889–97.
4. Essa M, Ross JS, Dhruva SS, Desai NR, Yeh RW, Faridi KF. Trends in spending and claims for P2Y12 inhibitors by medicare and medicaid from 2015 to 2020. J Am Heart Assoc. 2023;12:e028869.
5. Danielak D, Pawlak K, Główka F, Karaźniewicz-Łada M. Influence of genetic and epigenetic factors of P2Y(12) receptor on the safety and efficacy of antiplatelet drugs. Cardiovasc Drugs Ther. 2022. https://doi.org/10.1007/s10557-022-07370-8.
6. Limdi NA, Cavallari LH, Lee CR, Hillegass WB, Holmes AM, Skaar TC, et al. Cost-effectiveness of CYP2C19-guided antiplatelet therapy in patients with acute coronary syndrome and percutaneous coronary intervention informed by real-world data. Pharmacogenomics J. 2020;20:724–35.
7. Cavallari LH, Lee CR, Beitelshees AL, Cooper-DeHoff RM, Duarte JD, Voora D, et al. Multisite investigation of outcomes with implementation of CYP2C19 genotype-guided antiplatelet therapy after percutaneous coronary intervention. JACC Cardiovasc Inter. 2018;11:181–91.
8. Pereira NL, Farkouh ME, So D, Lennon R, Geller N, Mathew V, et al. Effect of genotype-guided oral P2Y12 inhibitor selection vs conventional clopidogrel therapy on ischemic outcomes after percutaneous coronary intervention: the TAILOR-PCI randomized clinical trial. JAMA. 2020;324:761–71.
9. Claassens DMF, Vos GJA, Bergmeijer TO, Hermanides RS, van 't Hof AWJ, van der Harst P, et al. A genotype-guided strategy for oral P2Y(12) inhibitors in primary PCI. N. Engl J Med. 2019;381:1621–31.
10. Yoon HY, Lee N, Seong JM, Gwak HS. Efficacy and safety of clopidogrel versus prasugrel and ticagrelor for coronary artery disease treatment in patients with CYP2C19 LoF alleles: a systemic review and meta-analysis. Br J Clin Pharm. 2020;86:1489–98.
11. Malik AH, Gupta R, Chakraborty S, Mahajan P, Bandyopadhyay D, Yandrapalli S, et al. Effect of genotype-guided oral P2Y12 inhibitor selection after percutaneous coronary intervention: a systematic review and meta-analysis of randomized clinical trials. Cardiovasc Revasc Med. 2022;41:115–21.
12. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. Circulation. 2009;119:2553–60.
13. Wallentin L, James S, Storey RF, Armstrong M, Barratt BJ, Horrow J, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. Lancet. 2010;376:1320–8.
14. Galli M, Benenati S, Franchi F, Rollini F, Capodanno D, Biondi-Zoccai G, et al. Comparative effects of guided vs. potent P2Y12 inhibitor therapy in acute coronary syndrome: a network meta-analysis of 61,898 patients from 15 randomized trials. Eur Heart J. 2022;43:959–67.
15. U.S. Food and Drug Administration. FDA Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug. 2010. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-drug-safety-communication-reduced-effectiveness-plavix-clopidogrel-patients-who-are-poor.
16. Roden DM, Van Driest SL, Mosley JD, Wells QS, Robinson JR, Denny JC, et al. Benefit of preemptive pharmacogenetic information on clinical outcome. Clin Pharm Ther. 2018;103:787–94.
17. Ji Y, Skierka JM, Blommel JH, Moore BE, VanCuyk DL, Bruflat JK, et al. Preemptive pharmacogenomic testing for precision medicine: a comprehensive analysis of five actionable pharmacogenomic genes using next-generation DNA sequencing and a customized CYP2D6 genotyping cascade. J Mol Diagn. 2016;18:438–45.
18. Weitzel KW, Cavallari LH, Lesko LJ. Preemptive panel-based pharmacogenetic testing: the time is now. Pharm Res. 2017;34:1551–5.
19. Petry NJ, Curtis B, Feldhege E, Khan S, Leedahl DD, Breidenbach JL, et al. Impact of automated best practice advisories on provider response to CYP2C19 genotyping results for patients on clopidogrel. J Pharm Pr. 2023;36:487–93. 2021:8971900211049589
20. O'Donnell PH, Wadhwa N, Danahey K, Borden BA, Lee SM, Hall JP, et al. Pharmacogenomics-based point-of-care clinical decision support significantly alters drug prescribing. Clin Pharm Ther. 2017;102:859–69.
21. Peterson JF, Field JR, Unertl KM, Schildcrout JS, Johnson DC, Shi Y, et al. Physician response to implementation of genotype-tailored antiplatelet therapy. Clin Pharm Ther. 2016;100:67–74.
22. Weitzel KW, Elsey AR, Langaee TY, Burkley B, Nessl DR, Obeng AO, et al. Clinical pharmacogenetics implementation: approaches, successes, and challenges. Am J Med Genet C Semin Med Genet. 2014;166c:56–67.
23. Luzum JA, Pakyz RE, Elsey AR, Haidar CE, Peterson JF, Whirl-Carrillo M, et al. The pharmacogenomics research network translational pharmacogenetics program: outcomes and metrics of pharmacogenetic implementations across diverse healthcare systems. Clin Pharm Ther. 2017;102:502–10.
24. van der Wouden CH, Cambon-Thomsen A, Cecchin E, Cheung KC, Dávila-Fajardo CL, Deneer VH, et al. Implementing pharmacogenomics in Europe: design and implementation strategy of the ubiquitous pharmacogenomics consortium. Clin Pharm Ther. 2017;101:341–58.
25. Swen JJ, van der Wouden CH, Manson LE, Abdullah-Koolmees H, Blagec K, Blagus T, et al. A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study. Lancet. 2023;401:347–56.
26. Food and Drug Administration. FDA issues warning letter to genomics lab for illegally marketing genetic test that claims to predict patients' responses to specific medications. 2018. https://www.fda.gov/news-events/press-announcements/fda-issues-warning-letter-genomics-lab-illegally-marketing-genetic-test-claims-predict-patients.
27. Petry N, Baye J, Aifaoui A, Wilke RA, Lupu RA, Savageau J, et al. Implementation of wide-scale pharmacogenetic testing in primary care. Pharmacogenomics. 2019;20:903–13.
28. Christensen KD, Bell M, Zawatsky CLB, Galbraith LN, Green RC, Hutchinson AM, et al. Precision population medicine in primary care: the Sanford Chip experience. Front Genet. 2021;12:626845.
29. Moyer AM, Rohrer Vitek CR, Giri J, Caraballo PJ. Challenges in ordering and interpreting pharmacogenomic tests in clinical practice. Am J Med. 2017;130:1342–4.
30. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123:2736–47.
31. Hajek C, Hutchinson AM, Galbraith LN, Green RC, Murray MF, Petry N, et al. Improved provider preparedness through an 8-part genetics and genomic education program. Genet Med. 2022;24:214–24.
32. Blout Zawatsky CL, Leonhard JR, Bell M, Moore MM, Petry NJ, Platt DM, et al. Workforce considerations when building a precision medicine program. J Pers Med. 2022;12:1929.
33. Martin J, Williams AK, Klein MD, Sriramoju VB, Madan S, Rossi JS, et al. Frequency and clinical outcomes of CYP2C19 genotype-guided escalation and de-escalation of antiplatelet therapy in a real-world clinical setting. Genet Med. 2020;22:160–9.
34. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N. Engl J Med. 2007;357:2001–15.
35. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N. Engl J Med. 2009;361:1045–57.
36. Chan NC, Eikelboom JW, Ginsberg JS, Lauw MN, Vanassche T, Weitz JI, et al. Role of phenotypic and genetic testing in managing clopidogrel therapy. Blood. 2014;124:689–99.
37. Capodanno D, Alfonso F, Levine GN, Valgimigli M, Angiolillo DJ. ACC/AHA versus ESC guidelines on dual antiplatelet therapy: JACC guideline comparison. J Am Coll Cardiol. 2018;72:2915–31.
38. Kalow W, Tang BK, Endrenyi L. Hypothesis: comparisons of inter- and intra-individual variations can substitute for twin studies in drug research. Pharmacogenetics. 1998;8:283–9.
39. Belle DJ, Singh H. Genetic factors in drug metabolism. Am Fam Physician. 2008;77:1553–60.

40. Brunette CA, Dong OM, Vassy JL, Danowski ME, Alexander N, Antwi AA, et al. A cost-consequence analysis of preemptive SLCO1B1 testing for statin myopathy risk compared to usual care. J Pers Med. 2021;11:1123.

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COMPETING INTERESTS

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ETHICS

The research protocol was approved by the Sanford Health and Harvard Pilgrim Health Care Institute Institutional Review Boards. Individual-level patient data were deidentified before being provided to the study team, and informed consent was not required.

ADDITIONAL INFORMATION

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