Research Article

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Pharmacogenomics

SLCO1B1 gene-based clinical decision support reduces statin-associated muscle symptoms risk with simvastatin

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Background: *SLCO1B1* variants are known to be a strong predictor of statin-associated muscle symptoms (SAMS) risk with simvastatin. **Methods:** The authors conducted a retrospective chart review on 20,341 patients who had *SLCO1B1* genotyping to quantify the uptake of clinical decision support (CDS) for genetic variants known to impact SAMS risk. **Results:** A total of 182 patients had 417 CDS alerts generated, and 150 of these patients (82.4%) received pharmacotherapy that did not increase risks for SAMS. Providers were more likely to cancel simvastatin orders in response to CDS alerts if genotyping had been done prior to the first simvastatin prescription than after (94.1% vs 28.5%, respectively; $p < 0.001$). **Conclusion:** CDS significantly reduces simvastatin prescribing at doses associated with SAMS.

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Approximately 26 million individuals in the United States suffer from atherosclerotic cardiovascular disease for which statin therapy improves clinical outcomes [1]. Statins, also known as 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, are the first-line therapy for the prevention of atherosclerotic cardiovascular disease [2,3]. Despite the compelling evidence surrounding statin use, statins are met with resistance due to patient nonadherence and adverse effects [4–6]. The use of genetic testing to identify individuals at increased risk for adverse effects may be pivotal in medication selection, medication dosage, adherence, and patient education [7].

Genotyping of the *SLCO1B1* gene can inform simvastatin dosing and prescribing [8–10]. Individuals with decreased function variants in *SLCO1B1* have reduced hepatic uptake of statins, which is required for medication clearance [11]. This impaired clearance increases the risks for adverse effects such as statin-associated muscle symptoms (SAMS), which include pain and weakness, cramping and fatigue [8,9,12,13]. Severe cases of SAMS can lead to rhabdomyolysis and hospitalization [14,15]. Numerous studies have concluded that genetic variants in *SLCO1B1* are associated with the development of SAMS with simvastatin usage [9]. Drug–drug interaction and dose–response extrapolation studies suggest that most SAMS cases are concentration dependent [16], and the Clinical Pharmacogenetics Implementation Consortium (CPIC) provides guidance about how statins should be prescribed based on *SLCO1B1* genotype [9].

Best practices for the implementation of pharmacogenomic (PGx) testing include integration of clinical decision support (CDS) where healthcare providers are alerted whenever medication orders are initiated in the presence of

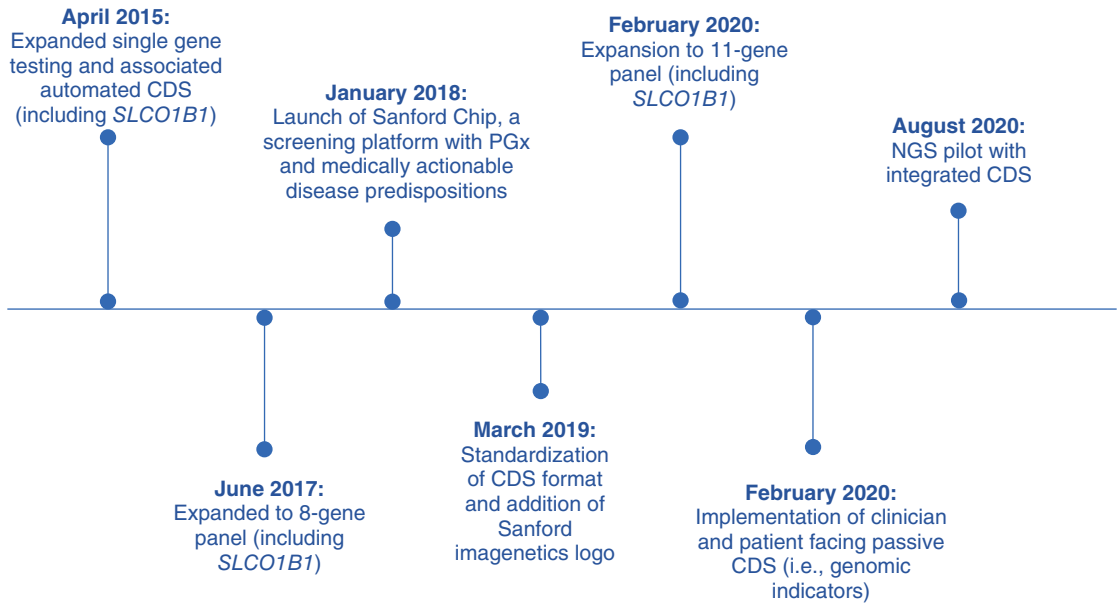

Figure 1. Timeline. The figure shows key moments for deployment of clinical decision support regarding drug–gene interactions for simvastatin and population genetic testing of *SLCO1B1*.

drug–gene interactions [17–21]. Evidence about how often providers follow PGx-informed CDS recommendations is limited, however. Prior studies have found that acceptance rates for CDS recommendations vary greatly based on drug–gene pairs and the severity of clinical outcomes [22–27]. A recent scoping review found that 12–73% of PGx CDS alerts result in an alteration in the medication order [28]. Obeng and colleagues found 64% of recommendations from simvastatin CDS alerts about drug–gene interactions were accepted within a pilot group of physicians who underwent targeted education [24].

The objective of this study is to investigate healthcare providers' responses to CDS alerts about drug–gene interactions for simvastatin to provide insight into their impact on statin prescriptions and factors that influence acceptance and override rates. In particular, the authors were interested in responses to CDS alerts that activated prior to a patient's first use of simvastatin. The overarching goal of the work presented here is to provide insight into PGx CDS implementation as a strategy to prevent adverse outcomes associated with simvastatin usage.

Materials & methods

Setting

The authors report data from Sanford Health, a large, rural, nonprofit healthcare system in the upper midwestern United States. Sanford Health developed a clinical PGx program in 2014 that included the implementation of CDS alerts that activate at the time of medication order entry [17,29]. The integration of CDS alerts for drug–gene interactions between simvastatin and *SLCO1B1* occurred in April 2015 (Figure 1). PGx testing options expanded over time to facilitate preemptive applications, where results are not needed immediately and information is stored until needed in the future. In 2017, *SLCO1B1* was included in a PGx panel consisting of eight genes, and in 2018, *SLCO1B1* genotyping was included in an expanded panel that included optional screening for monogenic disease risks and was offered to adult primary care patients across the health system as part of the Sanford Chip program [17,29]. In advance of the launch of the program, all physicians and advanced practice providers were required to complete web-based genetics education over 2 years [30]. Pre-post analyses of the educational program showed large increases in comfort ordering PGx testing and perceived utility [30]. Of note, all PGx results are evaluated by a PGx clinical pharmacist who provides recommendations for patients' existing medications based on available consortia guidelines. Pharmacist recommendations may be sought out and given prior to provider prescribing, thereby avoiding CDS alerts.

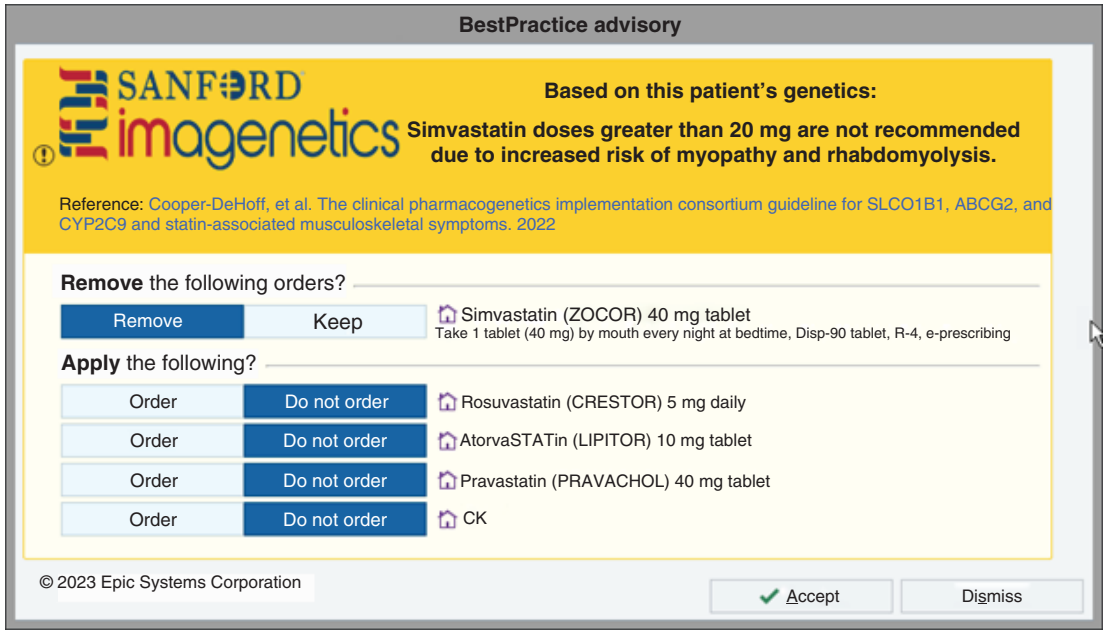

Figure 2. Example of an interruptive clinical decision support alert for simvastatin. The example activates for simvastatin and *SLCO1B1* interaction based on the 2022 CPIC guidelines. Prior alerts were similar in design and varied by the year the alert was encountered.

Development of CDS alerts

Automated CDS for simvastatin activates for patients with poor or decreased *SLCO1B1* function at the time of order entry and signing [31]. Interruptive alerts inform providers that simvastatin was not recommended or that a dose adjustment was warranted based on the patient's genetics (Figure 2). The initial CDS for simvastatin-*SLCO1B1* triggered for all simvastatin orders initiated for patients with an abnormal copy (loss of function allele), regardless of dosing, due to electronic health record (EHR) capabilities at the time. In 2019, all PGx CDS alerts were standardized to present the potential risks (toxicity or decreased efficacy) and recommendations. Additionally, all PGx alerts were branded with the Sanford Imagenetics logo to further indicate that recommendations were based on PGx variants. Default response options were to remove the simvastatin order, and structured single-click options allowed providers to order an alternative statin. In 2019, an additional structured option was added to allow providers to order a creatine kinase (CK) test to assist in identifying SAMS in patients with evidence of muscle symptoms. While routine monitoring of CK is no longer recommended, guidelines suggest CK monitoring in the presence of SAMS [32]. Further enhancements to CDS were implemented in 2022 to align with the latest CPIC guideline to refine alerts to trigger at specified doses for all statins and provide equipotent alternative options. This optimization aimed to minimize alert fatigue by only triggering alerts for doses associated with increased risk for SAMS [8].

Data

Data regarding the number of patients who received *SLCO1B1* genotyping and the associated phenotype were abstracted from patients' EHRs. The authors also abstracted data from patients' EHRs about all instances where healthcare providers viewed a PGx CDS alert about simvastatin from April 2015 through September 2021. Responses to CDS alerts included statin and test orders, if any, associated within the encounter that triggered the alert. Data do not reflect whether medication orders were subsequently filled.

Data analyses

Descriptive analyses focused on actions following the first CDS alerts for individual patients, as well as actions following the last observed CDS alert among patients for whom multiple alerts activated. Responses to CDS alerts were classified as safe if they did not increase patient risks for SAMS because simvastatin was ordered at 20 mg/day or less, an alternative statin was ordered or no statin was ordered within the encounter that triggered the CDS alert.

Statistical analyses examined the likelihood that the simvastatin order was canceled and the likelihood of a safe response. Analyses of CDS alerts were conducted using generalized estimating equations (GEEs) to account for correlated responses for multiple alerts activating for individual patients. Models used logit linking functions and binomial distribution. Overall model fit for GEEs was assessed as recommended using Corrected Quasi-likelihood under Independence Model Criterion (QICC) values [33], which showed improved (lower) QICC values for analyses that examined whether CDS alerts resulted in cancelation of the simvastatin order (QICC = 504 in the full model, 522 in the model with no predictors). GEEs of safe responses to CDS alerts are omitted from reporting because associated QICC values worsened compared with models that included no predictor variables (QICC = 454 in the full model, 415 in the model with no predictors). To provide insight into the impact of PGx testing that is ordered before a patient has any experience with a medication, the primary variable of interest indicated whether the CDS alert activated prior to a patient's initial signed order for simvastatin. Covariates included the date the CDS alert fired, the number of prior simvastatin orders (defined as a simvastatin order that was signed), the number of prior CDS alerts, the patient's age, whether a pharmacist had compared PGx results with the patient's medication lists prior to the simvastatin order, the department where the simvastatin order was placed (primary care vs other) and the time between PGx testing and the simvastatin order. The authors used an autoregressive working correlation structure with robust standard errors to account for multiple CDS alerts for individual patients, including simvastatin reorders. To examine the robustness of the findings, additional analyses were conducted on the first and last observed CDS alerts for each patient using a similar approach. The number of prior alerts was omitted as a covariate from analyses of patients' first alerts, and the date of the alert was omitted from analyses of patients' last alerts to minimize bias. These models used an independent working correlation structure with robust standard errors to account for multiple alerts being encountered by providers. The robustness of the findings was also explored using bivariate analyses of all variables included in GEE analyses using χ^2 and logistic regression for categorical and continuous variables, respectively (Supplementary Tables 1–4).

Statistical significance was set at p = 0.05. Analyses were conducted in R, version 4.3.0 [34]. The Sanford Health Institutional Review Board approved the research protocol.

Results

Through September 2021, 20,341 patients had PGx testing, which included *SLCO1B1* genotyping. Of these patients, 5124 (25.2%) had one loss of function allele and 499 (2.5%) patients had two loss of function alleles. Simvastatin orders generated 417 alerts regarding drug–gene interactions for 182 different patients (Table 1). Alerts fired a median of 273 days (interquartile range: 421 days) after genotyping (Supplementary Figure 1 & Supplementary Table 5). The majority of patients had received genotyping after being initiated on simvastatin (n = 166, 91.2%). A total of 147 patients (80.8%) had a review of their medications for potential drug–gene interactions by a clinical pharmacist before their first alert, although only 12 of these reviews (8.2%) occurred prior to a patient's initial simvastatin order. First CDS alerts for 105 patients (57.7%) activated in responses to simvastatin orders initiated at dosing that would currently be considered safe, while the alerts activated for another 22 patients (12.1%) before a dose was selected. Alerts were viewed by 288 unique providers, with each alert being reviewed an average of 1.2 providers apiece (Supplementary Table 5).

Responses to CDS alerts

Healthcare providers canceled simvastatin orders for 69 patients (37.9%) following the patient's first CDS alert and for 95 patients (52.2%) after the most recent alert (Table 2). Simvastatin orders above 20 mg per day were the last recorded response for only 32 patients (17.6%). Of the 39 patients who received prescriptions for simvastatin above 20 mg per day following their initial CDS alert, nine (23.1%) had simvastatin canceled or were continued on simvastatin at a low dose in response to a later CDS alert. Records for 38 patients (20.9%) showed simvastatin orders being canceled without an alternative statin ordered within the alert encounter as the last recorded response. Notably, only one of 16 patients (6.3%) who had no prior signed simvastatin orders at the time of the CDS alert was ultimately initiated on a statin in response to CDS alerts. The majority of patients were categorized as receiving pharmacotherapy that did not increase risks for SAMS after their last observed alert (150 of 182 patients, 82.4%).

Multivariable analyses showed that providers were far more likely to cancel simvastatin orders if patients had no previous prescriptions of simvastatin. Overall, providers canceled the simvastatin order after 30.2% of the alerts (95% CI: 21.8–40.2%), and responses were classified as safe after 80.5% of alerts (95% CI: 76.4–84.2%). The adjusted likelihood that providers canceled simvastatin orders differed greatly based on prior simvastatin

Table 1. Patient characteristics.

Characteristic	Estimate
Mean number of alerts per patient (range)	2 (1–10)
Daily dose of simvastatin order that triggered the first alert, n (%)	
5 mg	2 (1.1%)
10 mg	35 (19.2%)
20 mg	68 (37.4%)
40 mg	52 (28.6%)
60 mg	1 (0.5%)
80 mg	2 (1.1%)
Dose not selected prior to alert	22 (12.1%)
Lipid-lowering therapy prior to first alert, n (%)	
Atorvastatin 10 mg daily	3 (1.6%)
Atorvastatin 40 mg daily	2 (1.1%)
Gemfibrozil 600 mg twice daily	2 (1.1%)
Pravastatin 10 mg daily	2 (1.1%)
Pravastatin 40 mg daily	1 (0.5%)
Rosuvastatin 5 mg daily	2 (1.1%)
Rosuvastatin 10 mg daily	4 (2.2%)
Rosuvastatin 20 mg daily	1 (0.5%)
Rosuvastatin 40 mg daily	1 (0.5%)
Simvastatin 5 mg daily	2 (1.1%)
Simvastatin 10 mg daily	35 (19.2%)
Simvastatin 20 mg daily	65 (35.7%)
Simvastatin 40 mg daily	51 (28.0%)
Simvastatin 60 mg daily	1 (0.5%)
Simvastatin 80 mg daily	2 (1.1%)
No previous antihyperlipidemic	8 (4.4%)
Mean low-density lipoprotein at time of first alert, mg/dl (standard deviation)	99.3 (31.9)
Median patient age at time of first alert, years (IQR)	66 (13)
Median time from pharmacogenomic testing to last observed alert, days (IQR)	112 (235)
Median time from pharmacogenomic testing to last observed alert, days (IQR)	289 (442)
Median number of signed simvastatin orders before first alert (IQR)	11 (9)

IQR: Interquartile range.

Table 2. Responses to the initial and last observed clinical decision support alert for 182 patients with potential drug–gene interactions.

Action	Initial alert (182 patients)	Final alert (182 patients)	Last observed alert (93 patients)‡
Ordered simvastatin	113 (62.1%)	87 (47.8%)	54 (58.1%)
5 mg/day	3 (1.6%)	0 (0%)	0 (0%)
10 mg/day	24 (13.2%)	18 (9.9%)	13 (14.0%)
20 mg/day	47 (25.8%)	37 (20.3%)	26 (28.0%)
40 mg/day	38 (20.9%)	31 (17.0%)	15 (16.1%)
80 mg/day	1 (0.5%)	1 (0.5%)	0 (0%)
Ordered alternative statin	32 (17.6%)	57 (31.3%)	27 (29.0%)
Rosuvastatin	23 (12.6%)	43 (23.6%)†	21 (22.6%)†
Pravastatin	8 (4.4%)	11 (6.0%)	3 (3.2%)
Atorvastatin	3 (1.6%)	7 (3.8%)†	5 (5.4%)†
Fluvastatin	1 (0.5%)	0 (0%)	0 (0%)
Did not order a statin	37 (20.3%)	38 (20.9%)	12 (12.9%)

†For one patient, both rosuvastatin and atorvastatin were ordered following the clinical decision support alert.
‡Restricted to patients with multiple instances of clinical decision support alerts.

Table 3. Summary of models predicting cancelation of the simvastatin order.

Variable	Canceled simvastatin	
	Odds ratio (95% CI)	p-value
Intercept	0.4 (0.3–0.6)	<0.001
First simvastatin order (ref: no prior simvastatin orders)	41.5 (5.2–332.3)	<0.001
Date alert fired (per month)	1.0 (1.0–1.0)	0.294
Number of prior simvastatin orders	1.0 (1.0–1.1)	0.518
Number of prior alerts	0.9 (0.7–1.1)	0.358
Age (per year)	1.0 (1.0–1.0)	0.908
Pharmacist review before alert (ref: no review)	1.0 (0.5–1.9)	0.958
Order placed in primary care (ref: not primary care)	1.3 (0.7–2.4)	0.434
Time since pharmacogenomic testing (per month)	1.0 (1.0–1.0)	0.618
Prior statin order was unknown medication, dose (ref: safe order)	0.9 (0.4–1.8)	0.695
Prior statin order was simvastatin at over 20 mg/day (ref: safe order)	0.9 (0.4–1.8)	0.740

Models predicted the likelihood that a clinical decision support alert resulted in cancelation of the simvastatin order. Odds ratios were estimated with generalized estimating equations with logit linking functions and assuming a binomial distribution, with clusters defined by patient and an independent working correlation structure with robust standard errors.

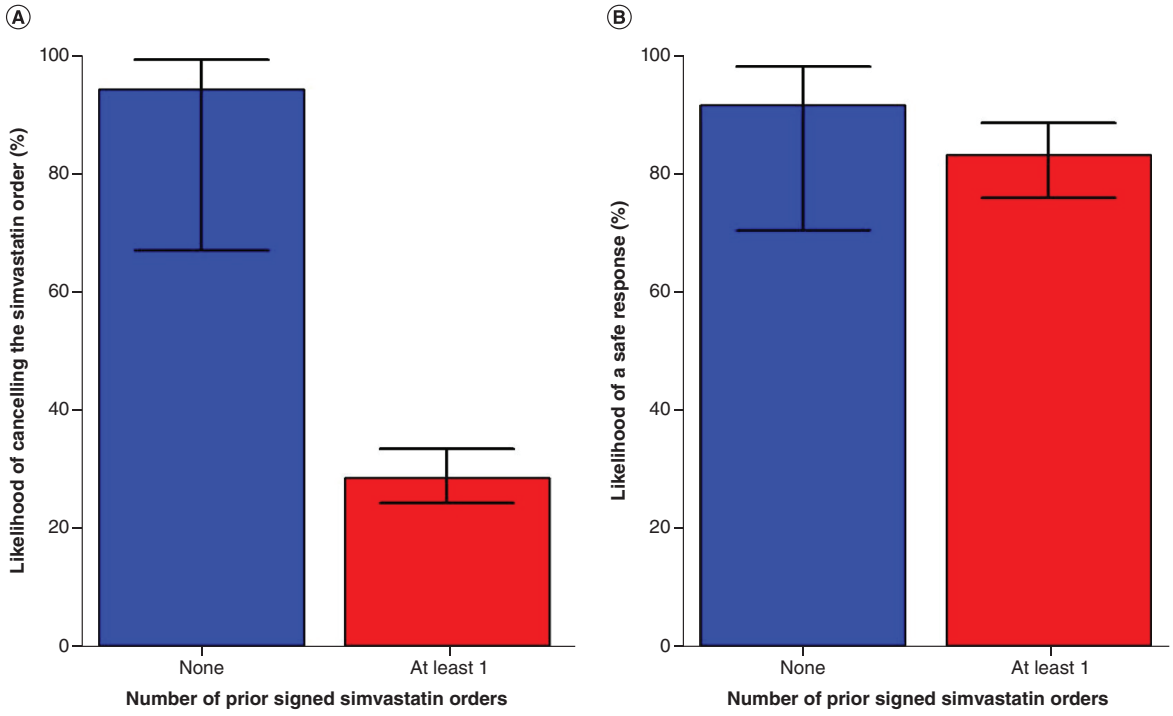

Figure 3. Responses to clinical decision support alerts, by simvastatin prescriptions. Figures examine instances where patients did or did not have prior signed orders for simvastatin to estimate the likelihood that clinical decision support (CDS) alerts resulted in **(A)** cancellation of the simvastatin order and **(B)** a safe response (an order for simvastatin at 20 mg or less per day, an alternative statin, or no statin order). Estimates were generated from linear models that used generalized estimating equations, and adjusted for the number of prior simvastatin orders, number of prior CDS alerts, patient age, date of the alert, time since pharmacogenomics testing, setting (primary care or other) and whether a pharmacist review had occurred prior to the alert.

prescriptions: 93.9% of orders were canceled when patients had no prior simvastatin prescription compared with 27.1% of orders when patients had previous prescriptions for simvastatin (odds ratio: 41.5; 95% CI: 5.2–332.3; $p < 0.001$; Table 3 & Figure 3A). The adjusted likelihood that responses to CDS alerts were considered safe did not differ by number of previous simvastatin prescriptions; however, 90.7% of responses to CDS alerts were considered safe in instances when patients had had no prior simvastatin prescription, compared with 73.7% of

responses when patients had had previous simvastatin prescriptions (p = 0.22; Figure 3B). No other examined factors were associated with either the likelihood of canceling the simvastatin order or the likelihood that responses were considered safe (all p > 0.05). Findings from analyses of all CDS alerts were consistent with sensitivity analyses that considered only the first and last CDS alert observed for each patient (Supplementary Tables 1 & 2).

Use of structured response options

When providers prescribed patients an alternative statin, they chose atorvastatin following four of 14 alerts (28.6%) that fired when atorvastatin was included as a structured response option provided within the alert but only two of 50 alerts (4.0%) that fired after atorvastatin was removed as a structured response option (p = 0.010). Simvastatin orders were accompanied with CK tests following one of 39 alerts (2.6%) before the alert was modified to include ordering CK testing as a structured response option and only one of 247 alerts (0.4%) that fired afterward (p = 0.26).

Discussion

This work provides some of the earliest evidence about the impact of point-of-order CDS alerts about drug–gene interactions for simvastatin generated from a population-based genetic screening cohort. The authors showed that over 80% of CDS alerts were followed by pharmacotherapy that minimized risks for SAMS. In this study, the majority of providers who continued with a simvastatin order after a CDS alert did so at doses that were not associated with increased risks for SAMS. These results add to the growing evidence base regarding the importance of point-of-ordering CDS alerts for drug–gene interactions to ensure the promise of PGx testing is realized. Recent related studies showed that acceptance rates of PGx CDS alert recommendations for simvastatin range from 60% to 70% in studies of research participants [24,27]. The slightly higher rates of safe orders following alerts observed in the present retrospective analyses of clinical populations may reflect differences in Sanford's implementation approach. These differences included provider education that was mandatory for all physicians and advanced practice providers and systemwide access to pharmacists with PGx expertise.

Out of over 20,000 patients genotyped for *SLCO1B1* between 2015 and 2021, simvastatin orders were initiated for only 182 with poor or decreased *SLCO1B1* function, and only 16 of those patients had no prior simvastatin experience at the time of the CDS alert. While this group is small, the likelihood that providers canceled their simvastatin orders following PGx CDS alerts increased from 30% overall to nearly 95%. This result may be because providers were less concerned with SAMS when patients had previously tolerated simvastatin, even if only for a short time. It is also possible that many providers who overrode CDS alerts were aware that lower-dose simvastatin orders were likely to be safe based on *SLCO1B1* genotyping. Nevertheless, these results have strong implications for the implementation of preemptive PGx testing. Advocates have long envisioned a future where individuals have PGx testing when they are healthy and storing the results until needed [35–37]. Some commentators, including former NIH director Francis Collins, believe comprehensive genomic profiling may become common at birth, with results providing lifeline utility [38,39]. As preemptive PGx testing becomes more available to patients without prior prescriptions on relevant medications, one can expect its results to become more influential.

These findings also suggest PGx alerts have an influence over time. Consistent with other work [27], nearly a quarter of patients for whom providers continued a high-dose simvastatin order after an initial simvastatin CDS alert had canceled or continued simvastatin at a lower dose in response to a later CDS alert. These results raise questions about the optimal frequency of CDS alerts and how often they should activate for subsequent medication orders. Patients may not experience SAMS until years after they have started simvastatin [40–42], and the present data show that repeated CDS alerts can influence medication reorders. These potential benefits need to be weighed against the potential to worsen "alert fatigue" where providers ignore alerts merely because they encounter them so often [20,43–45].

Additional findings from the present work demonstrate the impact of structured response options in CDS alerts. The single-click option to order CK testing in response to a simvastatin CDS alert was rarely utilized, likely because CK testing is only recommended when SAMS is suspected and providers may be reluctant to order statins in patients who are already symptomatic. Atorvastatin was less likely to be ordered as an alternative to simvastatin after single-click ordering capabilities were removed. Utilizing longitudinal data spanning nearly 10 years, the authors have shown that variants within *SLCO1B1* predict SAMS not only with simvastatin but also with atorvastatin [46]. Therefore, they modified structured ordering options within the CDS by removing atorvastatin. Additionally, these findings informed the most recent revision of the CPIC guidelines to encompass all statins [9]. Collectively, this expanding body of knowledge demonstrates that genetic variants in *SLCO1B1* contribute to roughly 10% of the

incidence of SAMS for highly utilized statins such as simvastatin and atorvastatin [46]. Statins are highly efficacious in the prevention and treatment of atherosclerotic cardiovascular disease; therefore, harnessing the potential to reduce the adverse events of these agents holds promise to ensure patient adherence to prescribed treatment, leading to improved cardiovascular-related morbidity and mortality.

Some findings raise concerns. Nearly 20% of patients with drug–gene interactions for simvastatin were retained on doses associated with increased risk of SAMS after their last observed CDS alert. The data provide limited insight into the reasons. In addition to alert fatigue, it is possible that providers may not feel confident in their PGx knowledge and may be hesitant to accept alerts they may not fully understand, especially if they lack time [30,47–50]. Providers also report that CDS alerts in general are often confusing and irritating, and they make it difficult to find additional information [51]. Additional data are needed to understand the reasons providers in the present study overrode CDS alerts. In addition, 20% of alerts resulted in cancelation of simvastatin without an order for an alternative statin. Concerns about the potential for providers to use PGx results inappropriately, including not prescribing a therapy that could benefit the patient, led the US FDA to issue a warning letter to the Inova Genomics Laboratory about its panel PGx program [52]. The use of *SLCO1B1* genotyping to inform simvastatin usage is among the most vetted applications of PGx testing [52], and statins are only one of many options available to reduce elevated cholesterol [53,54]. Data extraction for behaviors other than alternative statin prescribing in response to CDS alerts were not easily capturable in this dataset. Future work will examine how patients in this study who did not have statins ordered immediately following a CDS alert were managed.

Limitations to our analyses include generalizability, as data was abstracted from a single health system where genetics education of physicians and advanced practice providers was mandatory [30]. The authors do not have data on medication fills within the Sanford Health system or medication orders outside the system. Comprehensive patient lipid levels and need for pharmacotherapy were not assessed. Alternative, nonstatin antihyperlipidemics were not captured in this dataset. The authors' EHR does not capture clinical decisions made without a signed order or explicit provider note, which led to the inability to evaluate all possible decision-making points for statin medication dosing. Cases where healthcare providers initiated a simvastatin order, received an alert and then reduced dosing because of CDS alerts could not be adequately captured, since no order was finalized before the change was made and the authors did not evaluate all provider notes. Data were collected about CDS alerts that activated before CPIC recommendations for statins were updated to address additional medications and genes [9]. At the time CDS alerts were developed, dose-specific triggering criteria were not commonplace within the institution, resulting in difficulty in customizing alerts based on specific dosages. As shown, the authors identified more than half of the patients in which triggered CDS alerts were prescribed at doses not associated with increased risk for SAMS. As EHR capabilities improved, the authors updated algorithms to trigger alerts only for simvastatin doses above 20 mg. These findings highlight the importance of developing EHR systems that integrate multiple order characteristics into algorithms to ensure CDS remains reliable and actionable. CDS alerts for all statins were devised in 2022 following the CPIC guideline update to trigger at specific doses that were associated with increased risk of myopathy. Each statin alert was configured to provide structured response options of equivalent intensity regardless of previous statin duration due to potential risk of patient harm. Analyses also do not account for evolving recommendations for prescribing simvastatin, including the FDA recommendations in 2012 that the highest dose of simvastatin (80 mg) be limited to patients who have tolerated this dose for over 12 months [55]. Such recommendations are likely to have impacted simvastatin orders independent of PGx information.

Conclusion

Sanford Health was one of the first institutions to deploy simvastatin-*SLCO1B1* alerts within the Epic Systems Corporation EHR platform. Nearly a decade since implementation, the authors set forth to analyze the impact CDS has on prescribing patterns to circumvent SAMS. The data demonstrate that CDS to guide statin therapy is an effective strategy to minimize the potential risk for SAMS. It also provides unique insight relevant to preemptive PGx testing and the extremely high likelihood orders that CDS alerts would lead to cancelation of simvastatin orders for patients with no prior simvastatin prescriptions. Ongoing work will examine responses to CDS alerts that fire in response to other drug–gene interactions.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/pgs-2023-0056

Author contributions

Conceptualization: A Massmann, JV Heukelom, RC Green, C Hajek, MR Hickingbotham, EA Larson, ES Zoltick, KD Christensen, A Schultz; data curation: A Massmann, JV Heukelom, MR Hickingbotham, KD Christensen, A Schultz; formal analysis: MR Hickingbotham, KD Christensen; funding acquisition: RC Green, C Hajek, KD Christensen, A Schultz; investigation: A Massmann, JV Heukelom, MR Hickingbotham, ES Zoltick, KD Christensen, A Schultz; methodology: A Massmann, JV Heukelom, MR Hickingbotham, CY Lu, AC Wu, ES Zoltick, KD Christensen, A Schultz; project administration: C Hajek, MR Hickingbotham, A Schultz; supervision: KD Christensen, A Schultz; validation: A Massmann, JV Heukelom; writing – original draft: A Massmann, JV Heukelom, MR Hickingbotham, ES Zoltick, KD Christensen, A Schultz; writing – review and editing: A Massmann, JV Heukelom, RC Green, C Hajek, MR Hickingbotham, EA Larson, CY Lu, AC Wu, ES Zoltick, KD Christensen, A Schultz.

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Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

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

Data availability statement

Data and analytic code will be made available at request. Inquiries can be directed to the corresponding author.

Summary points

- Pharmacogenomic clinical decision support (CDS) alerts for statin therapy is an effective strategy to mitigate adverse effects such as statin-associated muscle symptoms.
- The majority of alerts (82.4%) resulted in pharmacotherapy that was not associated with an increased risk for statin-associated muscle symptoms.
- Providers canceled simvastatin after a CDS alert far more often when patients had no prior simvastatin prescriptions compared with even one prior simvastatin prescription (94.1% vs 28.5%; $p < 0.001$).
- Structured options within CDS alerts influence provider ordering behavior.

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