Improved Therapeutic Monitoring With Several Interventions

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A Randomized Trial

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Background: Medication errors are frequently related to failure to appropriately select medications or adjust for laboratory parameters. Differences between guideline recommendations and actual frequency of therapeutic laboratory monitoring are substantial. This study evaluated interventions to improve laboratory monitoring at initiation of medication therapy.

Methods: This cluster-randomized trial compared 3 interventions to usual care for 10 medications in 15 primary care clinics in a health maintenance organization with an electronic medical record system. Eligible patients, identified from electronic databases, had not received recommended laboratory monitoring within 5 days after new dispensing of a study medication. Interventions were an electronic medical record reminder to the prescribing health care professional, an automated voice message to the patient, and a pharmacy team outreach to the patient. Primary outcome was completion of all recommended baseline laboratory monitoring.

Results: A total of 961 patients participated in the study. At 25 days, 95 (48.5%) of 196 patients in the electronic medical record reminder group, 177 (66.3%) of 267 in the automated voice message group, 214 (82.0%) of 261 in the pharmacy team outreach group, and 53 (22.4%) of 237 in the usual care group had completed all recommended baseline laboratory monitoring ($P<.001$). After adjustments, the hazard ratios for completing laboratory monitoring compared with usual care were 2.5 (95% confidence interval, 1.8-3.5) for electronic medical record reminder, 4.1 (95% confidence interval, 3.0-5.6) for automated voice message, and 6.7 (95% confidence interval, 4.9-9.0) for pharmacy team outreach.

Conclusions: All 3 interventions were effective in increasing laboratory monitoring when initiating new medications in primary care. Further work is necessary to determine if these interventions improve patient outcomes.

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ERRORS AND PREVENTABLE adverse events associated with medication prescription and dispensing are common.[1] More than half of the adverse events in the inpatient setting are attributable to preventable errors.[2,3] In the outpatient setting, avoidable adverse drug events account for approximately 2% of outpatient visits based on medical record review and 18% according to patient self-report.[4] Errors are frequently related to failure to appropriately select or adjust medications for laboratory parameters.[3] Failure to monitor drug therapy is among the most frequent causes of preventable adverse drug events.[5]

Therapeutic monitoring is recommended when initiating therapy with many medications to assist with medication selection and dosing.[6] For example, the use of thiazolidinediones for diabetes has been associated with liver toxicity, and baseline liver enzyme testing is recommended.[7] The difference between guideline recommendations and the actual frequency of baseline medication laboratory monitoring is substantial[7,8]; only 61%

See also pages 1802, 1822, 1829, 1836, 1842, and 1855

of patients in a recent study[8] in 10 health maintenance organizations (HMOs) received monitoring. Methods to improve therapeutic monitoring are the subject of a new National Center for Quality Assurance Health Employer Data and Information Set quality-of-care measure (http://www.ncqa.org/Programs/HEDIS/HEDIS_2006_Summary.pdf).

It remains unclear what strategies can best assist health care professionals and patients to complete laboratory monitoring.

Although alerts and reminders to physicians and patients have been shown to be effective in several clinical areas,[9] less is known about their effectiveness in the context of medication safety, especially in the outpatient setting. Encouraging medication-related laboratory tests at the time of prescribing has enhanced ordering.[10] However, only 1 study[11] evaluated a "safety net" intervention to implement monitoring after a medication was prescribed without monitoring. How best to deliver medication safety reminders and to whom they should be delivered (eg, the patient, the primary care provider [PCP], or support staff) also remain important questions. This study evaluated 3 safety net interventions to improve laboratory monitoring when medications were initiated without baseline monitoring: an electronic medical record (EMR) reminder to the prescribing health care professional, an automated telephone voice message (AVM) to the patient, and a pharmacy team outreach to the patient.

METHODS

The study design and procedures were approved by the study HMO's institutional review board. The need for informed consent was waived. The study was conducted in a not-for-profit group model HMO with 15 primary care clinics and approximately 465 000 members. The HMO has used an EMR system since 1996. Comprehensive electronic databases are linked through the unique health record number of each HMO member. The databases capture more than 95% of the medical care and pharmacy services members receive,[12] including outside care, which is billed to the HMO. Nearly all the HMO's patients taking medications on a long-term basis have a prescription drug benefit, and most do not have to make a copayment for laboratory testing.

STUDY DESIGN AND PARTICIPANTS

In this cluster-randomized trial, the unit of randomization was the primary care clinic. The unit of intervention was either the PCP (1 arm) or the patient (2 arms). The unit of analysis was the patient. The study period was September 7, 2003, through January 19, 2005. The period September 7, 2003, through September 6, 2004, provided baseline laboratory-monitoring data (for the clinic randomization procedure); September 6, 2004, through December 20, 2004, was the enrollment and intervention period; and September 6, 2004, through January 19, 2005, was the follow-up period. The primary outcome was laboratory completion, which was defined as the completion of all recommended baseline laboratory monitoring when initiating use of a new study medication. Primary outcomes were obtained entirely from electronic records, and the study analyst was blinded to study group assignment before ascertainment of outcomes.

Figure 1 shows the study design and participant flow during the trial. The HMO's 15 primary care clinics were block randomized to the 4 study conditions (usual care [UC] and 3 interventions) by the study statistician according to their baseline laboratory completion rates for the study medications during the year before implementing the interventions. The random sequence was generated by a computerized random-number generator. All 15 clinics were randomized at one time; therefore, allocation concealment was not an issue.

All adult-medicine PCPs in the HMO were eligible to participate (n=293). We requested all eligible PCPs (regardless of study arm) to sign a clinical protocol that authorized other licensed staff to order laboratory testing for their patients initiating use of study medications if patients had not completed baseline laboratory testing. This was done as part of a routine protocol authorization through the pharmacy department. The PCPs were not aware that this was a study. The PCPs and patients understood the interventions to be new pilot programs. Of the eligible PCPs, 253 (83.4%) completed the orders. Of the 253 PCPs who completed orders, 200 (79.1%) had patients eligible and enrolled in the study; these PCPs were included in the analyses. The PCPs and their patients enrolled in the study received the study condition to which their clinic was randomized.

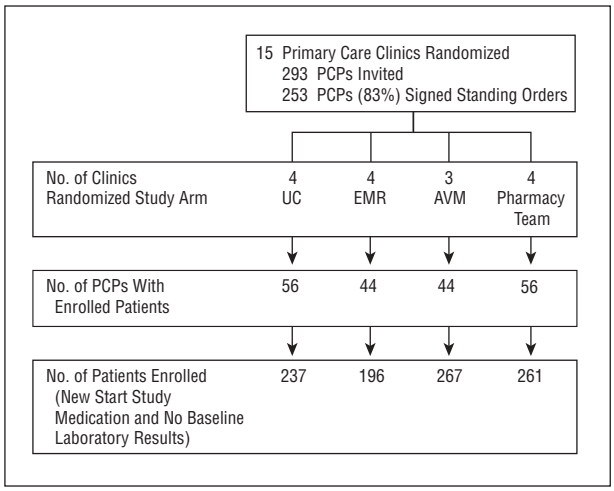

Figure 1. Study design and participant flow. UC indicates usual care; EMR, electronic medical record reminder; AVM, automated voice message; and PCP, primary care provider. Patients met the study eligibility criteria of age of 18 years or older, health maintenance organization enrollment of 12 months or more, prescription drug benefits, and telephone number. Exclusion criteria were hospice care, nursing home care, care outside the health maintenance organization, enrollment in other care management program, or need for translation services.

Eligible patients of participating PCPs were identified electronically using the HMO's linked databases. Eligible patients (n=1075) were older than 18 years; spoke English; had continuous HMO membership for at least 12 months, a pharmacy benefit, and a telephone number; had received a new prescription of a study medication from their PCP; and had not had recommended baseline laboratory monitoring within 5 days after the medication dispensing. Eligibility also depended on not having had care outside the health plan, where unascertainable outside laboratory monitoring could have occurred, in the prior 6 months. A new prescription was defined as no evidence of a supply of the medication in the prior 6 months. Baseline laboratory monitoring was defined as incomplete if all recommended monitoring tests (**Table 1**) were not completed within the window of 6 months before and 5 days after the dispensing of the new prescription.

Individual medical record reviews by the study nurse excluded those who had received outside care (n=33; 2.5%), had completed baseline laboratory tests (n=59; 4.4%), had stopped using the study medication between the electronic identification and enrollment date (n=4; 0.3%), or were enrolled in a case management program (n=18; 1.4%). All eligible patients identified during the enrollment period were automatically included. Patient participants were masked from the nature of the study. Because of the nature of the intervention, the study nurse conducting the interventions was not blinded to group assignment. No patients were lost to follow-up.

INTERVENTION DESIGN

To select the study medications, the investigators and an HMO expert advisory group reviewed HMO data regarding prescrib-

Table 1. Study Medications and Laboratory-Monitoring Recommendations at Medication Initiation

Medication	Baseline Laboratory Test(s)
ACE/ARB	Serum creatinine, serum potassium
Allopurinol	Serum creatinine
Carbamazepine	Serum ALT or AST, CBC, serum sodium
Diuretic	Serum creatinine, serum potassium
Metformin	Serum creatinine
Phenytoin	Serum ALT or AST, CBC
Pioglitazone	Serum ALT or AST
Potassium	Serum creatinine, serum potassium
Statins Serum	Serum ALT or AST
Terbinafine	Serum creatinine, serum ALT or AST

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; CBC, complete blood cell count.

ing frequency for primary care medications that required laboratory monitoring, monitoring rates before the intervention,[8] and HMO data and expert sources regarding potential adverse events and the severity of resulting health conditions.[6] The 10 study medications or medication classes selected and their laboratory-monitoring recommendations at initiation of therapy are presented in Table 1. The monitoring recommendations were consistent with prevailing guidelines, and most of the agents commonly used in primary care for which monitoring is recommended were included.[6,8] The guidelines for laboratory monitoring were posted on an HMO internal Web site and were available to all HMO health care professionals. All the interventions consisted of a reminder at baseline and again 9 to 10 days later for nonrespondents (**Figure 2**). All laboratory test results were returned to the PCP for follow-up.

EMR INTERVENTION

The EMR intervention consisted of a patient-specific electronic message to the PCP from the chair of the patient safety committee. The message stated that computer records indicated that the patient had been dispensed a new medication, laboratory monitoring was recommended, and the patient had not received the test(s) between 6 months before and 5 days after the dispensing. The message referenced internal and external guideline resources, recommended specific tests, and provided a sample letter the PCP could send to the patient to request that he or she go to the laboratory.

AVM INTERVENTION

The AVM intervention included privacy rule–compliant recorded telephone messages to prompt the patient to seek preordered laboratory tests. An initial message stated that a message was waiting for (named individual). A personalized message retrieved after entering a health record number and year of birth stated that the medication the patient had been dispensed required laboratory monitoring; messages referenced the actual drug dispensed and the monitoring tests required. The patient was advised that the testing had been ordered and could be completed at any HMO laboratory.

PHARMACY TEAM OUTREACH INTERVENTION

The pharmacy team outreach began with a telephone call from a nurse in the pharmacy department to the patient to encourage

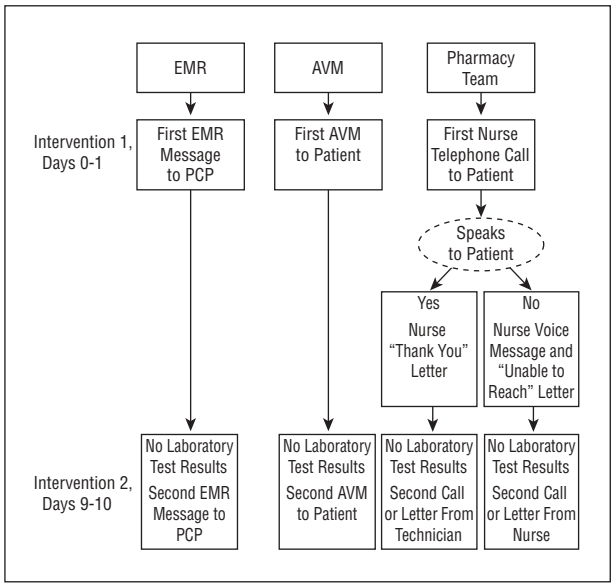

Figure 2. Intervention design. EMR indicates electronic medical record reminder; AVM, automated voice message; and PCP, primary care provider.

laboratory testing. If the nurse successfully contacted the patient, a follow-up letter reminded the patient to obtain the laboratory test(s). If telephone contact was not successful, the nurse sent a letter suggesting that the patient go in for testing. If patients had questions or concerns about their medication during the contacts, a pharmacist was available for consultation.

OTHER EXPLANATORY VARIABLES

Additional measures included PCP sex, professional degree (eg, MD, NP, or PA), and number of years of experience in the organization. Patient information included age, sex, chronic disease score,[13] medication initiated (grouped as statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and others), and the presence or absence of depression, laboratory copayment, and outpatient clinic visit during the follow-up period. We also collected laboratory test results during the follow-up period.

STATISTICAL ANALYSIS

We compared baseline characteristics of the clinics, PCPs, and patients using *t* tests for continuous variables and χ^2 tests for categorical variables. Using retrospective data, we estimated that 25% of the UC group would receive laboratory testing by 30 days after a new medication was dispensed. With 200 patients per group, we determined that we could detect a difference of approximately 13% between the groups with a probability of 0.80.

The effect of the interventions on time until the laboratory tests were completed compared with UC was estimated using Cox proportional hazards models[14] during 25 days of follow-up using SAS/STAT statistical software, version 8.2 (SAS Institute Inc, Cary, NC). All models included the covariates of patient age, office visit in the follow-up period, and indicator variables for study medication group. We found that the number of follow-up visits was independent of the interventions, so we used this as a control variable. The model included indicator variables that compared each intervention with UC and the covariates.

Multilevel logistic regression was used to examine the effect of the interventions on laboratory test completion during the 25-day follow-up period while controlling for the effect of intraclass correlation using hierarchical linear modeling software.[15] The first

Table 2. Baseline Participant Characteristics by Study Group

Characteristic	Usual Care	Electronic Medical Record	Automated Voice Messaging	Pharmacy Team
Clinics				
No.	4	4	3	4
Laboratory-monitoring rate, %*	60.4	59.7	53.2	59.1
Health care professionals†				
No.	56	44	44	56
Female, %	40.1	39.8	23.6	38.7
Age, mean (SD), y	46.8 (6.8)	48.0 (6.4)	46.9 (7.6)	48.8 (7.0)
Experience, mean (SD), y	10.5 (7.2)	11.6 (6.8)	11.5 (4.8)	12.6 (6.9)
Physician participants, %	84.8	89.3	94.4	85.1
Patients*				
No.	237	196	267	261
Female, %	53.6	54.1	51.7	54.0
Age, mean (SD), y	57.9 (13.1)	59.3 (12.2)	58.9 (13.4)	60.7 (12.8)
CDS, mean (SD)	2701.7 (1856.6)	2614.8 (1975.0)	2667.3 (2133.1)	2759.0 (1786.6)
Depression, %	13.9	9.7	8.6	10.0
Laboratory test copayment, % yes	10.1	13.8	14.9	12.3
Visit during follow-up, % yes‡	50.6	45.9	42.3	49.0
Study medication group, No. (%)§				
ACE/ARB	57 (24.0)	58 (29.6)	81 (30.3)	83 (31.8)
Statins	98 (34.6)	85 (27.0)	95 (34.1)	92 (32.9)
Others	82 (41.3)	53 (43.4)	91 (35.6)	86 (35.2)

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CDS, chronic disease score.
*Baseline data in the 1 year before the intervention period.
†Health care professionals with enrolled patients.
‡Outpatient visit between enrollment and end of follow-up period.
§Class of study medication initiated. Statins include 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors; others include diuretics, allopurinol, carbamazepine, metformin, phenytoin, pioglitazone, potassium, and terbinafine.

level of the logistic regression models included the covariates of patient age, office visit in the follow-up period, and indicator variables for study medication group. The second level included indicator variables comparing each intervention with UC.

An additional analysis to examine the effect of PCP characteristics included only the arms in which the PCP was involved, UC and EMR. Multilevel logistic regression was used to evaluate the outcome of whether the laboratory test was completed. The first level of the logistic regression models included the covariates of patient age, office visit in the follow-up period, and indicator variables for study medication group. The second level included the effect of PCP sex, PCP experience (in years), EMR vs UC, and the interaction of the PCP characteristics with study arm. We also evaluated the differences in the proportions of patients who had an abnormal laboratory test result, by study group, using the χ^2 test.

QUALITATIVE EVALUATION

We conducted telephone interviews with 16 PCPs and 22 patients who agreed to assess acceptability of the interventions after the follow-up period. Their responses were content analyzed.

RESULTS

Baseline characteristics of the 961 study participants are presented in **Table 2**. In the 12 months before the interventions, the laboratory-monitoring rate at the initiation of therapy (those who had initiated a study medication and had completed all recommended baseline laboratory testing) was similar in the study groups. The other characteristics of the study groups were also similar except that the AVM group had a smaller proportion of female PCPs.

By day 9 (immediately before the second reminder), 34 (14.3%) of 237 patients in the UC group, 61 (31.1%) of 196 patients in the EMR group, 117 (43.8%) of 267 patients in the AVM group, and 184 (70.5%) of 261 patients in the pharmacy team outreach group had completed all recommended baseline laboratory monitoring ($P<.001$). By day 25 (approximately 2 weeks after the second reminder), 53 (22.4%) of the 237 patients in the UC group, 95 (48.5%) of the 196 patients in the EMR group, 177 (66.3%) of the 267 patients in the AVM group, and 214 (82.0%) of the 261 patients in the pharmacy team outreach group had completed all monitoring ($P<.001$). All differences among arms were statistically significant at $P<.05$.

Figure 3 presents the hazard function for the final Cox proportional hazards model that predicted time until laboratory-monitoring completion for the intervention groups, adjusted for patient age, office visit in the follow-up period, and study medication group. The pharmacy team outreach intervention was the most effective during the observation period, followed by AVM and then EMR.

Table 3 presents the hazard ratios and associated 95% confidence intervals for the hazards model. Patients in the EMR group were 2.5 times more likely than patients in the UC group to complete laboratory monitoring ($P<.001$), patients in the AVM group were 4.1 times more

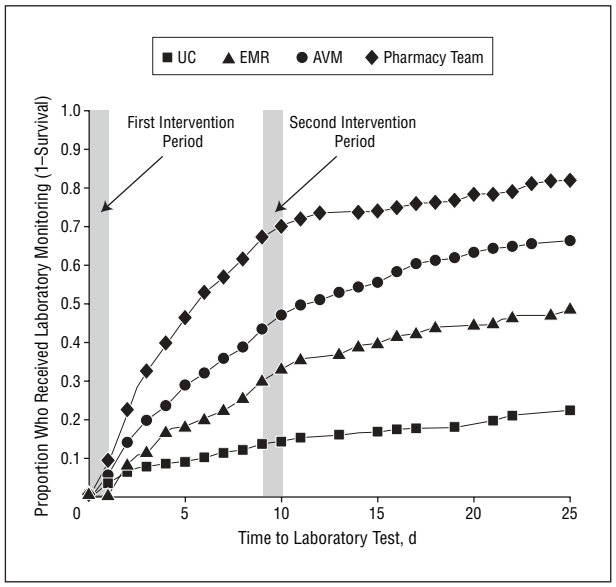

Figure 3. Laboratory monitoring after intervention by study group. UC indicates usual care; EMR, electronic medical record reminder; AVM, automated voice message.

Table 3. Final Cox Proportional Hazards Model Results*

Variable	HR (95% CI)	*P* Value
Intervention		
EMR	2.5 (1.8-3.5)	<.001
AVM	4.1 (3.0-5.6)	<.001
Pharmacy team	6.7 (4.9-9.0)	<.001
Patient age	1.01 (1.01-1.02)	<.001
Study medication group		
ACE/ARB	1.3 (1.1-1.6)	.009
Others	0.9 (0.7-1.1)	.24
Office visit during follow-up (yes/no)†	1.3 (1.1-1.6)	.001

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AVM, automated voice message; CI, confidence interval; EMR, electronic medical record reminder; HR, hazard ratio.

*The usual care group was the reference for the interventions; statin was the reference for the study medication group.

†Office visit during observation period.

likely ($P<.001$), and patients in the pharmacy team outreach group were 6.7 times more likely ($P<.001$). Three of the covariates were significantly related to time until laboratory-monitoring completion. For each 10-year increase in patient age, patients were 10% more likely to complete monitoring. Those taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (when compared with statins) and those having an office visit during the study follow-up period were 30% more likely to complete laboratory monitoring.

The multilevel logistic regression, which controls for the nesting of patients within PCPs, found the same pattern. The subgroup analysis that compared the UC and EMR arms found that the EMR intervention was more effective for female PCPs than for male PCPs (odds ratio, 4.8; 95% confidence interval, 1.9-12.1).

We evaluated the proportion of patients who had any abnormal result on monitoring tests during follow-up.

Table 4. Abnormal Laboratory Test Results Detected by Study Medication Group

Abnormal Laboratory Test Type	Abnormal Results, No. (%)	Range of Abnormal Results	Reference Range
Statins (n = 370)*			
Serum ALT, U/L	13 (3.5)	62-113	10-58
Serum AST, U/L	6 (1.6)	44-81	5-43
ACE/ARB (n = 279)			
Creatinine, mg/dL	8 (2.9)	1.3-1.9	0.6-1.3
Serum potassium, mEq/L			3.5-5.1
Low	6 (2.1)	3.1-3.4	<3.5
High	2 (0.7)	5.2-5.7	>5.1
Others (n = 312)			
Creatinine, mg/dL	14 (4.5)	1.3-3.6	0.6-1.3
Serum potassium, mEq/L	14 (4.5)	3.1-3.4	3.5-5.1
Serum ALT, U/L	7 (2.2)	64-149	10-58
Serum AST, U/L	2 (0.6)	62-69	5-43
WBC, $\times 10^3/\mu L$	2 (0.6)	11.5-19.7	4.0-10.5
Total (N = 961)	**72** (7.5)		

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; WBC, white blood cell count.

SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.

*Study medications included statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors), ACEs, ARBs, and others (diuretics, allopurinol, carbamazepine, metformin, phenytoin, pioglitazone, potassium, and terbinafine).

Of 961 patients, 57 had 1 or more abnormal results. The pattern of abnormal results followed the same pattern as laboratory completion. Although the proportion of abnormal test results did not differ significantly by arm, differential monitoring rates led to the lowest rates of abnormal results detected in the UC group (7/237 [3.0%]), followed by the EMR (10/196 [5.1%]), AVM (18/267 [8.4%]), and pharmacy team outreach (22/261 [8.4%]) groups ($P=.06$). The 57 patients had a total of 72 abnormal test results (72/961 [7.5%]) (**Table 4**).

The qualitative interviews found that all 3 interventions were acceptable to PCPs and patients. The PCPs preferred the assistance with therapeutic monitoring provided by the AVM and pharmacy team outreach interventions over the EMR intervention. Several PCPs stated that baseline therapeutic monitoring of statins was not warranted.

COMMENT

We found that all 3 of our interventions improved laboratory monitoring at the initiation of medication therapy. We know of no other study that has compared these outreach strategies to address guideline-based errors of omission in primary care, particularly in the medication safety arena. Our findings reinforce the notion that routine linkage of pharmacy and laboratory data holds great promise for reducing medication errors and adverse events.[16] This project applied reminder techniques that have been used successfully in other clinical areas[9,17] to increase medication safety in the outpatient setting. Our results regarding the acceptability and effectiveness of elec-

tronic and telephone reminders are consistent with previous studies.[10,11,17,18]

All 3 interventions had large effect sizes when compared with other clinical decision support systems to improve medication safety.[10] Several factors may account for the differential results. The EMR intervention depended on the PCP and his or her team to follow up with patients, adding at least 1 extra step in the process, whereas the AVM and pharmacy team outreach interventions went directly to the patient. Mirroring the findings in another study,[19] the PCPs expressed frustration regarding cluttered electronic in-boxes and the desire for assistance with managing tests. The EMR intervention also involved the most clinical judgment; the other 2 interventions were implemented by nonphysician staff according to guidelines. The PCPs may have doubts about the clinical utility of some laboratory monitoring, especially for statins.[20]

The AVM intervention may prove to be a cost-effective intervention to improve completion of many guideline-based procedures. Although the AVM intervention has proved effective for preventive education and reminders and has shown promise for improving medication compliance, disease management, and lifestyle change,[21-23] no previous studies have evaluated the use of AVM for encouraging laboratory monitoring to enhance medication safety.

Pharmacy was likely more effective because it involved the most systematic personalized interaction. Discussions with the pharmacy staff and an examination of their time log (including patient contact and record keeping) indicate that the outreach took approximately 9 minutes per patient. Consideration of the balance between resources expended and effectiveness is particularly important for health care systems to consider as electronic systems designed to address gaps in safety and quality become more ubiquitous. One prior effectiveness trial of a pharmacy telephone outreach program to improve baseline laboratory monitoring for 15 medications or classes found that 79.1% of medication dispensings were monitored in the intervention group compared with 70.2% in the UC group ($P<.001$).[24] Although our pharmacy team intervention appears more effective, the studies are not directly comparable. There were differences in the medications targeted; the prior study[24] included all patients given study medications, whereas our study included only patients identified as without monitoring. In addition, our study was an efficacy trial managed in a more controlled research setting.

Contrary to our expectation that older patients might have more barriers to laboratory completion and might have difficulty responding to AVMs, we found that older patients were more likely to complete laboratory tests consistently across all study arms. These interventions therefore hold particular promise for older patients, who are more likely to be taking these medications and who have much room for improvement in therapeutic monitoring.[25] We did not investigate why older individuals were more likely to receive laboratory testing. One possibility is that the opportunity costs associated with laboratory completion are less for older people than for other patients.

When comparing the 2 arms where PCP judgment may have played a role (UC and EMR), we found that patients of female PCPs were more likely to receive laboratory tests. This finding is consistent with the findings from 1 observational study,[8] a clinical trial that addressed medication-related laboratory testing,[24] and 1 study of an EMR reminder to order serum potassium testing for patients taking diuretics.[11]

This study has several limitations. It was conducted within a single HMO in 2 western states. The effect of the interventions (especially EMR) thus may not be completely generalizable to other practice settings. Because we enrolled all eligible patients during the enrollment period, however, we believe that the findings from the direct-to-patient interventions (AVM and pharmacy team outreach) likely are representative of this patient population and perhaps many similar communities. We found a small proportion (7.5%) of abnormal laboratory-monitoring test results in the study population and a nonsignificant difference between the study groups. The study was not designed to determine if the interventions led to improved detection of abnormal baseline laboratory test results or significant changes in patient care and outcomes. Further work in these areas and the relative cost-effectiveness of the interventions will be critical for guiding care. A hybrid approach to the intervention that includes AVM followed by pharmacy team outreach for nonresponders may prove particularly attractive.

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