Original Work

Pharmacogenetics Educational Series and Development of Clinical Decision Support Software

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Abstract

Objective: This project addresses two common barriers to the development of a pharmacogenetics (PGx) service. It assesses the effectiveness of a lecture series on clinicians' and managements' knowledge of PGx. Additionally, clinical decision support (CDS) was created to reinforce knowledge and allow application of PGx.

Methods: Six PGx lectures were provided over six months to clinicians and managers. Presentation topics included: introduction, neurology, cardiology, germline oncology, somatic oncology, and implementation. Teaching effectiveness was measured electronically through pre, post, and revisit assessments.

Additionally, the primary investigator and an informatics pharmacist developed CDS, starting with discrete documentation fields within the electronic medical record for PGx test results. Subsequently, alerts with specific firing criteria were designed to advise clinicians when ordering an interacting medication, and recommend alternatives. Alert frequency and acceptance/override frequency measured the effectiveness and relevance of the alerts.

Results: The average pre-lecture assessment score was 37.2%, with a post-lecture score of 77.9%, and a revisit-score of 68.5%. There was an increase in knowledge, though some knowledge was lost over time.

To date there have been two drug-gene interactions resulting in a PGx alert (n=31 patients with genetic test results). This is likely due to the limited number of patients with PGx test results available in the electronic medical record.

Conclusions: Clinicians and managers learned and retained PGx information over several weeks following a one-hour lecture. PGx tests are still too new and infrequent to assess effectiveness of CDS.

Pharmacogenetics (PGx) is the study and application of how genetic variances within individuals affect their responses to medications. PGx knowledge is constantly expanding through research, and the development of clinical guidelines aids in the application of this knowledge to the practice setting. Despite this, utilization of PGx in practice remains minimal for many reasons.[1]

Several barriers exist that discourage implementation of PGx services. One barrier is the limited knowledge of clinicians regarding PGx. Given the relatively new implementation of PGx knowledge in the clinical setting, medical and pharmacy schools have only recently begun to incorporate PGx into their academic curriculum. Even when PGx is incorporated into the medical school curriculum, the coverage is brief and physicians are still not comfortable using PGx in practice.[2-4] Surveys have shown that physicians agree drug response is affected by genetic variations, however they lack the necessary knowledge about genetic testing. Indeed, another survey described PGx information in medical schools as "poor or not at all adequate."[2]

Another common barrier to implementation of PGx services is the lack of software support.[1,5,6] Currently, very few vendors of electronic health record software support clinical decision support (CDS) tools in their basic genomic functionality. This is beginning to resolve as institutions across the nation are collaborating to develop PGx CDS under the Electronic Medical Records and Genomics (eMERGE) network.[7] However for smaller health systems that are not directly involved with this research, often the best solution is to design their own CDS within their electronic health record software systems.

Other barriers to regular use of PGx in practice include the expense of genetic testing, lack of reimbursement, slow turnaround time of test results, lack of clear guidelines for when to test patients, and inconsistencies between the available guidelines and testing companies in the interpretation of genotypes into phenotypes.[1,6,8]

The purpose of this study was to create a foundation upon which PGx services can be expanded in the future. This was achieved by overcoming two barriers that are most able to be controlled by individual institutions: limited clinician knowledge and absence of support software. First, the

effectiveness of a six-presentation series on clinicians' knowledge was assessed over a period of six months. Second, CDS was created in parallel with the lectures to reinforce this knowledge and allow practical application of PGx. The CDS here includes creation of a discrete field for recording PGx test results in the EMR as well as alerts to fire upon ordering a medication that interacts with an individuals' genome.

Methods

Part 1: Lecture Series

The PGx lecture series included six presentations provided over six months at a single community hospital. Each lecture was 1 hour long. Topics included an introduction to PGx, neurology/psychiatry, cardiology, germline oncology, somatic oncology, and implementation of PGx processes (Table 1).

Forty-two participants were invited to be part of the study group and committed to attending all six lectures. A variety of personnel were selected, including physicians, nurse practitioners, pharmacists, managers, and administrators. Other interested individuals were invited to attend as well for the continuing medical education (CME) credits, however their responses were not recorded as part of the research study.

Assessments were obtained via an electronic audience response system. Questions imbedded in the presentation allowed study participants to submit responses with a remote which were tracked over time. Each individual used the same remote at each lecture. Assessments consisted of three to five questions specific to each lecture. Each question was encountered on three separate occasions: before the lecture (pre assessment), during the lecture after the pertinent information had been covered (post assessment), and before the subsequent lecture (revisit assessment). These three time points allowed assessment of baseline knowledge of PGx, ability to learn and understand PGx concepts in the short term, and ability to retain PGx knowledge over time. Only the final lecture was accompanied with 3 questions, which has less of an impact on the results since retention was not assessed for this lecture. Also, only the third lecture had 4 questions. All other lectures contained 5 assessment questions.

TABLE 1. Summary of Lecture Series Content

Lecture	Lecture Title	Gene/Drug Pairs Covered	Date of Lecture
1	Introduction to PGx	*CYP2D6*/Codeine *CYP2D6*/Tramadol	9/12/16
2	Neurology	*CYP2D6*/SSRI's *CYP2C19*/SSRI's *CYP2D6* and *CYP2C19*/TCA's HLA-B*15:02/Carbamazepine and phenytoin HLA-A*31:01/Carbamazepine *CYP2C9*/Phenytoin	10/24/16
3	Cardiology	*CYP2C19*/Clopidogrel *CYP2C9* and *VKORC*/Warfarin *SLCO1B1*/Simvastatin *CYP2D6*/Metoprolol	11/10/16
4	Germline Oncology	*TPMT*/Thiopurines *G6PD*/ Rasburicase *DPYD*/Fluoropyrimidines *UGT1A1*/Irinotecan *CYP2D6*/ Tamoxifen *IFNL3* (IL28B)/Interferon-a HLA-B*57:01/Abacavir HLA-B*58:01/Allopurinol	12/15/16
5	Somatic Oncology	*EGFR*/Erlotinib, afatinib, cetuximab, panitumumab *EML4-ALK*/Crizotinib *HER2*/Trastuzumab, pertuzumab, lapatinib *ER, PR*/Tamoxifen, aromatase inhibitors *BRAF*/Vemurafenib, dabrafenib, trametinib *BCR-ABL*/Imatinib	1/16/17
6	Implementation Processes	None	2/6/17

PGx pharmacogenetics; SSRI selective serotonin reuptake inhibitor; TCA tricyclic antidepressant

TABLE 2. Statistics for Subgroup Analysis of Lecture Series Assessments

	Providers	Pharmacists	Leadership
Pre vs post	41.6% vs 81.3% P<0.0001 CI -0.49 to -0.31	42.1% vs 80.7% P<0.0001 CI -0.46 to -0.3	27.5% vs 71.3% P<0.0001 CI -0.57 to -0.30
Post vs revisit	81.3% vs 72.3% P=0.0906 CI -0.02 to 0.20	80.7% vs 68.0% P=0.0065 CI 0.04 to 0.21	71.3% vs 63.9% P=0.2473 CI -0.083 to 0.28
Pre vs revisit	41.6% vs 72.3% P<0.0001 CI -0.44 to -0.24	42.1% vs 68.0% P=0.0005 CI -0.38 to -0.14	27.5% vs 63.9% P=0.0249 CI -0.65 to -0.06
Number of participants	13	12	12

CI = confidence interval

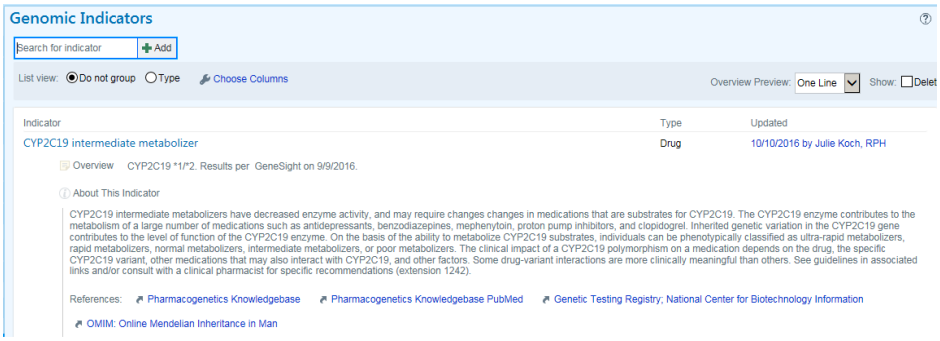
The main endpoint was change in group knowledge over time as determined by percent correct at each time point. A secondary objective was to assess changes in subgroup knowledge. Subgroups included providers, pharmacists, and leadership.

A paired, two-tailed t test was selected as the appropriate statistical test. This test was used to compare pre vs post, post vs revisit, and pre vs revisit assessments. A significance level of $p<0.05$ was selected a priori and was calculated using GraphPad software.

Part 2: Clinical Decision Support

The main goal of the CDS aspect of this project was to develop alerts that

FIGURE 1. Example of Genomic Indicator Entry



would fire upon ordering a medication that may be impacted by an interaction with an individual's genomic variance. In order to create these, it was necessary to first develop an area within the Epic EMR where patient's genetic test results could be entered as a discrete field. Genetic tests were processed by an outside lab, and the results were provided in the form of a PDF document, which would then be scanned into the patient's EMR. Contents of scanned PDF documents are not currently able to serve as a source of criteria for an alert to fire. Epic already has infrastructure for a unique, discrete area of the EMR specifically for housing genetic test results. This area is called Genomic Indicators. With the help of an informatics pharmacist from the institution pharmacy department, Genomic Indicators was configured to meet the needs of this project. This included allowing for the manual entering, editing, and viewing of genotype test results, corresponding phenotype, a short description of the implications of the phenotype, and links to websites including PharmGKB, PharmGKB Pubmed, Genetic Testing Registry National Center for Biotechnology Information, and Online Mendelian Inheritance in Man (OMIM) for further information. See Figure 1 for an example of an entry in Genomic Indicators.

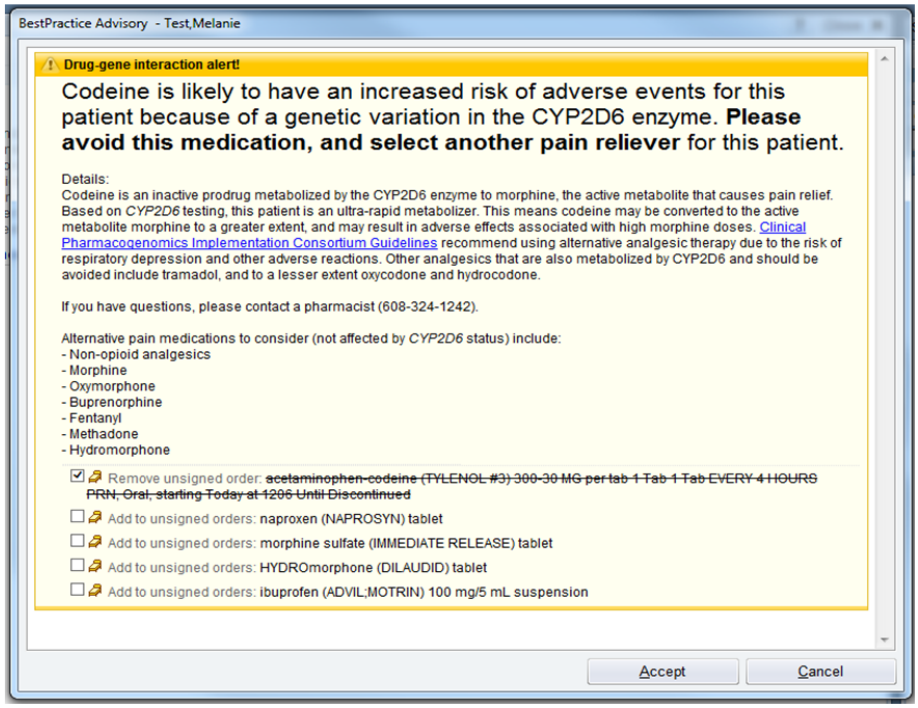
After the configuration of Genomic Indicators, alerts could then be created. The content of the alerts was based on available PGx guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC), Dutch Pharmacogenetics Working Group (DPWG), and the Canadian Pharmacogenomics Network for Drug Safety (CPNDS). The informatics pharmacist designed the alerts to fire upon ordering a medication that interacted with a patient's phenotype as entered into Genomic Indicators.

Each alert followed a standardized format, containing a summary statement with recommendation in bold, a paragraph with explanation and further details, a link to a website for further information, a prompt to remove the interacting medication, and suggestions for other medications with similar effects but no interaction with the gene (Figure 2). The criteria for each alert to fire varied somewhat depending on the properties of each medication, but usually considered whether the medication was new or existing, ordered as inpatient or outpatient, time since the medication existed on the patient's medication list (to prevent alerts from firing for refills), and which phenotype had been entered into Genomic Indicators (Figure 3). Each alert was presented to and approved by the Pharmacy & Therapeutics Committee. Alerts were created for codeine, tramadol, selective serotonin reuptake inhibitors, tricyclic antidepressants, phenytoin, carbamazepine, clopidogrel, warfarin, and metoprolol.

Outcomes for the CDS part of this study included tracking of the number of individuals with genetic test results available in Genomic Indicators, frequency of firing for each alert, and the override rate for these alerts.

Outside the existing platform of Genomic Indicators and a general template for alerts, all work was performed independently of the Epic corporation. The informatics pharmacist within the pharmacy department works with Epic programing interfaces and software regularly in order to tailor it to meet the needs of the hospital. The CDS in this project was developed in a similar fashion: using foundational structure purchased from Epic, and filling in substance, details, and criteria to best fit the hospital and its

FIGURE 2. Example of Gene-drug Alert



patient population.

This project was approved by the Pharmacy & Therapeutics Committee and follows the principles outlined in the Declaration of Helsinki.

Results

Part 1: Lecture Series

Average attendance was 28 study participants at each lecture. Of the subgroups, 13 providers, 12 pharmacists, and 12 leadership attended at least one lecture. Over the course of the study, attendance diminished slightly with each lecture as seen in Figure 4.

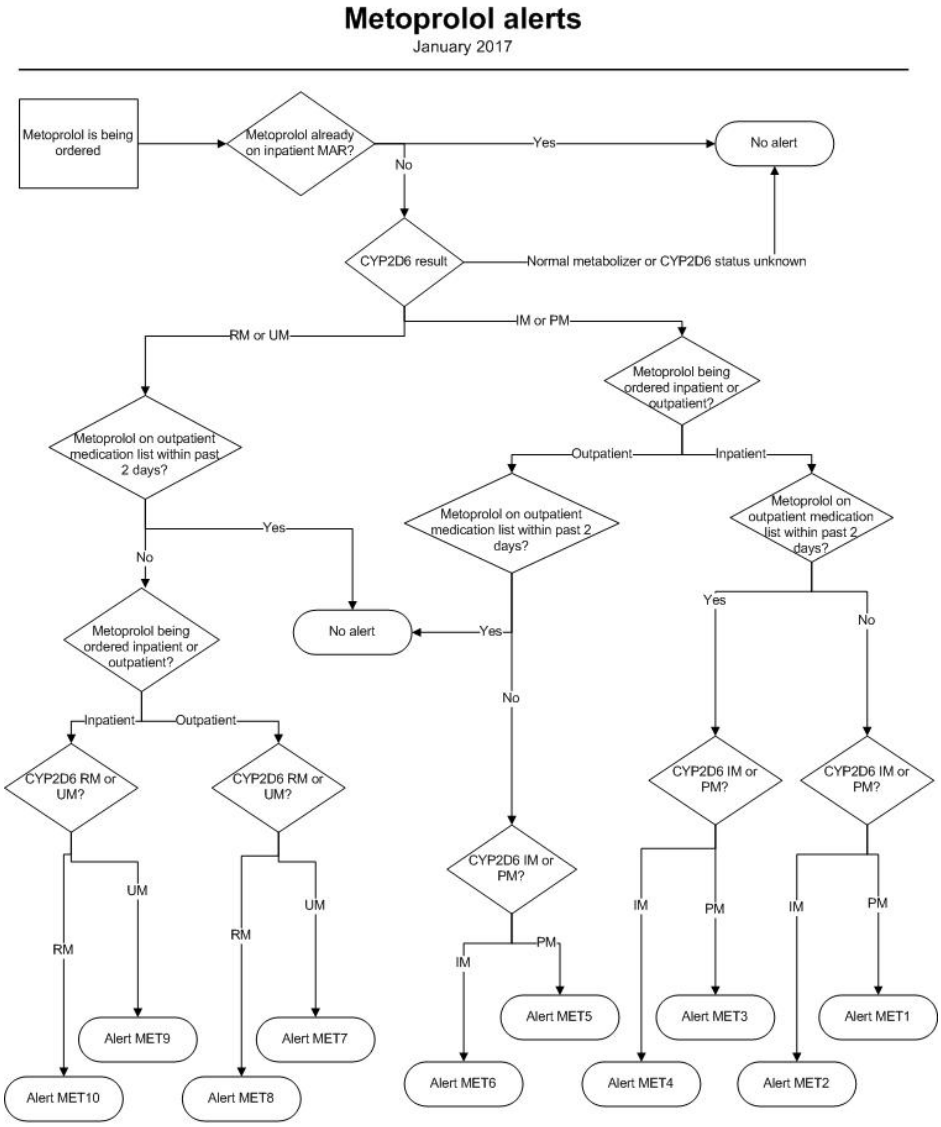
Most participants attended at least 4 presentations, and those who attended more lectures tended to score better overall (Figure 5). It should be noted that the scores of all individuals were included, even if they only attended one lecture. However, the revisit scores were not included for a participant who did not attend the previous lecture as this would not measure retention of knowledge, but a baseline knowledge.

Baseline knowledge of PGx was low at 37% correct, but increased significantly to 78% immediately after exposure to the material (absolute increase of 41%, p<0.0001, 95%CI 35.3-46%). This knowledge dropped significantly to 68% (absolute decrease of 10%, p=0.0013, 95%CI -16.8 - -4.5%) after several weeks, but maintained a significant increase from baseline (absolute increase of 31%, p<0.0001, 95%CI 22.7-40.2%).

Average scores of subgroups generally followed the pattern of the whole group average. Of note, the pharmacist score was the only one to drop significantly from the post assessment to revisit. Additionally, leadership scores were consistently below that of the providers and pharmacists (Table 2).

The questions used in the assessments were all original, developed specifically to reflect the objectives of each lecture. Because of this, they were not previously tested, and it was unknown if they would be an effective measure of PGx knowledge. Figure 6 shows a breakdown of score with each lecture. From this, it can be observed that lecture 4 had the most difficult questions, since participants scored just over 50% even after exposure to the material. Lecture 6 on the other hand had the easiest questions as nearly 60% of participants were able to answer correctly before exposure to the material.

FIGURE 3. Example of Decision Algorithm for Alerts to Fire



Part 2: Clinical Decision Support

Genetic test results for 31 individuals have been entered into the EMR so far. For reference, the overall patient population covered by the institution includes 53,000 patients over the past two years. Most of the tested individuals were referred from the Behavioral Health Department. All of the genetic test results were ordered through third party labs, the most common being GeneSight®.

To date, two gene-drug alerts have fired. The alerts did result in a change in the therapeutic plan for a patient. The patients were seen in the Behavioral Health Department, and had been genetically tested some time ago. The provider had forgotten the test results were available when ordering a medication, and when made aware of the alert, changed the plan. In one case, the provider decided to start a different medication within the same class as suggested within the alert. In the other case, the provider modified the starting dose of the medication triggering the alert.

Discussion

This study shows that a lecture series is effective in significantly increasing and maintaining clinician knowledge of PGx.

FIGURE 4. Attendance Over Time

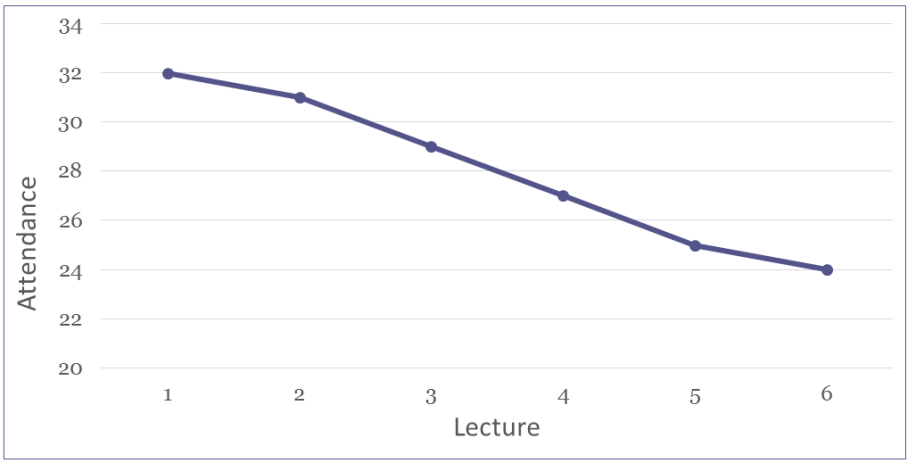
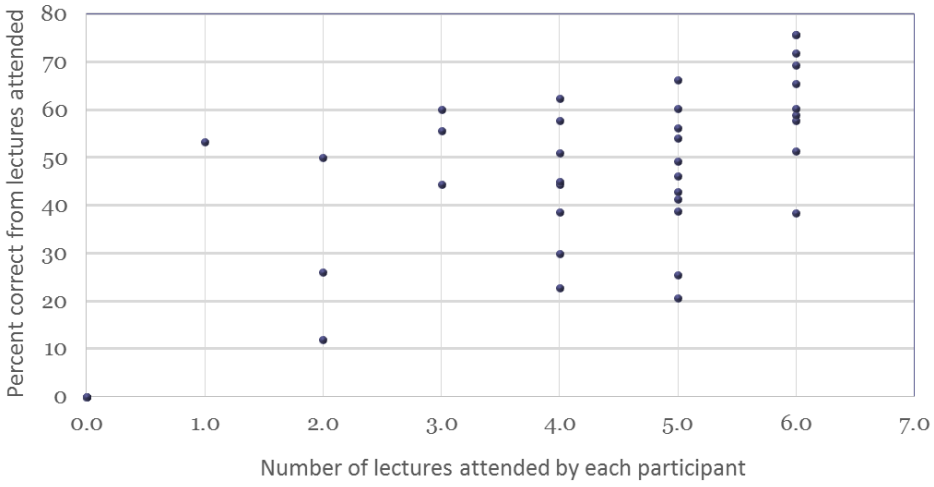


FIGURE 5. Relationship Between Attendance and Performance



Pharmacists, providers, and management follow this same pattern of progress. In general, managers tended to have the lowest scores, which is understandable given they have less opportunity to utilize clinical knowledge on a day to day basis. Overall, pharmacists were the only group to experience a significant drop from the post lecture to revisit questions (though they still retained significant improvement from the pre lecture assessment). The authors have been unable to isolate a clear explanation for this observation. Despite this, a lecture series is a great option for teaching PGx material to pharmacists, providers, and managers in a community hospital setting.

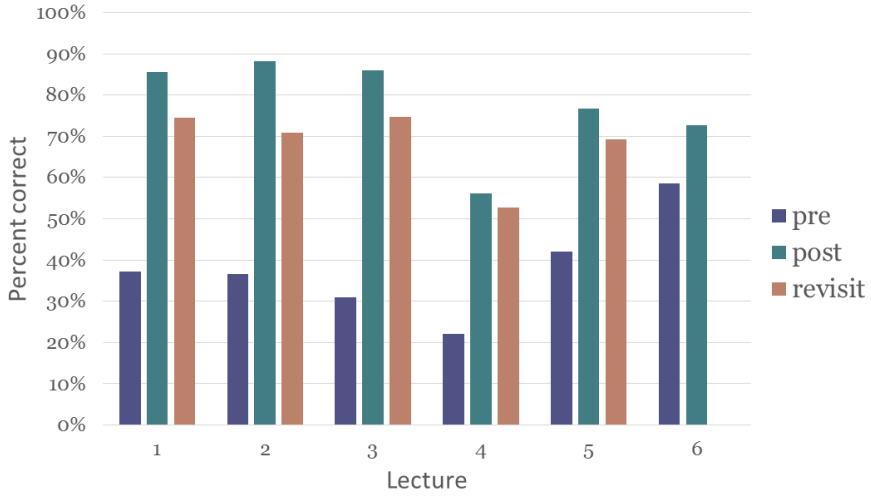
Unfortunately, not enough patients have undergone genetic testing at this institution to discuss the effects of the CDS developed through this project on patient outcomes, provider perceptions, and healthcare cost-benefit. This is also likely due to the short timespan since the existing results have been entered into the EMR, since as more time passes, the likelihood of an alert firing increases. However, for the instances an alert has fired so far, the CDS has been helpful in guiding the provider's clinical decision.

Given the experiences of the authors in developing the CDS and entering patient data, areas for process improvement can be identified. For instance, without developing a formal relationship with a single external lab and developing an interface between the reporting software and the EMR, the genetic test results cannot automatically transfer into the patient chart. These results are commonly sent to the physicians in a PDF format, which must then be entered into the chart manually. With any manual process, there are inefficiencies and opportunities for error. Thus, if an institution hopes to send for genetic tests on a semi-regular basis, it would be beneficial to select an external lab and work with them to develop an electronic interface. This interface was beyond the scope of this project, but could be considered for future development if and when genetic tests are ordered in higher volumes.

There are several limitations to this study. First, there were variations in lecture attendance, which is unavoidable in the setting of patient care, but may significantly impact assessment of change in knowledge over time. However, if anything, this would likely result in lower power which was not the case in this study with statistically significant knowledge improvements. Second, most lectures were 4 weeks apart, however, there was some variation in the timing between lectures. For instance, lectures 1 and 2 were six weeks apart, and lectures 2 and 3 were two weeks apart. Third, the pairings of participants with remotes for the electronic audience response system were tracked manually, allowing for some inconsistencies in the pairings. This may affect the accuracy of the subgroup responses, but should have no effect on the assessment of group knowledge. Fourth, the number of questions for each lecture did vary between 3 and 5. Only the last lecture had 3 questions, which less of an impact on the results since retention was not evaluated for these questions. However even the difference between 4 and 5 questions in the third lecture could affect the weighting of each question and bias the final results. An additional limitation is that the questions used to assess change in knowledge were all original. Because they were developed specifically to reflect the objectives of each lecture, it was unknown if they would be an effective measure of PGx knowledge. For instance the questions could be too easy or difficult for the audience, and may not accurately reflect evidence of improvement. Lastly, increased knowledge does not necessarily correlate with clinical skills. It is not known how clinical practice was affected by these lectures.

Regarding the software support side of this study, the study is limited by the minimal number of patients who currently

FIGURE 6. Percent Correct Per Question Type for Each Lecture



have PGx data available to enter into the EMR. Additionally, for those with PGx data, the results have existed as discrete fields for such a short duration, it is unlikely interacting medications will have been prescribed yet. However, the value of genetic data does not decrease over time, as the information remains relevant throughout a patient's lifetime, so it is likely that this information will be utilized again. There may also be difficulty in replicating this project at other institutions. The location of the informatics pharmacist in the hospital pharmacy department facilitated the dedication of the necessary time to develop the CDS described above. Time and availability of informatics pharmacists are resources that are very limited in many institutions.

Conclusion

The assessment of PGx knowledge over time revealed that providers, pharmacists, and healthcare leadership have a limited baseline knowledge of PGx. This is likely because PGx has only recently begun to be included in medical and pharmacy school curriculums. This study also showed that a six-lecture series is effective in increasing knowledge of PGx by approximately 50%, and that a significant portion of this knowledge is retained for at least two to five weeks following a lecture.

The two gene-drug alerts that have fired have been helpful in guiding provider decisions, however more alerts are needed before conclusions can be made regarding the effectiveness of the CDS. Given the small number of patients with PGx data available, and the short duration these results have existed in the EMR, it is not surprising that so few alerts have fired.

Elizabeth Neumann is a Pharmacy Resident, Julie Koch is an Informatics Pharmacist and Dave Grinder is the Director of Pharmacy at Monroe Clinic in Monroe, WI.

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