

4-6-2011

Factors Associated with Ordering and Completion of Laboratory Monitoring Tests for High-Risk Medications in the Ambulatory Setting: A Dissertation

Shira H. Fischer

University of Massachusetts Medical School, shira.fischer@umassmed.edu

Follow this and additional works at: http://escholarship.umassmed.edu/gsbs_diss

 Part of the [Health Services Research Commons](#), and the [Life Sciences Commons](#)

Repository Citation

Fischer, Shira H., "Factors Associated with Ordering and Completion of Laboratory Monitoring Tests for High-Risk Medications in the Ambulatory Setting: A Dissertation" (2011). University of Massachusetts Medical School. *GSBS Dissertations and Theses*. Paper 543.

http://escholarship.umassmed.edu/gsbs_diss/543

This material is brought to you by eScholarship@UMMS. It has been accepted for inclusion in GSBS Dissertations and Theses by an authorized administrator of eScholarship@UMMS. For more information, please contact Lisa.Palmer@umassmed.edu.

A Dissertation Presented

By

SHIRA HANNAH FISCHER

Submitted to the Faculty of the

University of Massachusetts Graduate School of Biomedical Sciences,

Worcester, MA

In partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

APRIL 6, 2011

MD/PHD PROGRAM

CLINICAL AND POPULATION HEALTH RESEARCH

**FACTORS ASSOCIATED WITH ORDERING AND
COMPLETION OF LABORATORY MONITORING TESTS
FOR HIGH-RISK MEDICATIONS IN THE AMBULATORY
SETTING: A DISSERTATION**

**A Dissertation Presented
By
SHIRA HANNAH FISCHER**

The signatures of the Dissertation Defense Committee signifies completion and approval as to style and content of the Dissertation.

Terry Field, D.Sc., Thesis Advisor

Gordon FitzGerald, Ph.D., Member of Committee

Barry Saver, M.D., M.P.H. Member of Committee

David Bates, M.D., M.Sc., Member of Committee

The signature of the Chair of the Committee signifies that the written dissertation meets the requirements of the Dissertation Committee.

Patricia Franklin, M.D., M.B.A., M.P.H., Chair of Committee

The signature of the Dean of the Graduate School of Biomedical Sciences signifies that the student has met all graduation requirements of the school.

Anthony Carruthers, Ph.D.,
Dean of the Graduate School of Biomedical Sciences

Clinical and Population Health Research

April 6, 2011

Dedicated to my family

ACKNOWLEDGEMENTS

This thesis work would not have been possible without all the support I received from so many wonderful people.

The MD/PhD program, first under Dr. Elliot Androphy and now under Dr. Gyongi Szabo, advocates for its students in so many ways. From travel and research opportunities to monthly dinners, we have been supported as we navigate from medicine to research and back. The program understands the variety of paths to this degree and I am ever grateful that I was able to do some of my clinical training before embarking on this research project, which I believe was greatly enriched by that experience.

My fellow students MD/PhD students have taught me about perseverance and hard work and continue to inspire me.

The Clinical and Population Health Research Program, a relatively new member of the team of research programs at UMass, has been my home these past few years. The staff has been helpful through coursework and paperwork, and the faculty is always responsive to students. Thank you in particular to Dr. Stephenie Lemon for her help with my proposal and to Dr. George Reed for his assistance and expertise.

I am grateful to Dr. Carole Upshur for helping me figure out my path, from my first days selecting research rotations to last-minute details regarding this thesis, and for introducing me to the Meyers Primary Care Institute.

Meyers is an amazing institution and I owe everyone there my gratitude for welcoming me into their family, for involving me in their projects and meetings, and for teaching me at every opportunity.

I am particularly indebted to the RAMPAGE team, including Jennifer Donovan, Dr. Larry Garber, Abir Kanaan, and Peggy Preusse, my closest colleagues at Meyers, who in addition to being excellent researchers also know how to brave adversity with humor and equanimity. Dr. Kathy Mazor was extremely helpful in designing the questionnaire and the analysis for the qualitative interviews, and Shawn Gagne, a star research assistant, conducted them all. He will make a great clinician if Meyers ever lets him leave. And for teaching me how to acquire and analyze other study data, Devi Sundaresan and Dan Peterson were invaluable.

Dr. Jerry Gurwitz, the director of Meyers, told me at the beginning that this process would be challenging and frustrating, but that in the end I would learn a lot and that ultimately, it would be a very rewarding experience. He was right on all counts.

Dr. Terry Field, my thesis advisor, has been so patient and supportive. She provided an environment where I could explore and learn but was always available if I needed advice or guidance. She encouraged me to branch out to qualitative research and to take courses in informatics along the way, greatly expanding my education.

I owe a particular debt of gratitude to Dr. Jennifer Tjia, who has been an anchor for me throughout this process. She models how to be an efficient, effective researcher and clinician while maintaining a rich family and personal life. She read every word of this thesis and not only suggested ways to improve it but also explained why it would be

stronger for the change. And when I ran into problems or when multiple paths presented themselves, she reassured me that I could trust my intuitions and that I did, in fact, know what I was doing. She shared stories of her own failures as well as successes so I could benefit from her experience. I am so grateful to her.

And to the friends who have supported me along the way, from meeting in coffee shops to work on drafts, to puzzling through STATA together, to commiserating on thesis challenges, to lending me clothes that would fit me for my defense—Michelle, Hilary, Marie, Erin, Elesheva, and Tovah—thank you! I wouldn't have made it through without all that love and all those lattes.

Finally, I would like to thank my family. My siblings have always kept me entertained and have been an amazing source of support and love. My parents have provided support and love as well, in addition to all-important home-cooked meals along the way. Their belief in me has made it possible for me to believe in myself.

My family has expanded since I began this dissertation. My husband has not only been a great source of encouragement. He has been an inspiration, not only because of his devotion to his research, but even more because of his devotion to his patients. He daily reminds me that no matter how wonderful a health care system we create, there is no replacement for a competent and caring clinician. His patients are lucky to have him as their doctor, and I am so blessed to have him as my partner.

ABSTRACT

Since the Institute of Medicine highlighted the devastating impact of medical errors in their seminal report, “To Err is Human” (2000), efforts have been underway to improve patient safety. A portion of medical errors are due to medication errors, and a large portion of these can be attributed to inadequate laboratory monitoring.

In this thesis, I attempt to address this small but important corner of this patient safety endeavor. Why are patients not getting their laboratory monitoring tests? Do they fail to complete them or do doctors not order the tests in the first place? Which prescribers and which patients are least likely to do what is needed for testing to happen and what interventions would be most promising?

To address these questions, I conducted a systematic review of existing interventions. I then proceeded with three aims: 1) To identify reasons that patients give for missing monitoring tests; 2) To identify patient and provider factors associated with monitoring test ordering; and 3) To identify patient and provider factors associated with completion of ordered testing.

To achieve these aims, I worked with patients and data at the Fallon Clinic. For aim 1, I conducted a qualitative analysis of their reasons for missing tests as well as reporting completion and ordering rates. For aims 2 and 3, I used electronic medical record data and conducted a regression with patient and provider characteristics as covariates to identify factors contributing to test ordering and completion.

Interviews revealed that patients had few barriers to completion, with forgetting being the most common reason for missing a test. The quantitative studies showed that: older patients with more interactions with the health care system were more likely to have tests ordered and were more likely to complete them; providers who more frequently prescribe a drug were more likely to order testing for it; and drug-test combinations that were particularly dangerous, indicated by a black box warning, were more likely to have appropriate ordering, though for these combinations, primary care providers were less likely to order tests appropriately, and patients were less likely to complete tests.

Taken together, my work can inform future interventions in laboratory monitoring and patient safety.

TABLE OF CONTENTS

COVER PAGE	i
SIGNATURE PAGE	ii
ACKNOWLEDGEMENTS	iv
ABSTRACT	vii
TABLE OF CONTENTS	ix
LIST OF TABLES	xii
LIST OF FIGURES	xiii
PREFACE	xiv
CHAPTER I: INTRODUCTION	1
A. Laboratory Monitoring	2
B. Interventions to Date	4
C. Ordering and Completion	4
D. Conceptual Model	5
E. Proposed Study	7
F. Dataset	8
G. Significance	11
H. Specific Aims	12
I. Summary	13
CHAPTER II: THE IMPACT OF HEALTH INFORMATION TECHNOLOGY INTERVENTIONS TO IMPROVE MEDICATION LABORATORY MONITORING FOR AMBULATORY PATIENTS: A SYSTEMATIC REVIEW	15
A. Abstract	16
B. Introduction	17
C. Methods	19
i. Literature Search	19
ii. Inclusion Criteria and Selection of Studies	19
iii. Data Abstraction and Evaluation	21
D. Results	22
i. Study Quality and Impact on Laboratory Monitoring	24
ii. Study Site Characteristics and Impact on Laboratory Monitoring	25
iii. Intervention Design and Impact on Laboratory Monitoring	26
E. Discussion	29
CHAPTER III: HIGH-RISK MEDICATION MONITORING TESTS: A MIXED- METHODS EXPLORATION OF COMPLETION AND BARRIERS	34
A. Abstract	34
B. Background	37
C. Study Design and Sample	39
i. Quantitative Analysis	43
ii. Qualitative Analysis	44
D. Results	47

i. Quantitative Study	47
ii. Qualitative Results	50
E. Discussion	55
i. Forgetting and Reminders	57
ii. Conclusion	59
CHAPTER IV: FACTORS ASSOCIATED WITH ORDERING LABORATORY	
MONITORING OF HIGH-RISK MEDICATIONS.....	61
A. Abstract	61
B. Background	64
C. Methods.....	66
i. Study Design and Setting.....	66
ii. Selection of Study Medications	66
iii. Medication Exposure	69
iv. Provider Factors	69
v. Drug-Test Pair Characteristics	70
vi. Conceptual Framework for Analytic Strategy	72
vii. Data Analysis.....	74
D. Results.....	77
i. Patient Population and Use of Medications Requiring Laboratory Monitoring....	77
ii. Provider Characteristics.....	77
iii. Unadjusted Analysis	78
iv. Multivariable analysis.....	81
E. Discussion	84
i. Physician Adherence to Guidelines	85
ii. Levels of Evidence	87
iii. Volume	88
iv. Specialists versus Generalists	89
v. Strengths	89
vi. Limitations	90
vii. Implications for Practice.....	91
viii. Future Research	93
ix. Conclusion	94
A. Abstract	95
B. Background	97
C. Methods.....	99
i. Study Design and Setting.....	99
ii. Selection of Study Medications	99
iii. Medication Exposure	100
iv. Provider Factors	101
v. Key Variables.....	101
vi. Data Analysis	103
D. Results.....	104
i. Patient Population and Use of Medications Requiring Laboratory Monitoring..	104
ii. Provider Characteristics.....	105

iii. Unadjusted Analysis	105
iv. Multivariable Analysis.....	108
E. Discussion	110
i. Adherence	111
ii. Tools to Improve Laboratory Monitoring.....	112
iii. Strengths and Limitations	114
iv. Future Research	115
v. Conclusion	115
CHAPTER VI: DISCUSSION AND CONCLUSIONS.....	116
A. Summary of Research Findings.....	116
B. Strengths and Limitations	118
C. Future Directions.....	121
i. Changing Behavior	121
ii. Role of Health Information Technology (HIT)	123
iii. Cost.....	125
D. Final Conclusions.....	125
BIBLIOGRAPHY.....	127

LIST OF TABLES

Table 2.1: Characteristics of Studies Included in the Systematic Review

Table 2.2: Comparison of Serum Potassium Monitoring for Diuretic Use Across Reviewed Studies

Table 3.1: Age and Gender Characteristics of Study Population vs. U.S. Population Aged 18 and Older

Table 3.2: Drugs with Recommended Tests and Test Frequencies

Table 3.3: Topics Covered in Qualitative Interviews

Table 3.4: Overall Completion of Indicated Tests for Chronic Users of Study Medications

Table 3.5: Interviewed Patient Characteristics

Table 4.1: Study Medications and Recommended Tests

Table 4.2: Summary of Provider and Patient Characteristics

Table 4.3: Unadjusted Characteristics Associated with Ordering Rate

Table 4.4: Adjusted Model: Factors Associated with Ordering, Including Stratification by BBW

Table 5.1: Summary of Provider and Patient Characteristics

Table 5.2: Unadjusted Characteristics Associated with Test Completion

Table 5.3: Adjusted Model for Test Completion

LIST OF FIGURES

Figure 1.1: Conceptual Model

Figure 2.1: Flow Diagram of Included and Excluded Studies

Figure 3.1: Qualitative Interview Recruitment

Figure 3.2: Completion and Non-Completion of Tests

Figure 3.3: Physician Test Non-Ordering Compared to Patient Non-Adherence

Figure 3.4: Reasons Given for Missed Tests

PREFACE

Publications related to this study but not presented in detail in this thesis are listed as follows:

Articles

Tjia J, Fischer SH, Raebel MA, Peterson D, Zhao Y, Gagne SJ, Gurwitz JH, Field TS. Baseline and Follow-up Laboratory Monitoring of Cardiovascular Medications. *The Annals of Pharmacotherapy*. In press, 2011.

Tjia J, Field TS, Fischer SH, Gagne SJ, Peterson D, Garber L, Gurwitz JH. Quality Measurement of Medication Monitoring in the ‘Meaningful Use’ Era, Under review, 2011.

Abstracts

Development and Pilot Testing of Guidelines to Monitor High Risk Medications in the Ambulatory Setting And Post-Hospital Discharge. Tjia J, Field TS, Garber L, Donovan J, Kanaan A, Fischer SH, Zhao Y, Fuller J, Gurwitz JH. AHRQ 2009 Annual Conference.

Laboratory Monitoring of High-Risk Cardiovascular Drugs in the Ambulatory Setting: The Relative Contribution of Physician and Patient Behavior to Undermonitoring. Fischer SH, Tjia J, Field TS, Raebel MA, Zhao Y, Garber L, Donovan J, Kanaan A, Gagne SJ, Gurwitz JH. AHRQ Annual Health IT Grantee and Contractor Meeting, 2010.

Why Patients Fail to Complete Ordered Laboratory Monitoring. Fischer SH, Gagne SJ, Preusse P, Mazor K, Field TS, Tjia JT. HMORN Conference, 2011.

Quality Measurement Issues in the Era of Meaningful Use: Lessons from the Laboratory Monitoring of High-Risk Medications. Tjia JT, Field TS, Fischer SH, Gagne SJ, Peterson D, Gurwitz JH. HMORN Conference, 2011.

Parents’ Role in Specialty Referrals: Views from Both Sides of the Exam Table. Fischer SH, Cooley WC, Mazor KM, Dworetzky MS, Stille CJ. PAS/ASPR Joint Meeting, 2011. Abstract selected for oral presentation at 2011 Pediatric CARE conference in Monterey, CA, February 2011 and selected for a platform presentation at PAS/ASPR Joint Meeting, 2011.

CHAPTER I

INTRODUCTION

“Between the health care we have and the care we could have lies not just a gap, but a chasm.” – IOM: Crossing the Quality Chasm¹

Medicine has made amazing progress in the past century. At the turn of the 20th century, penicillin had not been discovered, anesthesia was in its early stages, and maternal mortality was at about 1 in 100. We now have advanced technology, from robotic surgery to targeted radiation, a wealth of medications including monoclonal antibodies and antiretroviral drugs, and maternal mortality has declined by two orders of magnitude.

However, at the turn of this new century, the medical world uncovered a terrible truth. While much of our medicine was saving lives, we were also causing numerous deaths via medical errors. The Institute of Medicine’s “To Err is Human” (2000)² estimated there were 44,000 to 98,000 deaths per year from medical errors in the US, while “The Quality Chasm” (2001)¹ offered guidelines as to how to achieve a better system, calling for care that is safe, effective, patient-centered, timely, efficient, and equitable, together galvanizing the medical community to face the problem of medical errors.

A major portion of the medical errors described in these studies are medication errors, and 60.8% percentage of preventable adverse drug events (ADEs) in the ambulatory setting are associated with medical errors due to inadequate laboratory monitoring of high-risk medications.^{3,4} Among preventable ADEs requiring hospital admission, the most frequent drug therapy problem was inadequate monitoring (45.4%).⁵ In the inpatient environment, errors have been shown to occur most often during ordering and administration⁶ However, while we know the process differs in the outpatient setting, we have less information on ADEs in this setting,⁷ though it is where most drugs are prescribed.

This thesis studies failures in laboratory monitoring of high-risk drugs in the ambulatory setting as a contribution to the improvement of the problem of medical errors.

A. Laboratory Monitoring

When we refer to laboratory monitoring, we include monitoring that addresses both safety and efficacy. Many medications require monitoring of symptoms or test results to prevent toxicity or to monitor efficacy. For medications with narrow therapeutic windows, such as digoxin or antiepileptics, serum drug levels are monitored to reduce the risk of toxicity. For other medications, monitoring evaluates the physiologic effect of medications, either for side effects or for effectiveness; for example, angiotensin-converting enzyme inhibitors can cause elevated potassium and creatinine levels, while thyroid function tests are conducted regularly for those on thyroid hormones to ensure appropriate dosing. For some drugs, such as carbamazepine or lithium, monitoring involves measuring both drug levels and physiologic effects.⁸

Evidence has shown that inadequate monitoring is due both to inadequate ordering as well as to patient non-attendance once a test is ordered.⁹ However, separating monitoring failures due to lack of ordering (where the provider did not place an order for a monitoring test) versus those due to patient non-adherence (where the patient did not complete an ordered test) requires information beyond the scope of data typically captured from administrative claims alone. In studies of laboratory monitoring, generally only test completion rates have been reported from administrative claims,¹⁰⁻¹³ meaning that a test was either both ordered and completed, or that it was not ordered and completed, but the reason for the failure is not clear. However, when electronic medical records are used, a distinction can be made between the test ordering rate and test completion rate, and in some cases ordering rates have been reported;^{14, 15} occasionally, but rarely, both are available.^{9, 16} In addition to trying to identify a root cause, reporting these two factors separately provides potential for better quality measurement: rather than reporting simple completion rates, provider behavior can be evaluated.¹⁷

This is a major advantage of using electronic medical record systems to study this topic. As has been shown elsewhere, combining laboratory and medication data allow for evaluating the quality of treatment, studying adverse events, and investigating drug-test interference.^{18, 19} Furthermore, electronic systems have the potential to improve outcomes and lower costs.²⁰ Computerized physician order entry (CPOE) and clinical decision support (CDS) have been shown to be effective in reducing medication errors.^{21, 22} However, much less is known about the role of similar systems in improving laboratory monitoring rates.

B. Interventions to Date

A systematic review I conducted in preparation for this thesis research identified eight studies studying health information technology interventions targeting laboratory monitoring.²³ This review appears in Chapter II. In brief, I found that the results of the studies were inconsistent at best, perhaps due to variations in design. Five of the eight studies reported statistically significant improvements in laboratory monitoring attributable to the study intervention.^{9, 10, 13, 15, 24} We reported concern regarding the design of some studies (not all were randomized controlled trials^{10, 15}) and the analytic approach (some were not successfully randomized before the intervention, while most failed to account for clustering and confounding in their analysis^{9, 10, 12, 13, 15}), leading us to conclude that additional well-designed and rigorously analyzed studies are necessary. Another review of recent studies came to the same conclusion.²⁵

C. Ordering and Completion

Before embarking on another intervention to improve laboratory monitoring in the ambulatory setting, it is important to identify the factors associated with poor monitoring in the first place. As we will show, the research on factors associated with ordering and with completion of laboratory testing in the ambulatory setting is very limited.

We know that some missed laboratory tests are due to non-ordering and others due to non-completion, but the literature has not identified the reasons or associated factors for each. First of all, we do not know why patients miss ordered laboratory testing. Providers have been interviewed about when ordering of recommended tests does

not occur,²⁶ but patients have not been asked the same questions about their attendance. In Chapter III, we describe our study interviewing patients about their reasons for not completing ordered laboratory tests.

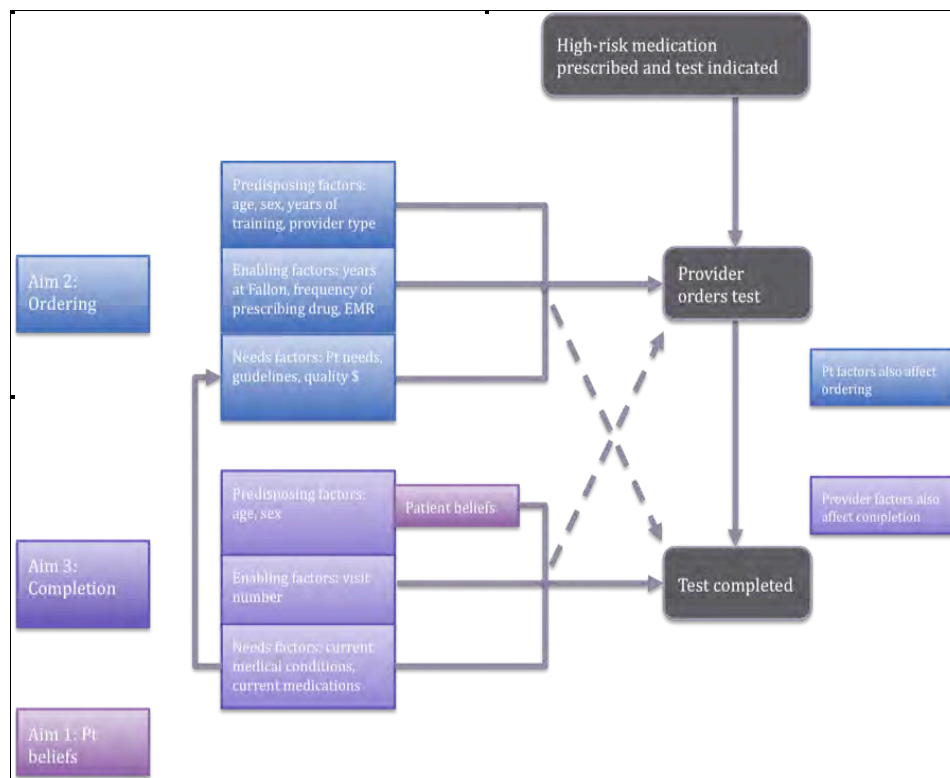
Past research has also shown poor provider adherence to guidelines.²⁷ In Chapter IV, we examine provider and patient factors and provider ordering in an attempt to identify those factors associated with ordering.

Similarly, there is good evidence for poor patient medication adherence²⁸ and poor appointment attendance,²⁹ but the data is sparse regarding laboratory testing completion, especially separated from ordering behavior. In Chapter V, we examine provider and patient factors associated with completion of ordered tests.

D. Conceptual Model

The initiating event in our conceptual model is the prescription of a high-risk medication. Based on provider characteristics, a test may or may not be ordered. Once ordered, a test may or may not be completed. As a result, outcomes occur at different rates. I examined each step in this process to determine factors that affect the branches in the decision tree using a theoretical framework from Andersen.^{30, 31}

Figure 1.1: Conceptual Model



Anderson's model of health services use can be used to guide inquiry into the association between patient and physician factors and recommended laboratory monitoring of prescription medications. This model, which guides our approach to this study, generally looks at the behavior of patients and families, and it classifies predictors of behavior into three categories: *predisposing factors* refer to demographic factors like age and gender as well as family structure and health beliefs that affect service use; *enabling factors* include resources that promote or inhibit use like income and health insurance; and *needs factors*, which comprise the illness and circumstances that necessitate use.^{30, 31}

I expected predisposing factors to affect both patient and physician behavior. For example, education and gender could be predisposing factors within both groups. Among patients, I expected differences based on number of medications. Among providers, specialty, years in practice, and provider type (physician versus nurse practitioner versus physician assistant) may affect behavior. Other factors that contribute to provider behavior may include past experiences with adverse events from failing to test for a specific drug, but those historical experiences are hard to measure with electronic data.

An enabling factor for patients could be frequency of clinical visits. Years at Fallon Clinic may be an enabling factor for physicians since it would affect familiarity with the records system. Frequency of prescribing is another factor that will likely affect test ordering, as providers expected to be more familiar with more frequently prescribed medications.

Current medical conditions and overall health status of the patient are the needs factors that drive health care use in general and need for laboratory monitoring specifically.

These determinants of behavior are expected to affect health behavior, in Andersen's model, which in turn should affect health outcomes.

E. Proposed Study

To gain further insight for development of improvements to laboratory monitoring in the ambulatory setting, I proposed a retrospective cohort study, examining the factors associated with inadequate monitoring prior to a randomized controlled trial of a health information technology (HIT)-based transitional care intervention. The data source is

Fallon Clinic, which uses Epic, the EpicCare Ambulatory electronic medical record (EMR), for all of their laboratory testing and results. Epic conforms to interoperability standards and meets a comprehensive set of criteria for functionality, interoperability, and security. Epic can be customized according to the specific needs of the local clinical site. I proposed to examine a selected list of high-risk medications and associated recommended monitoring and study the association of test ordering and completion with various patient and provider factors.

Furthermore, although estimates suggest that up to 95% of potential adverse drug events can be avoided with the adoption of advanced computerized systems,³² it is humans who use the technology, and humans will always make some errors. Understanding human factors is an essential component of designing systems to reduce errors. Therefore, I also proposed a qualitative study to examine patient reported factors associated with failing to complete ordered tests.

F. Dataset

There are two sources of data for this project: 1) the Fallon Clinic electronic medical record (EMR), EpicCare Ambulatory EMR system (Epic, Verona, WI, Spring 2007 IU3 at the time of the study) and 2) Fallon Community Health Plan (FCHP) claims and utilization databases. All data used encoded patient and physician identifiers.

Epic is a widely used EMR system certified by the Certification Commission for Healthcare Information Technology (CCHIT). Access to Epic is available using computer terminals throughout the inpatient and outpatient settings, and is also accessible off-site. All practitioners are trained on the documentation and order-entry system and are

supported by Epic training staff. Clinical data in the system are entered by medical staff. Registration data are entered by clinic staff. Clinical data are entered by medical assistants at the beginning of a visit and then completed by the provider. Lab tests orders are recorded when placed by providers. Results are automatically recorded into the patient record via internal systems when results are available. Patients do not enter any data into the Epic record. Epic contains information about physician diagnoses, radiology and lab reports, medications, and notes. The paper medical chart is also available at the primary care physician's office for further historical and in-depth data. Finally, automated databases include FCHP claims databases on services utilized by patients and Clarity databases on clinical encounters, procedures, and labs at Fallon Clinic and Saint Vincent Hospital/Worcester Medical Center.

The laboratory medication monitoring system and process currently in place

Currently, there are no electronic or other reminders in place to physicians regarding laboratory testing at the multispecialty group practice with which we worked. The process of laboratory monitoring to ensure the safety and effectiveness of drug therapy at this practice is similar to that in other ambulatory clinical settings. At the time when the data was collected, Epic tests that were ordered but not completed within a 25% time frame past the date set at time of ordering appeared in a "no-show" file for data purposes. However, reminders were not being issued to patients or to providers.

The importance of linked laboratory and pharmacy data

Without electronic tools, it is difficult to identify the reason for low completion of testing. When laboratory data are separate from medication data, test order rates cannot be compared to prescribing rates. The absence of a computerized system that links laboratory and medication information can lead to increased prescription errors and decreased quality of care.^{18, 19, 33, 34} Linking this data is important for studying adverse events.^{18, 35-37} Combining the data can reveal patients inappropriately treated given a physical condition, such as with potassium while hyperkalemic; can reveal conditions that require treatment, such as untreated elevated TSH; can identify the need for dose adjustments, given renal insufficiency, for example; can monitor toxicity, such as liver or kidney damage; and can measure efficacy.¹⁸ Even in places with electronic ordering of tests, it is often difficult to track which tests are not completed.³³

Combined data in electronic records can be used to improve testing rates with reminders to physicians as well as to generate reminders for patients, whether directly or through a system that generates letters or calls, at the time that will be most effective for patients. Relevance and timing of reminders are central to good informatics, or as the “Ten Commandments” of decision support put it, “applications must anticipate clinician needs and bring information to clinicians at the time they need it,”³⁸ and this principle applies to interventions directed at patients as well. Without EMRs, it is hard to achieve this level of coordination and personalization. Our access to EMR data allowed us to conduct this study.

Human subjects

The study protocol and all the study materials to be used in this project have been approved by the institutional review boards of the University of Massachusetts Medical School and the multispecialty group practice where the research was conducted.

G. Significance

The results of this study will inform the design of future interventions to improve laboratory monitoring. Attempts have been made to improve monitoring, the more recent of which have often used computerized systems or electronic reminders. There is reason to expect that CDS with CPOE could improve recommended monitoring as CDS systems have been shown to improve patient care and clinical outcomes.³⁹ Patient interventions have also been attempted such as automated voice messaging or nurse phone calls.²⁴ However, interventions intended to improve laboratory monitoring have thus far had varied success.^{10-12, 14, 24} In order to develop the most effective interventions, there needs to be a clearer understanding of what patient factors actually contribute to poor monitoring, both by looking across patient populations and also by speaking to patients directly about their experiences. Targeted interventions to specific patients can make interventions more effective, as has been shown with appointment non-attendance.⁴⁰ Furthermore, studies that have distinguished between ordering and completion rates show that inadequate monitoring results from both a failure to order the test and the failure to complete ordered tests, so provider factors also need to be examined. This study will identify the populations most at risk for inadequate monitoring as well as provider

characteristics associated with not ordering recommended tests in order to inform targeted intervention strategies.

H. Specific Aims

Therefore, the following specific aims and associated hypothesis were proposed for this thesis project:

Aim 1

Using qualitative methods, to identify patient-reported factors associated with non-completion of ordered laboratory tests.

Hypothesis: Patient factors that are not available in the electronic record may significantly contribute to missing laboratory tests. To this end, I conducted a series of interviews with patients to examine factors that contribute to non-completion of ordered laboratory tests, as factors that may not be determined from our quantitative studies, but which may well be modifiable, could account for some missed laboratory tests, such as a patient's lack of understanding of the reason for the test. Patient non-completion and provider non-ordering rates were also reported for study medications. The study conducted and its results are described in Chapter III.

Aim 2

To identify provider factors associated with ordering of laboratory monitoring, adjusting for level of test evidence and patient characteristics.

Hypothesis: One factor that contributes to inadequate laboratory monitoring is that recommended tests are not ordered. Some providers are less likely than others to order laboratory testing on the same medication. Familiarity with a medication, specialty, and

strength of the guideline driving the testing, among other factors, may contribute to variation among ordering rates. Patient factors must be accounted for as well. The study conducted and its results are described in Chapter IV.

Aim 3

To identify patient factors associated with completion of ordered tests, adjusting for provider characteristics.

Hypothesis: In addition to low ordering rates, another factor that contributes to inadequate laboratory monitoring is patient non-completion of laboratory testing that has been ordered. Demographic factors, including age, sex, medical condition and presence of certain diagnoses; number of study medications; and frequency of medical appointments were analyzed. Provider factors may also influence completion rate, so selected provider factors need to be accounted for as well. The study conducted and its results are described in Chapter V.

I. Summary

Lack of recommended laboratory monitoring has been identified as a major category of medical errors and is a source of preventable serious adverse drug events. The long-term goal of this study is to provide information about patients on high-risk medications and the physicians who order these medications in order to inform interventions to improve monitoring rates. Furthermore, speaking with patients directly can elucidate other reasons for missing opportunities for laboratory monitoring for high-risk medications.

Ultimately, our hope is to contribute to the process of improving our health care system. If patients on high-risk medications are better monitored, we can reduce adverse events and ensure that the health care system is solving, rather than creating, medical problems.

CHAPTER II

THE IMPACT OF HEALTH INFORMATION TECHNOLOGY INTERVENTIONS TO IMPROVE MEDICATION LABORATORY MONITORING FOR AMBULATORY PATIENTS: A SYSTEMATIC REVIEW

This chapter was previously published as:

Fischer SH, Tjia J, Field TS. Impact of health information technology interventions to improve medication laboratory monitoring for ambulatory patients: a systematic review. *Journal of the American Medical Informatics Association*. Nov 1 2010;17(6):631-636. doi:10.1136/jamia.2009.000794

Reproduced with permission from BMJ Publishing Group Ltd.

A. Abstract

Medication errors are a major source of morbidity and mortality. Inadequate laboratory monitoring of high-risk medications after initial prescription is a medical error that contributes to preventable adverse drug events. Health information technology (HIT)-based clinical decision support may improve patient safety by improving the laboratory monitoring of high-risk medications, but the effectiveness of such interventions is unclear. Therefore, we conducted a systematic review to identify studies that evaluate the independent effect of HIT interventions on improving laboratory monitoring for high-risk medications in the ambulatory setting using a MEDLINE search from January 1, 1980 through January 1, 2009 and a manual review of relevant bibliographies. We excluded all anticoagulation monitoring studies. Eight articles met our inclusion criteria, including 6 randomized controlled trials and 2 pre–post intervention studies. Six of the studies were conducted in 2 large, integrated health care delivery systems in the United States. Overall, five of the eight studies reported statistically significant, but small, improvements in laboratory monitoring; only one-half of the randomized controlled trials reported statistically significant improvements. Studies that found no improvement were more likely to have used analytic strategies that addressed clustering and confounding. Whether HIT improves laboratory monitoring of certain high-risk medications for ambulatory patients remains unclear, and further research is needed to clarify this important question.

B. Introduction

Since the Institute of Medicine (IOM) highlighted the impact of medical errors on patient morbidity and mortality in “To Err is Human,”² significant effort has focused on reducing medical errors and improving patient safety in the United States. Medical errors result in 44,000 to 98,000 deaths per year, a large proportion of which are due to adverse drug events (ADEs).² Laboratory monitoring errors are a major cause of potential ADEs, occurring in 60.8% of preventable ADEs in ambulatory older adults³ and in 45.4% of preventable ADEs requiring hospital admission.⁵ Baseline monitoring rates are low, with up to 58% of initial drug dispensings occurring without appropriate lab monitoring for ambulatory older adults.⁴¹ Because patients sometimes miss more than one test for a given drug and often take many drugs, the rate of all potential laboratory-monitoring errors was estimated to be extremely high (~80%) among patients taking chronic medications in 2001.⁴² Because poor adherence to guidelines leads to hospitalizations and significant morbidity,^{5, 11} and because basic human factors make it challenging for clinicians to adhere to complicated monitoring recommendations for a large number of medications, health information technology (HIT) holds promise for improving laboratory monitoring of high risk medications and may potentially reduce medication errors.^{32, 43}

Some experts estimate that up to 95% of potential ADEs can be avoided with the adoption of advanced computerized systems.³² As a result, tools to reduce errors continue to be developed, many of which are technology-based. However, the actual impact of these systems is unclear. Technology and clinical decision support (CDS) systems have

been shown to improve patient care and clinical outcomes in many clinical situations.³⁹ For example, computerized physician order entry with decision support can reduce medication errors,²¹ and interventions to improve laboratory-monitoring in the hospital setting can improve outcomes⁴⁴. Furthermore, computer access to laboratory data improves the opportunity for pharmacists to monitor medications,^{22, 45} and systematic reviews of interventions to improve monitoring in the hospital setting show that HIT can reduce errors.^{21, 46-48} Unfortunately, it remains unclear whether HIT CDS alerts in the ambulatory setting are as effective.

To address this gap in the literature, we conducted a systematic review to identify studies that evaluated HIT interventions to improve laboratory monitoring of selected high-risk medications in the ambulatory setting. The specific aims of this review are to answer the following questions regarding high-risk medications (excluding anticoagulants) in the ambulatory setting: (1) Do HIT interventions improve laboratory monitoring?, and (2) What are characteristics of HIT interventions that improve monitoring? This review should inform the planning of laboratory monitoring interventions and guide future researchers about important research design elements for HIT interventions.

C. Methods

i. Literature Search

To identify journal articles for this systematic review, we performed a Medline search of English-language human studies published between January 1, 1980 and January 1, 2009 using keywords for HIT and drug monitoring.

The search performed was as follows:

(“drug monitoring” OR “laboratory monitoring”) AND (computerized OR electronic OR informatics OR reminder systems OR “Medical Records Systems, Computerized”[MeSH] OR “Decision Support Systems, Clinical”[MeSH] OR “Decision Making, Computer-Assisted”[MeSH] OR “Database Management Systems”[MeSH])

We performed a manual review of relevant authors and journals including bibliographies from identified articles.

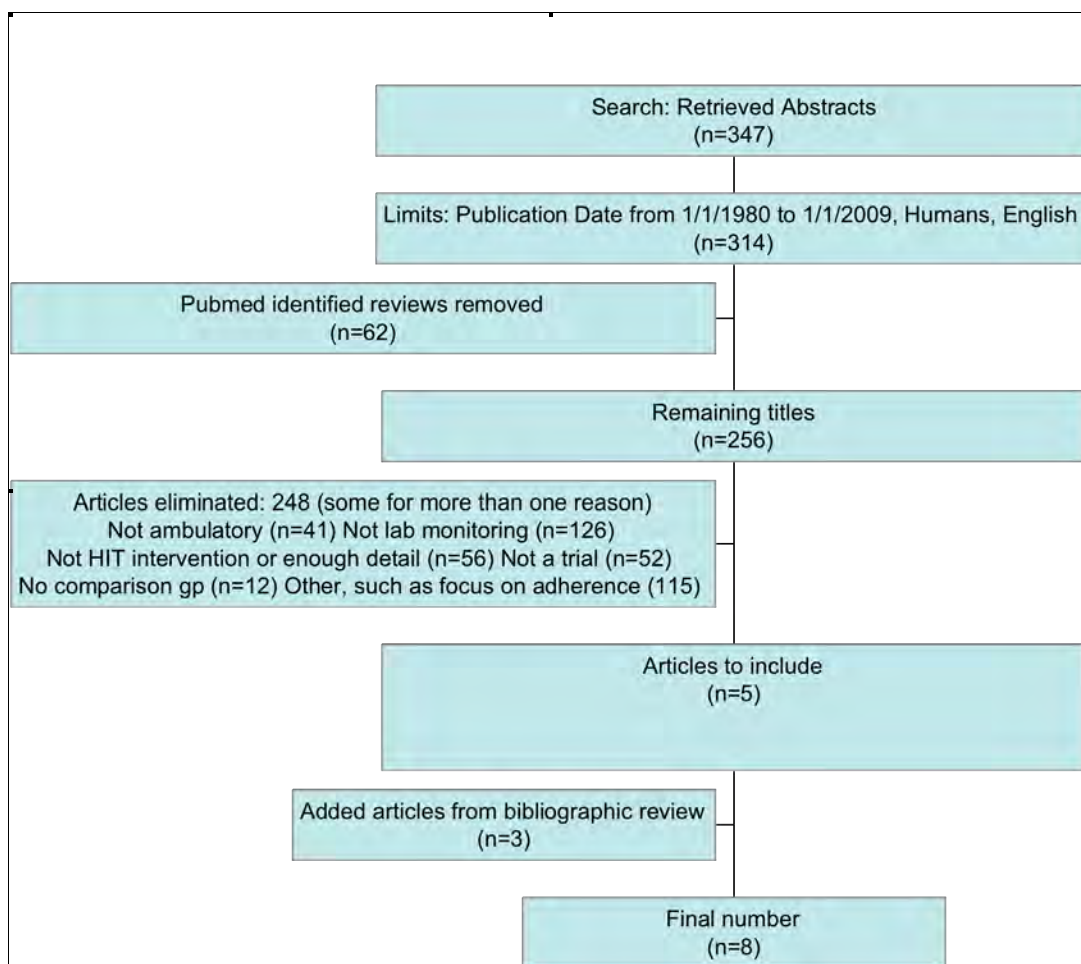
ii. Inclusion Criteria and Selection of Studies

We included studies that: were clinical trials, randomized controlled trials (RCTs), or comparative studies; were conducted in an ambulatory setting; had sufficient information about the HIT intervention for it to be assessed separately from other non-HIT interventions; and examined laboratory test monitoring rather than clinical tests (e.g., pulmonary function tests). We included studies evaluating the effect of HIT interventions on laboratory test monitoring, defined as laboratory tests to evaluate efficacy, toxicity, or side effects. We excluded studies that examined laboratory testing to evaluate medication adherence, computerized order interventions that did not include laboratory monitoring, at-home patient testing, in-hospital interventions, and literature reviews, meta-analyses, case studies, and opinion pieces. We also excluded studies in which the HIT monitoring

intervention was coupled with other interventions (e.g., HIT-based medication dosing and appointment scheduling recommendations) because it was not possible to identify the independent effect of HIT on laboratory monitoring; this included all studies evaluating anticoagulation interventions and several multipronged diabetes interventions. Additional studies identified from bibliographies and author searches were also evaluated for inclusion based on the same criteria.

The literature search produced 347 abstracts, of which 314 were in English and published from January 1, 1980 to January 1, 2009 (Figure 2.1). Each study was assessed independently by two investigators (SHF and JT) for inclusion. Disagreements were resolved by consensus. There were 256 studies after exclusion of review articles, and most were excluded after manual review for not meeting the inclusion criteria. Many studies were excluded for more than one reason, such as not being an actual trial and covering a topic other than laboratory monitoring.

Figure 2.1: Flow Diagram of Included and Excluded Studies



iii. Data Abstraction and Evaluation

We extracted data from the text and tables of the original publications and classified by clinical setting, targeted medications, time frame, HIT intervention type and duration, randomization, comparison group, and endpoint assessed. In one case investigators contacted a study author for additional results.

Quality scores were assigned by two investigators (SHF and JT) using an approach outlined by Downs et al.⁴⁹ to assess methodological quality. This approach standardizes and rates important aspects of study design and data presentation to assign

an overall study quality rating score. The maximum score possible for an original investigation was 27. Disagreements were reconciled by consensus.

D. Results

A detailed review of the potentially eligible articles identified a total of 8 articles for inclusion that evaluated the impact of HIT interventions on laboratory monitoring in the ambulatory settings published between 2003 and 2009. A brief description of these studies is presented in Table 2.1.

Table 2.1: Characteristics of Studies Included in the Systematic Review

Author	Date published	Study type	Intervention	Study Location	Sample size	Score	Unit of analysis	Confounding and clustering in analysis	Outcome measured	Results (+: statistically significant change in monitoring rate / -: no effect of the intervention on the monitoring rate)
Feldstein ²⁴	2006	RCT - cluster-randomized by clinic	EMR reminder via email as well as two other interventions	OR - Kaiser Permanente HMO, 15 primary care clinics	44 PCPs with 196 patients in EMR arm	25	Patient	Yes	Completed monitoring	+: EMR reminder ↑ baseline laboratory monitoring of 10 medications, from 22.4% to 48.5%; 26.1% absolute ↑/116% relative ↑; HR of 2.5, but less effective than voice message or pharmacy outreach
Hoch ¹⁰	2003	Pre-post, no control	EMR reminder via email	Israel - HMO	504 physicians	18	Patient	No	Completed monitoring	+: Reminders to clinicians ↑ potassium testing (78.5→81.5%; 3.0% absolute effect; 9.8% relative; p<0.001)
Lo ¹⁴	2009	RCT	EMR reminder	MA - Partners HealthCare	22 primary care clinics: 3673 events among 2765 patients	23	Clinic visit	Yes	Ordering	-: Reminders did not improve ordering of laboratory monitoring significantly
Matheny ¹¹	2008	RCT	EMR reminder	MA - Partners HealthCare	1,922 patients seen by 303 physicians in 2,507 clinic visits	24	Clinic visit	Yes	Completed monitoring	-: Reminders did not improve laboratory monitoring significantly
Palen ¹²	2006	RCT	EMR reminder	CO - Kaiser HMO	207 PCPs with ^{11, 14} 104 in the intervention arm caring for 26,586 patients	22	Dispensing (first)	No	Completed monitoring	-: Reminders did not improve laboratory monitoring significantly. Significant improvement for selected medications
Raebel ⁹	2005	RCT	Pharmacists reminded electronically about missing tests and then ordered them and reminded patients	CO - Kaiser HMO	10,169 drug dispensings for 9,565 patients	23	Dispensing (each unique initial drug dispensing)	No	Completed monitoring	+: Statistically significant ↑ monitoring in the intervention group, varying widely by medication (70.2→79.1% overall; 8.9% absolute effect; 12.6% relative; p<0.001)
Raebel ¹³	2006	RCT	Pharmacists reminded electronically about missing tests and then ordered them and reminded patients	CO - Kaiser HMO	9,139 patients with 4,871 patient-drug combinations	22	Patient-drug combination (ongoing therapy)	No	Completed monitoring	+: Statistically significant improved monitoring in the intervention group for only some of the medications (58→64% overall; 6% absolute effect; 10% relative; p<0.001)
Steele ¹⁵	2005	Pre-post, no control	EMR reminder	CO - Safety net outpatient clinics	Rule processed 16,291 times; 19,076 patients seen during the time period	16	Orders	No	Ordering	+: Increased ordering of the rule-associated laboratory test when an alert was displayed (39→51%; 12% absolute effect; 31% relative; p<0.001)

Abbreviations: ↑, increase; CO, Colorado; EMR, electronic medical record; HMO, health maintenance organization; HR, hazard ratio; MA, Massachusetts; OR, Oregon; PCP, primary care physician; RCT, randomized controlled trial.

Seven studies were conducted in the United States^{9, 11-15, 24} and one in Israel.¹⁰ Six of the eight studies were conducted in large, integrated health care delivery systems^{9, 11-14, 24}, including a series of studies by Raebel, et al. at Kaiser Permanente^{9, 12, 13, 24} and two studies at Partners HealthCare.^{11, 14} Five interventions sent electronic alerts to prescribing physicians alone.^{10-12, 14, 15} Three sent electronic alerts to a pharmacist who could then order the laboratory test and contact the patient.^{9, 13, 24} One of the three studies that involved pharmacists also included a comparison arm of computerized alerts to physicians only.²⁴ Seven studies targeted a broad range of medications,^{9, 11-15, 24} while the eighth targeted a single medication.¹⁰ Six studies evaluated completion of laboratory test monitoring as the outcome measure,^{9-13, 24} while two evaluated physician test ordering.^{14, 15} A meta-analysis of the data reported was deemed inappropriate due to the differences between the studies.

Five of the eight studies reported statistically significant improvements in laboratory monitoring attributable to the study intervention,^{9, 10, 13, 15, 24} whether an improvement in appropriate tests ordered or an increase in the completion rate, with the absolute percent improvement ranging from 3.0% to 26.1%. There was no consistent pattern of intervention efficacy based on outcome measurement. The number of patients enrolled in each study ranged from 196 to 26,586. The smallest study showed the largest absolute improvement in monitoring.²⁴

i. Study Quality and Impact on Laboratory Monitoring

Six of the eight studies were RCTs, while 2 were pre-post intervention studies. A brief description of the study methodologies and quality rating score is included in Table 2.1. The study quality rating scores ranged from 16 to 25 (possible score range 0 – 27). The RCTs were rated higher (quality score = 22-25) than the pre-post intervention studies (quality score = 16-

18). Studies with the highest scores differed from lower quality studies in their analytic approaches by including adjustment for confounding and clustering.^{11, 14, 24} Interestingly, randomization failed in two of the highest quality studies,^{11, 14} where the intervention and control groups were significantly different on key clinical characteristics such as gender, race, and insurance type.

Both pre–post studies showed statistically significant improvements,^{10, 15} while only three of the six RCTs did.^{9, 13, 24} All of the RCTs that showed improvements involved pharmacist-based interventions; this included the only RCT that showed improvement by an alert targeting physicians, and this intervention was evaluated as the comparison arm for more intensive pharmacist-based intervention.²⁴

All studies enrolled patients nested within providers; two multi-site studies were cluster randomized trials at the level of the clinic, nesting providers within each site.^{14, 24} Three studies accounted for clustering at the level of the clinic or provider in the analyses or design,^{11, 14, 24} and two of these reported no improvements in monitoring with HIT intervention.^{11, 14} While all studies listed some possible patient-level or facility-level confounders, only the same three studies adjusted for these possible confounders in their analyses,^{11, 14, 24} and two of these studies showed no intervention improvements.^{11, 14} Additionally, of the six RCTs, the three RCTs with failures in randomization reported no improvement in monitoring, after any adjustment.^{11, 12, 14}

ii. Study Site Characteristics and Impact on Laboratory Monitoring

Six of the eight studies were conducted in one of two large integrated healthcare delivery systems, Kaiser Permanente and Partners HealthCare; these included all of the RCTs.^{9, 11-14, 24} One study was conducted in a safety-net clinic,¹⁵ and one study in multiple health maintenance organization sites in Israel.¹⁰ Baseline rates of appropriate laboratory monitoring varied between

study sites, ranging from 14%¹¹ to greater than 95%⁹ depending on the study drug. Sites with lower baseline rates of monitoring reported greater improvements associated with HIT interventions.^{13, 15, 24} Both studies from Partners HealthCare showed no improvements with HIT interventions, but had high baseline rates of monitoring prior to the intervention.^{11, 14} The safety-net clinic study and the Israeli HMO study had different baseline levels (38.5% and 78.5%) but both showed significant monitoring improvements in their pre–post intervention assessments.^{10,}

15

iii. Intervention Design and Impact on Laboratory Monitoring

All the studies were conducted within health care systems with electronic records. Four interventions were based on homegrown electronic medical records programs^{10-12, 14} while four were based on modifications to proprietary systems.^{9, 13, 15, 24} Six of the eight interventions were built in systems with computerized physician order entry (CPOE), with the alert going to the physician. Of these, two sent messages via email,^{10, 24} while four provided alerts during patient profile reviews.^{11, 12, 14, 15}

Of the CPOE interventions, alerts within the electronic record system were either interruptive (requiring the provider to respond to the alert) or non-interruptive (not requiring action). In one study, the intervention was interruptive and required action on the part of the provider to dismiss an alert;¹⁵ however, this intervention did not shorten the process of test or medication ordering. Other studies had real-time alerts that appeared on the prescribing page as a warning, but they were non-interruptive and did not stop the workflow.^{11, 12, 14} No aspect of the CPOE design itself was found to be consistently more effective than any other. Interestingly, the two studies that alerted pharmacists directly, but not physicians, demonstrated significant improvements in monitoring.^{9, 13}

Most interventions reviewed targeted multiple high-risk medications, while one involved only a single drug.¹⁰ When we examined the impact of interventions on the same drug, diuretics, across all the studies, we found no significant effect of the HIT intervention except in the study for which this was the only drug targeted.¹⁰ (Table 2.2) There was no consistency between the medications targeted and whether there was a significant intervention effect.

Table 2.2: Comparison of Serum Potassium Monitoring for Diuretic Use Across Reviewed Studies

Study	Drug	Outcome Measure	Effect Measurement	Effect Size	Confidence Interval	P - value	Pre-intervention monitoring rate or control group	Post-intervention monitoring rate or intervention group
Feldstein ²⁴	All diuretics*	K testing	Hazard ratio	0.9*	0.70-1.10	0.24		
Hoch ¹⁰	All diuretics	K testing	Absolute % increase prevalence of testing	3.0%		<0.001	78.5%	81.5%
Lo ¹⁴	All diuretics	K	Adjusted odds ratio‡	1.32	0.87-2.023	0.20		
Matheny ¹¹	Potassium sparing diuretic	K	Odds ratio	0.82	0.12-5.60	0.84	60.7%	68.4%
Matheny ¹¹	Thiazide diuretic	K	Odds ratio	1.30	0.63-2.67	0.47	51.7%	64.5%
Palen ¹²	All diuretics	K	Absolute % increase prevalence of testing	1.60%		0.11	44.0%	45.6%
Steele ¹⁵	Diuretics not reported separately	n/a	n/a	n/a	n/a	n/a	n/a	n/a

* Not specific to diuretics, but embedded in composite measure for non-ACE/ARB drugs

‡ Corrected numbers based on correspondence with the authors

Abbreviations: ACE, Angiotensin-Converting Enzyme Inhibitors; ARB, Angiotensin II Receptor Blockers; HR, hazard ratio; K, Potassium; OR, odds ratio

E. Discussion

By 2009, eight studies reported the results of HIT interventions to improve laboratory monitoring of medications in the ambulatory setting, including six RCTs. Surprisingly, 50% of the RCTs reported significant improvements in monitoring while 50% did not. A detailed review of each of the studies identified important aspects of study quality, analysis and intervention design that help explain these conflicting results.

Higher quality studies were less likely to show significant improvements in monitoring with HIT interventions compared to lower quality studies. Studies with lower quality scores^{10, 15} used less rigorous study designs (such as pre–post intervention timing rather than RCT) and analytic approaches. These differences may explain some of the differences in intervention efficacy across studies. Because most of the HIT intervention studies were introduced in clinical systems with multiple clinical sites, it is important to account for non-independence of outcomes within each site due to local practice variations that can explain differences between different sites. Likewise, because clinicians cared for multiple patients within a site, it is important to consider non-independence of outcomes (i.e., lab testing) between patients of the same provider because differences in care delivery between providers can also affect outcomes. Our review found that studies that addressed clustering in their design and analysis were less likely to show improvements in lab monitoring.^{11, 14}

We also found that all of the RCTs were conducted in one of two large integrated healthcare systems in the US. Study setting appears to be related to study results in two ways. First, both studies conducted outside of a large integrated health care system in the

US were less rigorous pre–post intervention trials,^{10, 15} and each showed significant improvements. Second, one of the integrated healthcare systems had high baseline rates of monitoring,^{11, 14} and our review indicates that studies in sites with lower baseline rates of monitoring reported greater improvements from HIT interventions compared to sites with higher baseline monitoring rates.^{13, 15, 24}

Intervention design features may also explain the conflicting study results. Our review revealed that the 2 interventions that targeted pharmacists were effective^{9, 13}, while only 3 of 6 interventions targeting physicians were effective.^{10, 15, 24} One study compared 3 arms, including an arm with electronic alerts to physicians, a second arm with voice mail messages to patients, and a third with pharmacy team outreach to patients, and found that the physician alert arm was the least effective.²⁴ Past evidence suggests that changing physician behavior is challenging, and that passive approaches (non-interruptive alerts) to such physicians may not be effective.⁵⁰⁻⁵² It does not appear that the intrusiveness of the alert explains the difference in study findings, and this is not inconsistent with several studies where nonintrusive reminders did not improve physician adherence to alert recommendations.⁵³

It is helpful to consider our results in the context of other literature on the effectiveness of HIT interventions and their effects on prescribing errors and adverse drug events.^{21, 32} Most reviews included a small number of studies, and many report that the studies reviewed were of low quality. For example, a 2003 review reporting error-rate improvement from clinical decision support-only interventions included seven studies, many of which were under-powered.²¹ Another review of HIT interventions to improve

drug dosing, mostly in the inpatient setting, found that many studies were of low quality.^{47, 48} None of these studies addressed laboratory monitoring.

Variation in intervention effectiveness is also reported in other reviews of HIT interventions. For example, one review of the effect of computerized physician order entry and clinical decision support on ADEs found that only half of the studies showed a reduction in ADEs⁵⁴, and another systematic review of CPOE and medical errors reported that while more than half of studies found significant reductions in ADEs the results varied widely. Although the investigators concluded that CPOE can reduce prescribing errors, they noted, “Reporting quality and study quality was often insufficient to exclude major sources of bias.”⁵⁵ The findings of our review are similar, with a slight majority of studies finding a positive impact of the interventions, but with variation in quality. As with reviews, the number of studies addressing this issue is still limited.

There are several limitations to our review that should be noted. First, given the relatively small number of studies identified, it is difficult to draw conclusions about the overall impact of HIT intervention on rates of laboratory monitoring. By limiting our search to Medline English-language studies, we may have missed some non-US studies, but this allowed us to adequately review the study methodologies. Further, all studies regarding anticoagulation were excluded because it was not possible to identify the independent effect of interventions to improve lab monitoring (i.e., INR testing) from dosing recommendations for warfarin. This limits the inferences we can make about HIT interventions on lab monitoring overall. Second, the studies were conducted in a limited number of clinical settings: three of the studies were conducted at one site and two at a

second site. Further, all but one of the studies were conducted in large managed care organizations, limiting generalizability of the findings outside of these settings. Finally, differences in study design made it difficult to compare outcomes across studies. While we were unable to use meta-analysis to pool the effect sizes, we did compare the effects of the interventions across several studies on a single drug common to all studies, and did not find any consistent effect of HIT interventions on monitoring.

While the idea of using HIT to improve quality of care is not new,⁵⁶ this goal has not yet been achieved. Many questions still remain, as posed by Kuperman et al. in 2007: “To what extent does alerting impact on clinician behavior and patient outcomes? What is the optimal way to present alerts to prescribers? Which member of the health care team—for example, physician, nurse, pharmacist, other—is the best recipient of any kind of alert?”⁸ These questions have yet to be answered. As more outpatient clinics adopt electronic records and electronic prescribing, it will be increasingly important to know the impact of decision support in this setting to support implementation of the most effective interventions. This is particularly true with regard to laboratory monitoring, which is often a locus for preventable adverse effects.

While numerous reviews and studies have attempted to answer these questions, our systematic search identified more interventions in the inpatient setting than in the ambulatory setting. Of the studies identified, concerns about study quality and design could not exclude sources of bias in the reported results. Future studies of laboratory monitoring should better address patient and provider characteristics and account for fixed physician or clinical site effects by multilevel analysis. Studies can also better

clarify outcomes (i.e., improvements of test ordering versus test completion), and should also be expanded to include settings outside of the large integrated health care delivery systems.

While this systematic review found evidence suggesting information technology interventions may improve lab monitoring for high-risk prescribed medications (exclusive of anticoagulants) in the ambulatory setting, the evidence is conflicting. Of the well-considered, well-designed studies reviewed, there appears to be little improvement of lab monitoring for high-risk medications with HIT interventions targeting physicians only. However, five of eight studies found some positive effect, and this suggests that this using HIT may be a promising avenue for improving laboratory monitoring. More research is needed to determine how to maximize the full potential benefit of HIT to monitor high-risk medications and ultimately improve patient safety.

CHAPTER III

HIGH-RISK MEDICATION MONITORING TESTS: A MIXED-METHODS EXPLORATION OF COMPLETION AND BARRIERS

A. Abstract

Objectives

To quantify physician ordering and patient completion of laboratory monitoring tests for high-risk medications in the ambulatory setting and to describe patient reasons for non-adherence to physician test orders. We hypothesized that both physician and patient factors would contribute to patients not receiving appropriate laboratory monitoring.

Design

Using a mixed-methods approach, we used a cross-sectional study to measure the frequency of physician ordering and patient completion of laboratory tests for selected chronic medications (including cardiovascular medications [ACE inhibitors and ARBs, statins, digoxin, diuretics, fibrates, and niacin], anti-convulsants [phenytoin, valproic acid, carbamazepine and phenobarbital], potassium supplements, and thyroid replacement therapy) prescribed in a large multispecialty ambulatory group practice between January

1, 2008 and July 31, 2008. To elicit reasons for completing or not completing the ordered test, we additionally conducted qualitative interviews with a sample of patients who completed and those who failed to complete an ordered test.

Participants

Patients aged 18 and older in a large multispecialty group practice who were prescribed a high-risk medication requiring laboratory monitoring, including 23 patients who participated in structured interviews.

Measurements

For a list of 14 medications and associated recommended laboratory monitoring tests, resulting in a list of 23 high-risk drug-test pairs, we quantified the proportion of tests missed due to provider non-ordering compared to patient non-completion. From a series of patient interviews, we explored reasons for not completing ordered laboratory tests.

Results

During the observation period, there were almost 50,000 prescriptions for the study medications, of which almost 43,000 were to chronic users. The unit of analysis was the first prescription and first incidence of the recommended test—a drug-test pair—during the study pair. Test ordering and completion varied across drug-test pairs. Physician non-ordering of recommended tests, ranged from 1% to over 50% across drug-test pairs; patient non-completion of ordered tests ranged from 2% to almost 25%. Overall, 71% of drug-test pair non-completion was due to lack of test ordering; 29% was the result of patients not completing the test. In structured interviews, the reasons patients provided

for not completing lab tests were from two major domains: human factors, including cognitive reasons (e.g., they simply forgot) and competing demands; and systems issues, including transportation. Other logistical issues (e.g., long waiting times at the lab) were not mentioned by patients as reasons for missing tests, nor were patient beliefs about the tests or lack of understanding of the reasons for them.

Conclusions

While most missed opportunities for laboratory monitoring of high-risk medications in the ambulatory setting are attributable to lack of physician orders, patient non-adherence contributed to under-testing. Interventions to improve laboratory monitoring should target patients as well as physicians. Reminders to patients about due dates for ordered tests could improve adherence.

B. Background

Many prescription medications, including those commonly prescribed in the outpatient setting, pose serious risks. Drug-induced injury is common in this setting.^{3, 57} Failure to monitor high-risk medications has been shown to be a leading factor contributing to adverse drug events (ADEs).³ However, data about monitoring rates are limited.

For adults treated in the ambulatory setting, initial drug dispensing occurs without recommended laboratory monitoring in as many as 39% of cases.⁴ This is higher among older adults, where up to 58% of initial drug dispensings have been shown to occur without recommended lab monitoring.⁴¹ For maintenance therapy, rates of recommended follow-up testing are generally lower than for baseline monitoring.¹¹ In one study focused on chronic medications, more than 40% of patients did not receive at least one of the tests recommended for drug safety monitoring.⁴² Because many patients take multiple medications and some medications have more than one recommended laboratory test, potential laboratory-monitoring errors affected up to 80% of patients in this study.

Overall completion necessarily represents a subset of the ordering. The completion rate is therefore lower, yet reporting the completion rate alone conflates physician behavior and patient behavior. While previous studies show that overall test completion for monitoring high-risk medications is low,^{4, 12, 24} most studies do not disentangle the independent contributions of lack of physician test ordering and incomplete patient adherence to lab test orders. Some studies report clinician ordering only,^{14, 15} while others report test completion rates only;^{10-12, 24, 58} none report patient

adherence to ordered testing. This knowledge gap makes it difficult to determine whom to target to improve laboratory monitoring.

In cases where tests are ordered but not completed, we have little information on the reason patients fail to complete the tests. It is possible that patient understanding of the reason for testing may correlate with test completion. This has been found for warfarin, where patients' knowledge about warfarin has been found to be a determinant of anticoagulation control.⁵⁹ Work on abandoned prescriptions has suggested that patients' relationships with physicians, wait times in the pharmacy, condition of the testing facility, and co-payment costs are associated with increased abandonment,⁶⁰ factors that may be important in test completion as well. Forgetting is known to be a common reason for missing appointments,^{61, 62} but it is not known what its role is in failing to complete laboratory tests.

To quantify physician ordering and patient completion of laboratory monitoring tests for high-risk medications in the ambulatory setting and to identify factors associated with completion, we conducted a mixed-methods study in a large multispecialty ambulatory group. We focused on medications commonly implicated in ADEs or those with narrow therapeutic windows. To understand reasons for non-adherence to physician test orders, we also conducted interviews of patients prescribed one of these medications who had missed recent monitoring tests.

The specific aims of this study were to determine: 1) the prevalence of completion of recommended laboratory tests to monitor high-risk medications; 2) the proportions of incomplete testing attributable to lack of clinician test ordering and to patient non-

adherence to ordered tests; and 3) what factors might be contributing to patient non-adherence. We hypothesized that while incomplete ordering would be an important factor, non-completion would have more influence on overall rates, and that patients would identify many barriers to completion, including timing and access, as well as limited understanding of the reasons for testing, that would not be measurable in the electronic medical record (EMR).

C. Study Design and Sample

This study was conducted in a large multispecialty group practice that provides most of the medical care for members of a closely associated, New England-based health plan. In 2010, the group practice employed 330 outpatient clinicians, including 250 physicians, at 23 ambulatory clinic sites covering 30 specialties. The study population was derived from the Fallon Community Health Plan (FCHP) members who receive medical care from Fallon Clinic (n=72,611 in 2008). The age and gender characteristics of the study population are generally similar to those of the general population of the United States, though the Fallon Clinic patients are generally older.

The practice uses the EpicCare Ambulatory electronic medical record (EMR) system (Epic, Verona, WI, Spring 2007 IU3 at the time of the study) and provides medical care to approximately 180,000 individuals. The study population was derived from the health plan membership aged 18 years and older who received care at the multispecialty group practice. The age and gender characteristics of the study population are similar to those of the general population of the United States, and include 36% who are aged 65 years and older (Table 3.1). While the health plan does not systematically

measure race, the plan's market research indicates a patient racial mix consistent with the plan's catchment area, which includes whites 79%, Hispanics 12%, African Americans 5%, and other races 4%.

Table 3.1: Age and Gender Characteristics of Study Population vs. U.S. Population Aged 18 and Older

<u>Age Group</u>	<i>Target Study Population</i> (n=72,611)			<i>United States</i> (n=210,430,341)*		
	<u>Male</u>	<u>Female</u>	<u>Total</u>	<u>Male</u>	<u>Female</u>	<u>Total</u>
18 – 44	15%	17%	32%	26%	26%	53%
45 – 54	9%	9%	18%	9%	9%	18%
55 – 64	7%	7%	14%	6%	6%	12%
65 – 74	6%	8%	15%	4%	5%	9%
75 – 84	6%	9%	15%	2%	4%	6%
85 +	2%	4%	6%	1%	2%	2%
Total	46%	54%	100%	48%	52%	100%

*Aged 18 years or older, 2000 census⁶³

For the quantitative portion of this study, patients were included if they received care from the multispecialty group, were aged 18 or older, and had insurance coverage from the associated health plan between January 1, 2007 and July 31, 2008. Patients were included only if continuously enrolled during the observation period and not residing in a long-term care facility.

A subset of these patients was interviewed for the qualitative study. Data about medication exposure were derived from the prescription drug claims of the health plan. Data about the date of laboratory test ordering and completion were obtained from the EMR. At the time of the study, the EMR did not have clinical reminders to obtain laboratory testing if patients were taking particular medications or had relevant medical conditions.

Selection of drugs and monitoring tests

The medications included in this study were selected from a list of ‘high-risk’ medications with recommended laboratory monitoring tests developed for a clinical decision support system that was intended to be embedded in the EMR by our research group, working with the practice. The development process included a multi-step review process by a national advisory committee as well as local expert review of a comprehensive list of medications as described in detail elsewhere.¹⁶ For that study, medications were considered ‘high-risk’ and candidates for inclusion in the clinical decision support system included those commonly implicated in ADEs in the ambulatory setting,³ adverse events leading to emergency department visits,⁶⁴ drugs previously determined to be associated with low rates of recommended monitoring,^{4, 24} drugs with monitoring recommended in national quality guidelines,⁶⁵ and drugs with laboratory-monitoring-associated black box warnings (BBW).⁶⁶ The list of indicated laboratory monitoring tests for each drug was developed in close conjunction with two research pharmacists who reviewed the literature and product labeling to determine the appropriate test frequency for each drug-test pair. The final guideline list is listed in Chapter IV and includes 34 drugs or drug classes, some with multiple recommended tests, for a total of 60 drug-test pairs, of which 16 (27%) have BBWs. For the purpose of the studies described in this dissertation, we use the following terminology: any drug from the guidelines list is referred to as a high-risk medication, given the potential risk associated with these drugs. A subset we specifically refer to as a BBW drug-test combination, if the medication has a black box warning that is associated with a specific

laboratory test. Warfarin was not included in the analyses for this dissertation because it is primarily managed by a specialized anticoagulation clinic in most health care systems, including our system.

This chapter describes a study that included a subset of these high-risk medications: those often prescribed in the outpatient setting for common chronic conditions that require monitoring, specifically cardiovascular medications (ACE inhibitors and ARBs, statins, digoxin, diuretics, fibrates, and niacin); anti-convulsants (phenytoin, valproic acid, carbamazepine and phenobarbital); potassium supplements; and thyroid replacement therapy (Table 3.2).

Table 3.2: Drugs with Recommended Tests and Test Frequencies

Drug	Test	Minimum recommended testing frequency
ACE AND ARBS	BMP	Yearly
AMIODARONE	AST/ALT	Twice yearly
	TSH	Twice yearly
ALL DIURETICS	BMP or Cr&K	Yearly
DIGOXIN	Cr&K	Yearly
FENOFIBRATE	AST/ALT	Yearly
	CBC	Yearly
GEMFIBROZIL	AST/ALT	Yearly
NIACIN	AST/ALT	Yearly
STATIN	AST/ALT	Yearly
POTASSIUM SUPPLEMENT	K	Yearly
THYROID SUPPLEMENT	TSH	Yearly
CARBAMAZEPINE	AST/ALT	Yearly
	CBC	Yearly
	CARBAMAZEPINE	Yearly
PHENOBARBITAL	AST/ALT	Yearly
	CBC	Yearly
	PHENOBARB	Yearly
PHENYTOIN	AST/ALT	Yearly
	PHENYTOIN	Yearly
VALPROIC ACID	AST/ALT	Yearly
	CBC	Yearly

	VALPROIC ACID	Yearly
--	---------------	--------

Abbreviations: ACE inhibitors = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMP = basic metabolic panel; CBC = complete blood count; Cr = creatinine; K = potassium; TSH = thyroid stimulating hormone:

i. Quantitative Analysis

We used drug dispensing claims to identify the first dispensing of one of the high-risk medications of interest prescribed after January 1, 2008 for an ambulatory patient.

Chronic drug use was defined as a dispensing with evidence of another drug dispensing in the 6 months prior to that date. Each medication (or drug class) had one or more recommended test. Only one instance of each drug-test pair was included for analysis.

Clinician test ordering was defined as having occurred if there was at least one recommended test for the drug-test pair ordered up to 365 days before the index dispensing in 2008 through 14 days after the dispensing if the test was indicated annually (or 180 days before to 14 days after index dispensing if the test was indicated every 6 months). Patient test completion for each ordered test was then determined by matching the test order with test results based on a unique order identifier. Tests ordered outside of the group practice (e.g., in the hospital or other clinician practice) were not captured. For each drug-laboratory test combination, the proportion of ordered and completed recommended tests was determined for all index dispensings in the observation period. Analyses were conducted in SAS 9.2 (SAS Institute, Cary, NC, USA). This study was approved by the institutional review boards of the University of Massachusetts Medical School and the multispecialty group practice.

ii. Qualitative Analysis

To better understand patient non-adherence to lab testing as measured in the quantitative analysis, we undertook a qualitative approach to identify patient factors that might contribute to missing laboratory tests. The open-ended semi-structured interview approach allows broader identification of issues, limits the impact of researcher bias in exploring patient reasons for non-attendance, and is able to solicit information not available in the electronic record.⁶⁷

Qualitative Interview Guide Development

Using a semi-structured interview format, we examined why patients themselves missed laboratory tests and what barriers to completion they thought existed for both themselves and others. Questions were developed based on the literature^{29, 61, 62, 67-73} and were designed to elicit personal experiences of missed laboratory tests and understanding of the reason for them (Table 3.3). Patients were also presented with educational material to be used for a potential, future intervention and were asked for feedback. Two pilot interviews were conducted to provide training for the interviewer and to test the protocol, leading to further refining of the questions.

Table 3.3: Topics Covered in Qualitative Interviews

Lab tests in past year For what? Understanding of reason? Is it important to you to understand why? Did your doctor explain why? Explain the procedure? Do you remember missing a test? Why did that happen? Experience of lab test (convenience, treatment at lab, time, concerns)
Relationship with doctor
Communication, specialty
Reminders

From clinic? What would be most helpful? Your own system?
Specific questions Transportation? Cost? Scheduling? Missed because of stopping a med? What makes it easier? Harder?
Speculation about others' reasons for missing a test

Recruitment, Data Collection, and Analysis

We used a purposive sampling approach to select patients for qualitative interviews in order to capture patients who did complete ('shows') and did not complete ('no-shows') a laboratory test ordered for a subset of the medications analyzed in the quantitative portion (ACE inhibitors and ARBs, statins, phenytoin, valproic acid, digoxin, and thyroid replacement therapy). This sampling strategy aimed to include both men and women and a representation of older adults (age > 65).

To identify potential study candidates, a member of the research team reviewed a list of patients who missed a scheduled laboratory test between July 2008 and October 2010. Missed tests were identified by reviewing the completion date for the test and determining whether the date had passed without a test registered in the system. We also identified patients who completed a laboratory test in the same time period using the same approach.

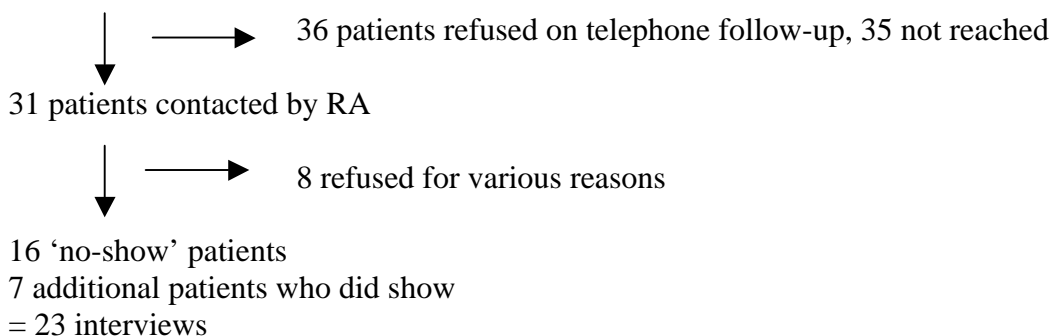
To determine study eligibility, we reviewed the EMR for patients having a prescription for one of the study medications, having an order for a related lab test, receiving care at the multispecialty group practice, and being aged 18 or older. Eligible patients were contacted via telephone by a research nurse, assessed for interest and ability in participating in an English-language interview, and invited to participate in the study (Figure 3.1). Patients contacted were offered in-person interviews in our research office

as well as the option of participating in a telephone interview if there was an indication of transportation difficulties in the medical record or if the patient suggested that travel would limit participation.

Patients with an indication of inability to provide informed consent, including those with a history of cognitive impairment, dementia, or severe thought or mood disorders, were not contacted.

Figure 3.1: Qualitative Interview Recruitment

102 patients received study invitation letters



Each participant was sent a consent form and a description of the study and was then contacted by a research assistant to schedule the interview. The research assistant was blinded to the test completion status of the patient and to the patient's medical history. Interviews took about 45 minutes and patients were given a \$25 stipend. All interviews were recorded and transcribed.

Using a grounded theory approach,⁷⁴ two researchers developed codes based on four randomly selected transcripts and then met to review and reconcile differences in the codes. Grounded theory is a qualitative research approach developed in the late 1960s in

order to study data on caring for dying patients.⁷⁴ The method aims to generate theories from the data by researchers reviewing documents or transcripts and then coding each section (constant comparative data analysis). Codes are then compared and refined and used to identify themes. Sample size is determined using ‘theoretical saturation.’⁷⁵ Quantitative approaches can also be applied once the data are coded.

The codebook developed by the two researchers was then used to code the remaining transcripts. Interviews were conducted until theme saturation was achieved, meaning we reached a point in the interviews where we no longer heard new ideas from participants.⁷⁶⁻⁷⁸ Prior studies suggest that saturation can be reached with as few as 12 interviews.⁷⁶ We interviewed 16 patients who did not complete ordered tests. We additionally interviewed 7 patients who did complete ordered tests, and their comments were very similar to those who had missed at least one test. We completed 23 interviews and terminated data collection.

Analyses were conducted using NVivo qualitative data analysis software (QSR International Pty Ltd. Version 8, 2008, Victoria, Australia).

D. Results

i. Quantitative Study

Table 3.4 shows the number of prescriptions and overall completion rates (test ordered by provider and completed by patient) for chronic prescriptions of study drugs. Completion rates varied from 37.9% (Valproic Acid-AST) to 96.8% (Niacin-AST), with more similar completion rates within a specific medication and varying rates of the same

test (for example, AST), suggesting the differences were due to the medications and perhaps their indication. For example, the psychiatric medications had lower completion rates than others in this data set.

Table 3.4: Overall Completion of Indicated Tests for Chronic Users of Study Medications

Drug (Test)	# chronic prescriptions for this medication (# drug-test pairs)	% of indicated tests completed
ACE AND ARBS (BMP)	8765	88.3%
AMIODARONE (AST)	79	59.5%
AMIODARONE (TSH)	79	48.1%
ALL DIURETICS (BMP or Cr&K)	9784	88.5%
DIGOXIN (Cr&K)	1015	90.2%
FENOFIBRATE (AST)	190	86.3%
FENOFIBRATE (CBC)	190	70.0%
GEMFIBROZIL (AST)	697	81.3%
NIACIN (AST)	95	96.8%
STATIN (AST)	13351	84.0%
POTASSIUM SUPPLEMENT (K)	1610	90.4%
THYROID SUPPLEMENT (TSH)	4660	70.0%
CARBAMAZEPINE (AST)	193	57.5%
CARBAMAZEPINE (CBC)	193	72.5%
CARBAMAZEPINE (CARBAMAZEPINE)	193	57.0%
PHENOBARBITAL (AST)	52	46.2%
PHENOBARBITAL (CBC)	52	69.2%
PHENOBARBITAL (PHENOBARB)	52	53.8%
PHENYTOIN (AST)	313	46.3%
PHENYTOIN (PHENYTOIN)	313	75.7%
VALPROIC ACID (AST)	248	37.9%
VALPROIC ACID (CBC)	248	62.1%
VALPROIC ACID (VALPROIC ACID)	248	44.8%

Abbreviations: ACE inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMP, basic metabolic panel; CBC, complete blood count; Cr, creatinine; K, potassium; TSH, thyroid stimulating hormone.

Figures 3.2 and 3.3 show the rates of completion and reasons for non-completion for included medications. While the cardiovascular and potassium and thyroid replacement therapy medication-test pairs generally had completion rates of 60-80% rates were lower for the anti-convulsant medications. Overall, provider non-ordering was

responsible for the larger portion of the non-completion for these pairs (Figure 3.3). Provider non-ordering rates varied from 1.1% (Niacin–AST drug-test pair) to 51.6% (Valproic Acid–Valproic Acid level drug-test pair), while patient non-completion varied from 2.13% (Niacin–AST) to 24.19% (Valproic Acid–AST).

Figure 3.2: Completion and Non-Completion of Tests

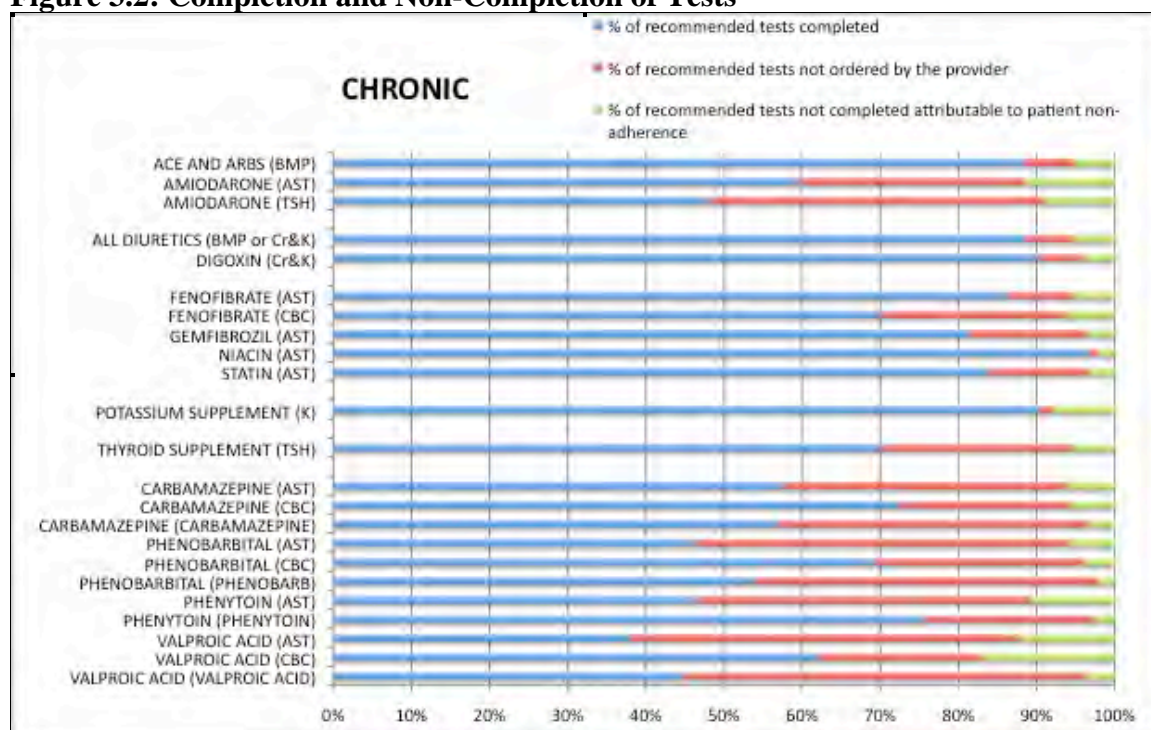
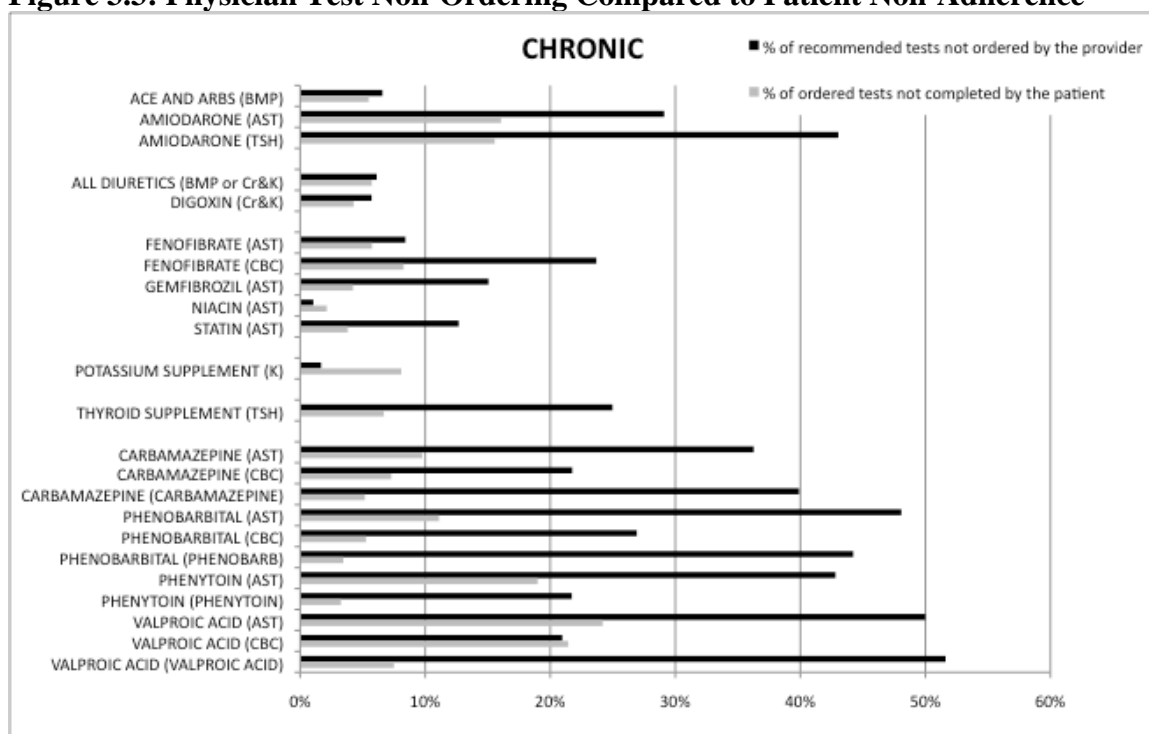


Figure 3.3: Physician Test Non-Ordering Compared to Patient Non-Adherence

ii. Qualitative Results

Interviewed patients had a mean age of 63, were mostly female, and were all white (Table 3.5). Most were selected because they were taking an ACE inhibitors or a statin. Several themes regarding laboratory monitoring emerged during the qualitative data analysis, including human factors and system factors that contribute to lab attendance.

Table 3.5: Interviewed Patient Characteristics

Patient Characteristics	Total Sample N=23	No-show Patient N=16	Show Patient N=7
Patient Age			
Mean (Range, SD)	63.1 (34-89, 13.6)	60.3 (34-89, 15)	69.57 (62-80, 6.2)
Gender			
Female	17 (73.9%)	14 (87.5%)	3 (2.9%)
Male	6 (26.1%)	2 (12.5%)	4 (57.1%)
Interview format			
In-person	17 (73.9%)	12 (75%)	5 (71.4%)

Telephone	6 (26.1%)	4 (25%)	2 (28.6%)
Medication			
ACE Inhibitor	7 (30.4%)	6 (37.5%)	1 (14.3%)
ARB	1 (4.3%)	1 (6.3%)	0 (0%)
Phenytoin	3 (13%)	2 (12.5%)	1 (14.3%)
Statin	10 (43.5%)	6 (37.5%)	4 (57.1%)
Thyroid	2 (8.7%)	1 (6.3%)	1 (13.3%)
Highest Degree			
Some high school	1 (4.3%)	1 (6.3%)	0 (5)
High school graduate	9 (39.1%)	6 (37.5%)	3 (42.9%)
GED	1 (4.3%)	1 (6.3%)	0 (0%)
Some college	5 (21.7%)	4 (25%)	1 (14.3%)
Associates degree	3 (13%)	2 (12.5%)	1 (14.3%)
Bachelors degree	4 (17.4%)	2 (12.5%)	2 (28.6%)

Abbreviations: SD, standard deviation; ACE, Angiotensin-Converting Enzyme; ARB, Angiotensin II Receptor Blockers; GED, General Education Diploma.

Factors That Affect Completion

When asked why they had missed lab tests, 7 of 16 patients said they simply forgot (Figure 3.4). While many patients (11) said they used a calendar as their system to remember to get tests, including the majority of the patients who completed their tests (4 ‘show’ patients), others said they had no system at all (3 ‘no-show’ patients).

Forgetting

Forgetting was the most frequent cause of a missed lab test. The interviewer asked each patient if he or she recalled missing a lab test. While some patients denied missing a lab test, most patients acknowledged missing a lab test and cited forgetting as the reason. When explaining why she forgot, one patient noted that it was probably because the test was due at a time without a visit to the provider: “[The physician] does [the lab tests] not just yearly, but in between sometimes.” A number of patients could not indicate a reason why they could not remember to complete the test.

Competing demands

Three patients identified competing demands that led them to delay or miss their lab tests. They understood the importance of the test but simply had extenuating circumstances or other factors that led these patients to postpone test completion. As one patient said, “I missed that one [test], but I was having a lot of problems with the family and things were going on and I just couldn’t be bothered. But that was my own fault; it was nothing to do with the procedure.”

Transportation

One patient identified transportation barriers, stemming from a disability, as the reason for the missed test. A second patient indicated challenges with finding transportation, but noted that she had never failed to complete an order because of such problems.

Other concerns

A majority of participants indicated that they did not have concerns about undergoing a lab test. In response to a question about lab concerns, a few patients noted that they disliked needles, but they clarified that the process has become routine and their needle aversion does not affect attendance. As one patient said, “Well, who likes [needles]?...I don’t love them, but...you’ve got to do what you’ve got to do.” However, one patient did note that a dislike of needles influenced him to delay a lab test past the desired completion date.

Access and logistics

Most participants did not indicate any problems with reaching a lab facility to complete their test orders. Patients noted that the option to choose from several locations

and lack of appointments made the process easier. “Easy, you can go any time...you’re right in and out.” Many praised the convenient locations, the short waits, and the friendly and competent staff.

Frequency of lab tests

‘No-show’ patients reported a greater frequency of ordered lab tests per year than the ‘show’ patients. Many patients with a missed test said that they tended to have an order for blood work every three months. In contrast, of the ‘show’ patients, those who had not missed a test, only one reported having to perform a blood test more than two times per year.

Factors That Could Improve Completion

Reminders

Most patients, including those who missed a lab test, said they had some sort of personal reminder system, with a paper calendar as the most popular tool. Some patients with an incomplete test did not have a reminder system, while all patients who had completed all tests used some type of personal reminder. Some participants noted that they used the health practice group’s online health portal to check for upcoming appointments. “It helps me set up my medications, set up my appointments, look at my appointments, missed appointments...and get the results.”

Some patients indicated that the clinic did not send reminders for lab tests. When asked, many agreed that they received no reminders about lab tests, but neither did they express concern about this. When prompted regarding what type of reminder the clinic should send for lab tests, most participants expressed preference for a telephone call. “A

call is the best thing...just like when they call to remind you that you have an appointment [with a provider].” A few patients did not have a preference for reminder type or thought a reminder would be unnecessary.

Comprehension and education

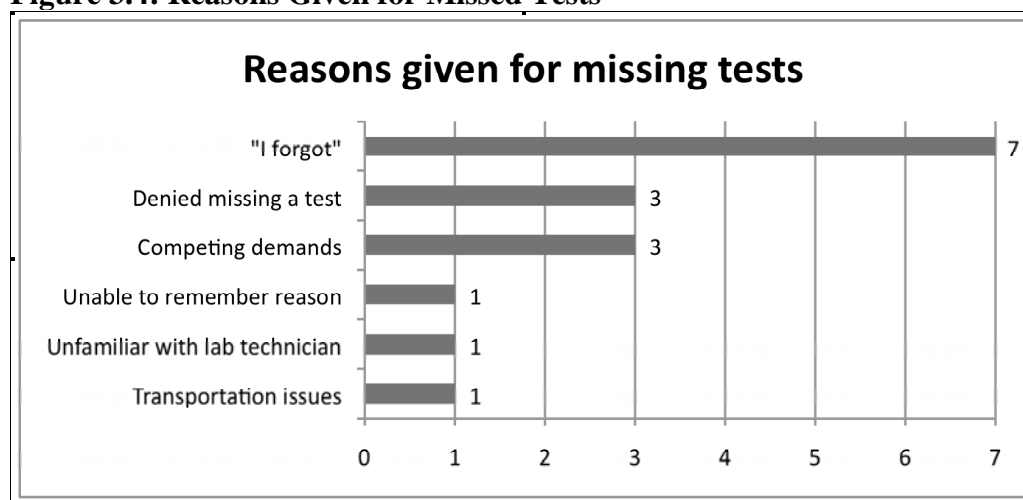
Many patients were able to explain the reason for the lab test. Patients most commonly spoke about tests as necessary for preventing side effects, adjusting medication dose, and checking organ function. Some were very specific about the connection between the test and their medications: “Every blood test is critical... especially the [phenytoin] levels, because they have to keep them at that therapeutic level rather than the toxic.” Others spoke in more vague terms about the reason for testing, as in the following answer to the question of why a test was being conducted: “I’m a diabetic and they have to read the range of my something from zero to seven, or whatever it is. I don’t know what it is they do, but that’s why I go.”

A number of patients, both those with and without an incomplete lab test, said that it was important to understand the purpose of the test. One explained the purpose as, “...To understand my medication levels, and when my levels go up and down to readjust things—it’s very important for me if I want to be healthy.” No participants indicated that they missed a lab test due to not knowing its purpose. Furthermore, patients generally stated they understood the reasons for their tests and were satisfied with the explanations from their physicians.

Patients also gave feedback about potential educational messages. While some liked the idea of a message as a reminder, overall, patients did not feel the messages

would add to their understanding, given the information they already receive. As one patient said, “I think I would want one [message] just in case something happened and I have this to fall back on. But usually if I go on a new medication or something, she [physician] tells me up front what can happen, and if I’m going to need additional lab work. And then if I get the medication at the pharmacy, it tells me what to look for.” They also generally thought that they already understood the information presented, though it might help others.

Figure 3.4: Reasons Given for Missed Tests



E. Discussion

This mixed-methods study adds to the literature on laboratory monitoring for high-risk medications by quantifying the relative contributions of physician test ordering behavior from patient adherence behavior to overall under-monitoring, and by directly soliciting patient perspective about how to improve test adherence. In our setting, we found that provider non-testing was greater than patient non-adherence. Further,

qualitative interviews suggested that patient reminders might help improve test completion, but improving patient understanding about testing probably would not.

Prior literature either evaluates physician test ordering^{14, 15} or patient test completion;^{10, 11} however, rarely are both reported.^{9, 16} Our study found slightly higher rates of physician test ordering than in previous studies,^{14, 15} though it is difficult to compare given the different tests recommended, the lack of detail in publications, and the lack of a look-back period (for certain tests completed before the prescription, obviating the need to test after) in some studies.¹⁴

Patient non-adherence once a test was ordered was lower, ranging up to 24.2% for AST test completion in patients taking valproic acid. These completion rates are in fact high; other literature about patient non-adherence,⁴ and our completion data for patients on new medications and for patients with less common medications (not reported here), show even higher rates of non-completion.

Human factors connected to attendance were for the large part cognitive. Patients identified forgetting as the dominant reason for missing tests, even as they demonstrated understanding of the reasons for the tests and denied other barriers to attendance. They did also identify a number of concerns, when prompted, like fear of needles, but these concerns did not seem to be barriers to test completion.

Health systems factors have also been identified as reasons patients miss appointments,^{67, 73} but the patients in this study did not identify major barriers either to access or with logistics for attendance.

i. Forgetting and Reminders

The current system may contribute to forgetting, because patients are told to get tests within a certain time frame but not at a specific time. This flexibility generally works—overall completion rates are relatively high—but without a concrete appointment, human factors make it easy to forget to complete a lab test order. Our multi-specialty practice is responding to these findings with interventions to address the reminder issue, including phone calls prior to lab test deadlines.

However, addressing patient compliance via reminders and scheduling changes will never lead to a 100% completion rate, as shown through the quantitative data, without considering the physician factors that contribute to ordering as well. One study interviewing physicians about lack of ordering drug monitoring tests found that important factors include lack of clarity about which provider was responsible for ordering a test and lack of certainty regarding the necessity of monitoring as well as lack of reminders to physicians.²⁶ These problems should also be targets for interventions.

There is not a single explanation for incomplete laboratory monitoring. Interventions to improve monitoring will have to target both ordering and completion, and data should report the two rates separately, which is currently rarely done.²³ Part of this is due to a lack of electronic record usage, which is required for accurate ordering rates (most studies report completion rates, as determined from claims data, which is easier to access but may be less accurate).⁷⁹

One strength of our study is the computerized system from which we derived our quantitative finds. While prescriptions are often trackable using claims data, it is very

difficult to track test orders without an electronic medical record. Furthermore, because this study was conducted in a single system with electronic ordering and claims data, plus information about enrollees and providers, we were able to conduct analyses that might be hard to do elsewhere. We were able to then identify and conduct interviews with patients whom we knew had missed a test. This allowed us to target our study to the patients with whom we hope to effectively intervene.

Limitations of our study should be noted. As above, patients receiving care from the multi-specialty group practice are representative of the population of central Massachusetts. Although the practice is similar to many similar healthcare provider groups across the US, it is different in that it is an integrated health care system and it is one of the early providers to have full implementation of electronic medical records and computerized physician order entry (CPOE). Second, laboratory tests may have been ordered for another reason (i.e., not for high-risk medication monitoring), so that we may have overestimated the prevalence of recommended testing. At the same time, we may have missed monitoring that was done at a hospital. Third, for the quantitative portion, we were unable to confirm patient adherence to drugs and were unable to identify patients who did not complete tests because they were no longer using the medication. Fourth, for many drugs, further study is necessary to determine whether laboratory test monitoring improves health outcomes, and these differing levels of evidence may have affected provider choice in choosing what tests to order. This issue is discussed further in Chapter IV. Fifth, while we interviewed patients about their reasons for missing tests, we did not speak to physicians about their reasons for failing to order tests. Lastly, the

patients who were interviewed for the qualitative piece may not be representative of the whole population, given that the same barriers that prevent completing testing may also impede appearing for an interview. We attempted to overcome that issue with telephone interviews, but we cannot rule out that we missed patients who had more significant barriers to both testing and interviewing.

ii. Conclusion

Our study demonstrates higher rates of completion than some similar studies, but still low rates overall given the importance of laboratory monitoring. However, our results further suggest that systems factors like transportation, wait time, or co-payment were not major reasons for test non-completion. Similarly, patient understanding did not seem to be a large factor in the decision to complete a test. Rather, patients reported that they simply did not remember to get tests, which unlike appointments were not set for specific times and dates, and that the reminder systems that they did use were unreliable.

This work furthers the evidence for the potential for improvement in monitoring rates and the potential benefit of the EMR in improving quality of care. As patients miss appointments because of forgetting, reminders need to be implemented, but they will only be successful if done in a way that patients will receive them. More than half of the interviewed patients were amenable to phone reminders. While many patients did not use the health system's patient portal at all, those who did found it to be a useful way to find out more about lab tests and get reminders regarding deadlines, thus suggesting it the portal would be effective for improving testing among a certain population.

As EMRs become more prevalent, researchers will be better able to separate provider behavior and patient behavior. This will allow better targeting of interventions to improve health care quality. At the same time, much behavior is driven by human factors. Everyone, provider or patient, is prone to forgetting, and without a reminder at the right time, we may not be able to affect human behavior.

CHAPTER IV

FACTORS ASSOCIATED WITH ORDERING LABORATORY MONITORING OF HIGH-RISK MEDICATIONS

A. Abstract

Purpose

To determine physician factors that are correlated with ordering of recommended laboratory monitoring tests for high-risk medications after adjustment for patient characteristics. We hypothesized that providers with less experience with a specific drug, specialty training, weaker testing recommendations, and healthier patients would be associated with lower ordering laboratory tests for study medications.

Design, Participants, Measures, and Data Analysis

Cross-sectional analysis of the administrative claims and electronic medical records of patients prescribed a high-risk medication requiring laboratory monitoring in a large multispecialty group practice between January 1, 2008 and December 31, 2008. The outcome is a physician order for each recommended laboratory test for each prescribed medication. Key predictor variables are physician characteristics, including age, gender, specialty training, years since completing training, and prescribing volume. Potential

confounders include patient characteristics such as age, gender, comorbidity burden, whether the medication requiring monitoring is new or chronic, and drug-test characteristics such as inclusion in black box warnings and consensus or evidence-based guidelines. We used multivariable logistic regression to identify the independent association of physician and patient characteristics with ordering of laboratory tests to monitor medications after adjustment for potential confounders, taking into account clustering of drugs within patients and patients within providers.

Results

Physician orders for laboratory testing varied across drug-test pairs and ranged from 9% (Primidone–Phenobarbital level) to 97% (Azathioprine–CBC) with 50% of drug-test pairs in the 85-91% ordered range. Failure to order a test was associated with lower provider prescribing volume for study drugs, and whether the physician was a specialist (primary care providers were more likely to order tests than specialists). Additional factors included lower patient comorbidity burden and younger patient age were less likely to have tests ordered. Drug-test combinations with black box warnings were more likely to have appropriate tests ordered.

Conclusions

This study identifies factors associated with ordering of laboratory monitoring of high-risk medications. Interventions targeting providers should be addressed at those subgroups with the greatest potential for improvement: providers with lower frequencies of prescribing, and healthier and younger patients. Drug-test combinations with black box

warnings have higher ordering rates, suggesting some effectiveness of warnings to providers, but many medications without such warnings also have evidence of harm, even if not as well-established, thus efforts to improve testing are necessary for all medications shown to be high-risk.

B. Background

Little is known about provider factors that contribute to ordering recommended laboratory monitoring. Beginning with the Institute of Medicine's seminal report, "To Err is Human,"² on the 44,000 to 98,000 deaths caused each year by medical errors, efforts have been underway to improve patient safety and reduce the incidence of medical errors in the United States. Errors in prescribing and monitoring medications constitute a major portion of these medical errors.³

For preventable adverse drug events (ADEs) in the ambulatory setting, recommendations have targeted prescribing and monitoring errors,⁵ based on studies identifying inadequate monitoring as the most common cause of preventable ADEs among older adults, occurring in 60.8% of these events (followed by prescribing errors and errors involving patient adherence).³ In the ambulatory setting, this has been shown to lead to hospitalizations and significant morbidity.¹¹

Medication monitoring refers to the need to monitor symptoms or lab results of patients on specific medications to prevent toxicity or to monitor efficacy. For narrow therapeutic window medications such as phenobarbital, serum drug levels are monitored to reduce risk of toxicity. For other medications, monitoring evaluates the physiologic effect of medications. For example, angiotensin-converting enzyme (ACE) inhibitors can raise potassium and creatinine levels. And for some drugs, such as aminoglycoside antibiotics or lithium, monitoring involves measuring both drug levels and physiologic effects.⁸

One major challenge to appropriate laboratory monitoring by health care providers is the lack of national guidelines and lack of expert agreement on appropriate monitoring standards.⁸⁰ However, even when guidelines are introduced, monitoring does not meaningfully improve.⁸¹ And when recommendations do exist, whether from expert guidelines or product inserts, they are not routinely followed.¹¹

Therefore, we conducted this study to identify provider characteristics associated with decreased ordering of recommended laboratory tests for high-risk medications in the ambulatory setting, taking into account patient factors and whether drug-test recommendations were included in black box warnings (BBW) or clinical guidelines.

We also included physician volume, as volume has been shown to correlate with better outcomes in other settings, such as surgery, where post-operative mortality is correlated with higher surgeon and hospital volume.⁸²⁻⁸⁴ Providers with high frequency of prescribing a given medication or those with more patients in their panels may be more familiar with testing guidelines or may have seen potential adverse outcomes more often than less familiar prescribers, but this has not been studied with regards to monitoring. Similarly, specialty has been shown to be associated with clinical behavior in providers, with specialists often offering more care if not better outcomes,⁸⁵⁻⁸⁷ but this factor has not been studied for laboratory monitoring guideline adherence.

The specific aims were to identify factors associated with provider ordering of laboratory monitoring, including age, gender, specialty training, and years in practice for providers and age, gender, comorbidities, and new versus chronic user status for patients,

in adjusted and unadjusted models, as well as to stratify by evidence level for the testing and to compare the factors associated with ordering in each of these subgroups.

C. Methods

i. Study Design and Setting

This study was conducted within the Fallon Clinic, a large multispecialty group practice closely aligned with the Fallon Community Health Plan, a non-profit, Central Massachusetts-based integrated health care delivery system, as described in Chapter III. The practice uses the EpicCare Ambulatory electronic medical record (EMR) system (Epic, Verona, WI, Spring 2007 IU3 at the time of the study).

For this analysis, we included patients if they received care from the multispecialty group practice, were 18 years or older, and had insurance coverage from the health plan between January 1, 2007, and December 31, 2008. Patients had to be continuously enrolled during the observation period and not residing in a long-term care facility.

ii. Selection of Study Medications

The medications included in this study, as in Chapter III, were based on a list of high-risk medications with recommended laboratory monitoring tests developed for a clinical decision support system that was intended to be embedded in the EMR. The development process included a multi-step review process by a national advisory committee as well as local experts review of a comprehensive list of high-risk medications as described in detail elsewhere.¹⁶ Medications reviewed included those

commonly implicated in ADEs in the ambulatory setting,³ adverse events leading to emergency department visits,⁶⁴ drugs previously determined to be associated with low rates of recommended monitoring,^{4, 24} drugs with monitoring recommended in national quality guidelines,⁶⁵ and drugs with laboratory-monitoring-associated BBWs.⁶⁶ The list of indicated laboratory monitoring tests for each drug was developed in close conjunction with two research pharmacists who reviewed the literature and product labeling to determine the appropriate test frequency for each drug (Table 4.1).

Table 4.1: Study Medications and Recommended Tests

Persons prescribed the following high-risk medications (or classes) during 2008 were included in the analysis.

DRUG	TEST
ACE/ARB	BMP
ALLOPURINOL	CREATININE
AMIODARONE	AST or ALT
	TSH
AZATHIOPRINE	AST or ALT
	CBC
AZOLE ANTIFUNGAL	AST or ALT
CARBAMAZEPINE	AST or ALT
	CARBAMAZEPINE
	CBC
COLCHICINE	CBC
	CREATININE
CYCLOSPORINE	AST or ALT
	CREATININE
	CYCLOSPORINE
DIGOXIN	CREATININE
	DIGOXIN
	POTASSIUM
DIURETIC-LOOP	BMP or K+Cr
DIURETIC-NOT-K-SPARING	BMP or K+Cr
DIURETIC-POTASSIUM SPARING	BMP or K+Cr
DIURETIC-THIAZIDE	BMP or K+Cr
FENOFIBRATE	AST or ALT
	CBC
GEMFIBROZIL	AST or ALT
ISONIAZID	AST or ALT

LITHIUM	CBC
	CREATININE
	LITHIUM
	TSH
METFORMIN	CREATININE
METHOTREXATE	AST or ALT
	CBC
	CREATININE
METHYLDOPA	AST or ALT
	CBC
NEFAZODONE	AST or ALT
NIACIN	AST or ALT
PHENOBARBITAL	AST or ALT
	CBC
	PHENOBARBITAL
PHENYTOIN	AST or ALT
	PHENYTOIN
POTASSIUM	POTASSIUM
PRIMIDONE	CBC
	PHENOBARBITAL
	PRIMIDONE
QUINIDINE	AST or ALT
	CREATININE
	POTASSIUM
	QUINIDINE
RIFAMPIN	AST or ALT
STATIN	AST or ALT
TERBINAFINE	AST or ALT
THEOPHYLLINE	THEOPHYLLINE
THIAZOLIDINEDIONE	AST or ALT
THYROID REPLACEMENT	TSH
VALPROATE SODIUM	AST or ALT
	CBC
	VALPROIC ACID

Abbreviations: ACE/ARB, ACE, Angiotensin-Converting Enzyme Inhibitors/Angiotensin II Receptor Blockers; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMP, basic metabolic panel; Cr, creatinine; K, potassium; TSH, thyroid stimulating hormone.

* Test completion for a new dispensing defined as occurred if there was at least one associated monitoring test ordered 180 days before to 14 days after dispensing, and for chronic dispensing as occurred if there was at least one recommended test for the drug-test pair up to 365 days before or 14 days after the index dispensing in 2008 (or 180 days before to 14 days after index dispensing if test was indicated every 6 months).

† Baseline serum drug level for new dispensings measured from date of index dispensing to up to 14 days after index dispensing.

iii. Medication Exposure

Data about medication exposure were derived from the prescription drug claims of the health plan, while data about laboratory test orders were derived from the multispecialty group practice electronic medical record. Use of claims data for medication exposure allowed for the measurement of medications actually filled at the pharmacy, avoiding possible exposure misclassification by using EMR prescribing data that may include prescriptions that were never filled or taken. In addition, the EMR includes “historical medications” which reflect over-the-counter medications and medications from outside providers but are inconsistently recorded across patients and providers. These medications are not included in the claims data and thus not included in this study, again meaning the possibility of not accounting for medications a patient is taking but also decreasing the risk of erroneously considering a patient to be taking a medication and thus underestimating appropriate testing.

In cases where a patient had more than one new start of the same drug during the study time frame (no refills or prescriptions for 180 days and then a new prescription), we used the first prescription for that drug only.

iv. Provider Factors

Provider data were collected from an internal provider demographic database containing demographic information for past and present providers employed by the multi-specialty practice. To maximize the dataset, we also included outside providers for whom we had specialty and gender. For many prescriptions, we did not have any individual provider information (the prescriber code was a generic code, specific to site

but not to provider), and they were therefore excluded from analysis for provider characteristics with regard to ordering rates. These providers accounted for less than 15% of the number of providers matched to prescriptions in the dataset. Once exclusion criteria were applied to patients (no provider link, wrong age, death within the time frame, etc.) and providers (no prescriptions in that time period, not hired in the right time frame), the only remaining unknowns had basic demographic data (gender, specialty, and type), and thus were included in the analysis, though their birthdates, hiring dates, and fulltime status were not available. These “unknown” providers were all physicians and more likely to be specialists (58% versus 42%). They also had many fewer patients in the study (mean of 3 patients each versus 153 for the rest of the providers). As a result, their drug prescribing frequency was lower and the number of medications they prescribed was smaller.

v. Drug-Test Pair Characteristics

Because we know that physician clinical practice behavior is affected by level of evidence and guidelines to various extents,^{50, 88} we included measures of whether the study drug-test pairs were included in BBWs or in clinical guidelines. For the analysis of factors associated with ordering (this study) and completion (Chapter V), each drug-test pair was additionally categorized based on the evidence basis for the test. In general, the level of evidence for medical guidelines widely varies, with as many as half of guideline recommendations based on low-quality evidence.⁸⁹ It is outside the scope of the parent project or of this dissertation to exhaustively review the literature to summarize the levels of evidence for each and every drug-test pair. Instead, we have started with the premise

that drug manufacturers' recommendations for monitoring represent knowledge of and evidence of harm. Ample recent evidence demonstrates that drug manufacturers are well aware of the potential of harm from their products and actively work to suppress the public release of this knowledge.⁹⁰ Therefore, there is a publication bias that hampers any systematic effort to document levels of harm. Furthermore, this absence of information and recent history with documented harm in post-marketing surveillance studies (e.g., the case of rosiglitazone/Avandia⁹¹⁻⁹³) demonstrates a lag in the knowledge of drug harm relative to FDA approval.

Therefore, we used the following approach to classify the monitoring guidelines.

- At the highest level, we identified whether there were BBWs on specific medications recommending certain tests. These warnings, which can be required by the FDA, are the most serious warnings in prescription drug labeling. Therefore, the presence of such a warning suggests strong evidence of risks associated with the medication as well as serious quality of care implications for not heeding the warnings. Even these are inconsistently reported,⁹⁴ and adherence is poor even to these warnings,^{95, 96} but they are validated, well-disseminated, and the strongest form of guideline available to a practitioner, thus most likely to drive ordering behavior. These drugs are commonly prescribed.⁹⁵
- We next identified guidelines by physician practice groups or quality of care organizations with recommendations for monitoring.

- At the next level, we classified drugs for which there were no clear guidelines, but for which testing was recommended in standard references, specifically UpToDate, Micromedex, Pharmacist's Letter, and the Physician's Desk Reference.
- Separately, laboratory testing occurs to monitor clinical efficacy or toxicity in drugs with narrow therapeutic windows. We created a separate category to classify these monitoring guidelines.

vi. Conceptual Framework for Analytic Strategy

Variables included in this analysis were selected based on Anderson's model of health services use which can be used to guide analyses of the association between patient factors, physician factors, and health service utilization (i.e., laboratory monitoring of prescription medications). This model generally looks at the behavior of patients and families, and it classifies predictors of behavior into three categories: *predisposing factors* refer to demographic factors like age and gender as well as family structure and health beliefs that affect service use; *enabling factors*, resources that promote or inhibit use like income and health insurance; and *needs factors*, the illness and circumstances that necessitate use.^{30, 31}

Outcome variable:

Ordered status for a monitoring test, dichotomous for each patient-drug-test combination (1=ordered, 0=not ordered), based on the electronic record, was the outcome variable.

Key predictor variables:

Provider characteristics, including gender, age (continuous and by decade), type (physician, nurse practitioner, physician assistant, or other), primary care provider versus specialist, full-time working status, years of experience (continuous), frequency of prescribing a given drug (continuous and quartiles), and number of patients to whom drug was prescribed (continuous and quartiles) were included. Provider variables that were not in or calculable from the EMR (such as full-time status and year of hire and graduation) were captured deidentified from the practice's employment database.

Other variables

Patient characteristics, including age (continuous and by decade), gender, number of study prescriptions (categorized into two and three groups), and visit frequency (continuous and quartiles), as well as specific diagnoses including dementia and heart disease (categorical), and number of other study medications were included. Comorbidity was measured using the Charlson score using ICD-9 codes from encounter data in the EMR via a tool in STATA using ICD9 codes.⁹⁷ The Charlson score is correlated with 1-year mortality⁹⁸ and is the most widely used comorbidity index.⁹⁹ We examined both the weighted index (0-16) and a categorical three-point index (0-2) defined as a weighted Charlson of 0, 1, or ≥ 2 . The Romano adaptation of the Charlson score was also calculated in STATA from the disease-specific scores and also categorized into a dichotomous variable (Romano ≤ 2 vs. Romano ≥ 3).¹⁰⁰

Prescription characteristics, including drug, evidence for testing category (BBWs, other type of guideline, and testing for narrow therapeutic window category), whether the drug had single or multiple recommended tests, and testing frequency were included. The BBW category was identified by individually checking whether a given test addresses a warning via online databases (labeling only relevant drug-test combinations as BBW, not by drug) with the caveat that even BBW status is reported differently in different locations.⁹⁴

For analysis, we categorized many continuous variables into quartiles to account for possible non-linearity. For example, we calculated quartiles for visit number per patient, drug prescribing frequency for providers, prescription number per provider, and number of patients per provider. We categorized age by decade, starting with patients and providers below 40 and ending with providers >60 and patients >80, due to frequencies. We also categorized the number of drugs per patient (which ranged from 1 to 9) to a dichotomous variable (one or more than one), and to three categories, 1, 2-4, and 5-9, to enable comparison to similar studies.⁹⁶

vii. Data Analysis

Using the integrated EMR, prescriptions and laboratory orders were extracted for the study time period. Each prescription, linked to scrambled IDs for both prescriber and patient, were then linked to laboratory orders for the patient in question during the relevant time period, as well as to demographic and medical information for provider and patient.

Our analytic modeling strategy accounted for multiple prescriptions nested within a patient and multiple patients nested within a provider. The unit of analysis was a prescription-test pair. The outcome was whether an indicated test was ordered (yes/no). For each prescription, the recommended test was either ordered or not, resulting in a “yes”/“no” for “test ordered.”

Because some patients have multiple providers who prescribed them study medications as well, we initially developed a series of unadjusted and adjusted models that accounted for crossed effects in our analysis. In this approach, we used a multilevel mixed-effects logistic regression specifying both patients and providers as random effects. Initial models examined predictor variables individually, and subsequent multivariable models further adjusted for potential confounders. However, most multivariable models did not converge because of the high prevalence of patients with single tests as well as perhaps because some providers had single patients.

We therefore developed logistic regression models with a robust covariance estimator (sandwich estimator) to adjust standard errors for clustering. This approach provides conservative nonparametric estimates¹⁰¹⁻¹⁰⁴ We first calculated robust standard errors based on clustering of medications within patient and separately performed calculations based on clustering within providers. The models with patient and provider clustering both produced similar parameter estimates to each other, as well as to the cross-effect models when they did converge, but when we clustered by provider the models yielded more conservative estimates of the standard errors and therefore is what

we present here. Parameter estimates are reported as odds ratios (ORs) of factors associated with test ordering.

Our modeling approach aimed to develop an explanatory model to identify factors that could be changed through intervention, rather than simply to obtain a best predictive model.¹⁰⁵ Therefore, initial models included all factors hypothesized to be associated with test ordering *a priori*. Unadjusted models examined relationships between each predictor and confounding variable with the outcome of test ordering. We also tested for correlation between patient visits, Charlson comorbidity score, and Romano comorbidity score, and found correlation among these variables at the $\sigma > 0.40$ level given that they all reflected patient health status. Therefore, we only included the number of patient visits as the single health status proxy indicator in each model. We developed separate models for Charlson scores and Romano scores in sensitivity analyses. Similarly, prescribing frequency and patient panel size were correlated, leaving us to include only one volume measure in each adjusted model. We also examined for interactions of BBW (yes/no) status with provider status and number of drugs per patient. Because we found a significant interaction of BBW in adjusted analysis, we developed models stratified by BBW. Final multivariable models included factors hypothesized to be associated with test ordering *a priori* and factors associated with test ordering at the $p < 0.20$ level in unadjusted analysis. Goodness of fit for the models were examined using the c statistic and receiver operating characteristic (ROC) curve.

Analyses were conducted in SAS 9.2 (SAS Institute, Cary, NC) and StataSE (Stata Statistical Software: Release 11.1, Stata Corporation, College Station, TX, USA).

D. Results

i. Patient Population and Use of Medications Requiring Laboratory Monitoring

After excluding ineligible patients, providers, and prescriptions and after linking all prescriptions to patients and prescribing providers, the study data included 31,417 unique patients and 278 providers for a total of 65,135 drug-test pairs. This included prescriptions for 34 high-risk medications or medication classes, some of which had multiple recommended tests, for a total of 60 drug-test combinations (Table 4.1).

ii. Provider Characteristics

Primary care caregivers accounted for about 56% of the prescribers, including primary care nurse practitioners, and physician assistants. The most frequent specialty was Internal Medicine followed by Family Practice and Pediatrics (who often see patients well beyond age 18). The mean number of prescriptions per provider was 215, with 50 percent of providers having between 3 and 247 prescriptions. Providers had as few as 1 patient or as many as 784 to whom they prescribed a medication in the study, with 50% having 2 to 179 patients. The mean number of times a given drug was prescribed by a provider was 43, though that ranged from once to 420 prescriptions of the same medication in the study period. 47% of patients had a single prescription in the study, with 98% having 4 or fewer but some having as many as nine prescriptions of study medications. BBW drug/test combinations made up 16% of all prescriptions. Baseline characteristics of patients and providers are described in Table 4.2 (not all information was available for all providers).

Table 4.2: Summary of Provider and Patient Characteristics

Providers		N, of 278 providers
Mean age (years)	48.1	235
Female	42.6%	275
Physician vs. other kind of prescriber	86.0%	278
Primary care physician (PCP) vs. specialist	56.3%	247
Fulltime	74.4%	195
Years of experience (years since graduation)	20.3	235
Mean number of prescriptions in study	215	278
Patients		31,417
Mean age (years)	66.1	
Female	56.8%	
Study medications per patient	1.9	
Drug-test pairs		65,135
New vs. chronic use	38.6% new	
Black box warning	15.6%	

iii. Unadjusted Analysis

Many variables were significantly associated with rates of test ordering (Table 4.3). Of particular interest was the BBW status of the drug-test pair, which was associated with higher rates of ordering (OR 1.18 compared to all other prescriptions, $p < 0.001$); having multiple providers, which increased ordering (OR 1.34, $p < 0.001$); primary care status of provider, which increased ordering (OR 1.67, $p < 0.001$); age of the patient, which was associated with increased ordering (OR by year 1.03, $p < 0.001$; OR 4.48 for >70 years old compared to <40 , $p < 0.001$); and user status, in which new user status decreased ordering (OR of 0.45, $p < 0.001$). Provider characteristics like fulltime status and years of experience were not significantly associated with ordering, though the number of drugs per patient (OR 1.33, $p < 0.001$ for each additional study drug a patient was prescribed) and the number of prescriptions by provider (OR 6.6 for top quartile compared to the bottom, $p < 0.001$) were both associated with increased test ordering. Frequency of prescribing a drug was also correlated with ordering, with the highest

frequency quartile prescribed associated with test ordering more than twice as often as those prescribing least often (OR 2.41, $p < 0.001$). Drugs-test pairs with multiple tests or with tests to be ordered more frequently were less likely to have tests ordered (OR 0.49 and 0.34 $p < 0.001$ for both). Sicker patients were more likely to have a test ordered, whether measured by Charlson score (OR 1.3 and 1.8, $p < 0.001$, for Charlson Index = 1 or 2, respectively), by Charlson summary score (OR 1.14 per unit of score, $p < 0.001$), Romano high status (OR 1.7, $p < 0.001$), and quartile of visit number (1.9, 2.5, and 3.2, $p < 0.001$ for all).

Table 4.3: Unadjusted Characteristics Associated with Ordering Rate

Patient characteristics	Unadjusted Odds Ratio (OR) [95% Confidence Interval (CI)]
Patient gender	
Male	1 [Reference]
Female	0.93 [0.84 – 1.03]
Patient age	
<40 years old	1 [Reference]
40-50	1.75 [1.56 – 1.97]
50-60	2.42 [2.14 – 2.74]
60-70	3.72 [3.20 – 4.31]
70-80	4.47 [3.88 – 5.15]
≥ 80	4.49 [3.91 – 5.15]
Number of patient visits (quartiles)	
0-5 visits	1 [Reference]
6-10 visits	1.91 [1.75 – 2.09]
11-18 visits	2.46 [2.20 – 2.76]
≥ 19 visits	3.16 [2.82 – 3.53]
Charlson score	
Charlson score = 0	1 [Reference]
Charlson score = 1	1.27 [1.17 – 1.38]
Charlson score ≥ 2	1.80 [1.67 – 1.95]
Romano index	
Romano index < 3	1 [Reference]
Romano index ≥ 3	1.67 [1.53 – 1.81]
Specific diseases, compared to not present	

Heart disease	1.77 [1.59 – 1.96]
Dementia	0.73 [0.60 – 0.90]
Number of providers per patient	
One	1 [Reference]
More than 1	1.34 [1.21 – 1.49]
Number of study drugs patient is taking	
Single drug	1 [Reference]
Multiple drugs	2.13 [1.98 – 2.28]
Provider characteristics	
Provider gender	
Male	1 [Reference]
Female	0.92 [0.73 – 1.16]
Provider age	
<40 years old	1 [Reference]
40-50 years old	0.89 [0.67 – 1.18]
50-60 years old	0.82 [0.63 – 1.07]
>60 years old	0.40 [0.31 – 0.51]
Provider specialty	
Specialist	1 [Reference]
PCP	1.67 [1.23 – 2.26]
Provider type	
MD	1 [Reference]
NP	0.92 [0.59 – 1.44]
PA	0.76 [0.57 – 1.00]
Provider years at this health care system	0.99 [0.98 – 1.01]
Provider years since graduation	0.98 [0.97 – 1.00]
Working status	
Part-time	1 [Reference]
Fulltime	1.25 [0.95 – 1.63]
Prescriptions per provider	
First quartile (<3 prescriptions)	1 [Reference]
Second quartile (3-12)	2.24 [1.38 – 3.66]
Third quartile (13-247)	4.59 [2.91 – 7.25]
Fourth quartile (\geq 216)	6.55 [4.28 – 10.04]
Patients per provider	
First quartile (1 patient)	1 [Reference]
Second quartile (2-11)	1.58 [0.84 – 3.00]
Third quartile (12-179)	3.68 [1.96 – 6.88]
Fourth quartile (\geq 190)	4.97 [2.71 – 9.10]
Prescription characteristics	
Evidence for test	
Recommended test	1 [Reference]
BBW	1.29 [1.11 – 1.51]
Guidelines	1.49 [1.28 – 1.75]
Evidence base	

Other	1 [Reference]
Narrow therapeutic window	0.45 [0.37 – 0.54]
Test frequency	
Yearly	1 [Reference]
More frequent	0.34 [0.25 – 0.46]
Prescription type	
Chronic use	1 [Reference]
New use	0.45 [0.42 – 0.49]
Multiple vs. single test for this drug	
Single test	1 [Reference]
Multiple tests	0.49 [0.42 – 0.58]

Abbreviations: BBW, black box warning; MD, medical doctor; NP, nurse practitioner; PA, physician assistant; PCP, primary care provider.

iv. Multivariable analysis

In multivariable analyses, the final models included the following variables: primary care status or patient volume, BBW or other evidence level, patient health status, and sex, age, and gender covariates for prescribers. We included patient age, gender, BBW status, and provider specialty *a priori*, and because of significance kept in the model the following additional covariates: number of drugs per patient, number of providers per patient, patient comorbidities, test frequency, new or chronic use, number of tests per drug, number of patients per provider, provider experience, and provider type (Table 4.4).

Prescriptions without BBWs, those for patients who were healthier, and those written by providers who were older were again associated with lower ordering. Tests that were to be ordered more frequently were also less likely to be ordered, and patients on only one medication were less likely to have a test ordered, as were female patients. Older patients were more likely to have tests ordered, as were patients with more visits in the study year. There was also a significant interaction between the BBW status and the

number of drugs a patient was taking, with BBW status having a larger effect among those on more medications.

Sicker patients were more likely to have a test ordered in the multivariable model. We included a model using number of visits as a proxy for health status in Table 4.4 (OR of 2.6 for top quartile compared to bottom quartile, $p < 0.001$); models using Romano comorbidity (OR 1.3, $p < 0.001$) and Charlson Score (OR 1.1 and 1.4 for Index = 1 and 2, respectively, both $p < 0.05$) yielded similar results. The model with visit number has a c statistic of 0.72, while the model using the Romano variable had a c statistic of 0.70. Similar models using the Charlson score, whether categorized or not, also had c statistics of 0.70.

Certain variables were closely related. For example, primary care providers had much larger patient panels (number of patients) than their specialist colleagues, resulting in an association between patient number or prescription number and specialty status. In the unadjusted model, both primary care status and provider volume, however measured, were associated with higher ordering rates, and these two categories were associated with each other.

Table 4.4: Adjusted Model: Factors Associated with Ordering, Including Stratification by BBW

Variable	Unstratified Fully Adjusted Model N=60347 OR [95% CI]	Stratified Models	
		Non-BBW pairs N=51132 OR [95% CI]	BBW pairs N=9215 OR [95% CI]
Patient gender			
Male	1 [Reference]	1 [Reference]	1 [Reference]
Female	0.83 [0.75 – 0.92]	0.85 [0.76 – 0.94]	0.79 [0.64 – 0.98]
Patient age			
<40 years old	1 [Reference]	1 [Reference]	1 [Reference]
40-50	1.38 [1.21 – 1.57]	1.14 [0.98 – 1.33]	1.45 [1.12 – 1.88]

50-60	1.74 [1.56 – 1.95]	1.38 [1.21 – 1.57]	1.96 [1.51 – 2.56]
60-70	2.25 [1.95 – 2.58]	1.73 [1.48 – 2.01]	3.06 [2.28 – 4.12]
70-80	2.19 [1.89 – 2.54]	1.68 [1.41 – 2.00]	3.36 [2.57 – 4.39]
≥80	2.04 [1.73 – 2.41]	1.59 [1.30 – 1.93]	3.06 [2.29 – 4.08]
Number of patient visits, by quartile			
0-5 visits	1 [Reference]	1 [Reference]	1 [Reference]
6-10 visits	1.65 [1.50 – 1.82]	1.64 [1.48 – 1.81]	2.00 [1.58 – 2.53]
11-18 visits	2.02 [1.78 – 2.30]	2.04 [1.78 – 2.34]	2.38 [1.91 – 2.97]
≥19 visits	2.63 [2.26 – 3.06]	2.56 [2.19 – 3.00]	4.54 [3.55 – 5.80]
Number of study drugs patient is taking			
Single drug	1 [Reference]	1 [Reference]	1 [Reference]
Multiple drugs	1.55 [1.43 – 1.68]	1.55 [1.44 – 1.68]	1.77 [1.46 – 2.14]
Number of providers per patient			
One	1 [Reference]	1 [Reference]	1 [Reference]
More than one	0.98 [0.88 – 1.10]	0.97 [0.87 – 1.09]	1.00 [0.78 – 1.27]
Provider gender			
Male	1 [Reference]	1 [Reference]	1 [Reference]
Female	0.81 [0.58 – 1.13]	0.82 [0.58 – 1.15]	0.82 [0.54 – 1.23]
Provider age			
<40 years old	1 [Reference]	1 [Reference]	1 [Reference]
40-50 years old	0.80 [0.52 – 1.23]	0.81 [0.51 – 1.27]	0.60 [0.34 – 1.06]
50-60 years old	0.71 [0.40 – 1.28]	0.67 [0.37 – 1.20]	0.86 [0.35 – 2.10]
>60 years old	0.30 [0.13 – 0.70]	0.30 [0.12 – 0.72]	0.48 [0.14 – 1.64]
Provider specialty			
Specialist	1 [Reference]	1 [Reference]	1 [Reference]
PCP	0.71 [0.45 – 1.10]	1.01 [0.68 – 1.52]	0.30 [0.15 – 0.62]
Patients per provider			
First quartile (1 patient)	1 [Reference]	1 [Reference]	1 [Reference]
Second quartile (2-11)	2.16 [0.93 – 5.02]	2.19 [0.69 – 6.92]	2.33 [0.86 – 6.31]
Third quartile (12-179)	2.77 [1.22 – 6.30]	2.16 [0.72 – 6.51]	4.65 [1.85 – 11.70]
Fourth quartile (≥190)	3.38 [1.49 – 7.64]	2.65 [0.87 – 8.02]	5.15 [2.12 – 12.55]
Working status			
Part-time	1 [Reference]	1 [Reference]	1 [Reference]
Fulltime	1.05 [0.75 – 1.48]	1.13 [0.81 – 1.59]	0.86 [0.53 – 1.39]
Years of experience, per year	1.00 [0.97 – 1.03]	1.00 [0.97 – 1.03]	1.00 [0.96 – 1.04]
Prescription type			
Chronic use	1 [Reference]	1 [Reference]	1 [Reference]
New use	0.52 [0.48 – 0.56]	0.57 [0.52 – 0.62]	0.39 [0.31 – 0.49]
Evidence for test			
Recommended test	1 [Reference]	1 [Reference]	1 [Reference]
BBW	1.78 [1.49 – 2.13]		
Guidelines	1.31 [1.10 – 1.56]		
Test frequency			
Yearly	1 [Reference]	1 [Reference]	1 [Reference]
More frequent	0.38 [0.29 – 0.49]	0.51 [0.39 – 0.65]	0.18 [0.13 – 0.24]

Number of tests recommended for this medication			
Single	1 [Reference]	1 [Reference]	1 [Reference]
Multiple	0.48 [0.40 – 0.57]	0.43 [0.37 – 0.51]	0.62 [0.38 – 0.99]

Abbreviations: BBW, black box warning; CI, confidence interval; OR, odds ratio; PCP, primary care provider.

Subanalysis – stratification

We ran the same model stratifying by BBW status of the drug-test pair. The BBW subgroup model had a c statistic of 0.83, while the non-BBW model had a c statistic of 0.70. The relationships of the covariates were the same when stratified, except for provider type: PCPs were more likely to order a test in the lower-risk pairs, though not significantly (OR 1.01, p=0.943), while in the drug-test pairs with warnings, PCPs were much less likely, compared to specialists (OR 0.30, p=0.001). This interesting difference may be related to the panel size of PCPs (25 mean number of patients for specialists versus 227 for PCPs) and the number of different drugs prescribed by each (4.6 for specialists versus 12.7 for PCPs). Specialists are more likely to be prescribing the drugs in the BBW pairs, meaning that even if the two types of providers are ordering tests at similar rates (unadjusted and not clustered, PCPs ordered for 75% of indicated tests, while specialists did 67% of the time), specialists would have more opportunities with the BBW drug-test pairs.

E. Discussion

Our results suggest an association between many factors and test ordering rate of high-risk medications in the ambulatory setting, most notably the provider specialty status (specialists ordering less often), the medical status of the patient (healthier patients having lower rates of test ordering), provider volume (number of patients and frequency

of prescribing) and both provider and patient age (more test ordering was associated with older patients and younger providers). Provider full-time working status and years of experience were not related to ordering rates given provider age.

Little is known about physician factors associated with medication test monitoring. Prior studies have shown that barriers to monitoring identified by physicians include lack of clarity regarding which physician was responsible, uncertainty about the necessity of monitoring in the first place, a lack of automated reminders, and physician specialty, as well as patient non-adherence with their recommendations.²⁶ However, physician characteristics such as experience and prescribing volume have not been examined, and physician demographics associated with monitoring are relatively understudied. One study found that younger physicians and female physicians were more likely to order potassium tests for patients on diuretics,¹⁰ and another study focused on prescribing showed that patient factors like sex and worsening renal function might drive provider compliance with alerts for medication dosing.¹⁰⁶ More is known about physician factors associated with patient attendance at appointments, but studies focused on health system factors such as waiting time¹⁰⁷ and scheduling errors.¹⁰⁸ Patient factors such as sex and age may also contribute to monitoring,¹⁰⁹ though whether those effects are due to changes in ordering rates or in completion rates has not previously been examined.

i. Physician Adherence to Guidelines

One major factor in adherence to monitoring is adherence to clinical guidelines, which is known to be low.^{16, 110, 111} Overall, in one study, general guidelines were followed one 67% of the time, with large variations between physicians and between

guidelines⁸⁸ We expected poorer adherence when providers believed guidelines less strongly, though outcomes research suggests few incidents have resulted from non-adherence to even the strongest guidelines,^{95, 112} and when specific interventions are introduced to target adherence to BBWs, improvement is limited, if there is any.⁹⁶ BBWs as a class include varying levels of alerts,⁹⁶ perhaps accounting for the low overall adherence rate to monitoring recommendations even in this class, below 50% in one recent study.⁶⁶

The reasons for physician non-adherence are complex. In addition to lack of familiarity with guidelines, research suggests other barriers to guideline adherence include lack of awareness, lack of agreement/expectation of outcomes, lack of self-efficacy, inertia, and other external barriers.¹¹³ A recent focus group series with physicians on adherence to guidelines suggests a taxonomy including concerns about patient adherence and patient preferences as well as provider-centered concerns such as limited benefits and causing adverse events.¹¹⁴ Even when providers are aware of guidelines and want to follow them, they are often difficult to interpret: more than half of the BBWs in one study required clarification from a specialist.⁹⁵ Doctors addressing multiple issues may also have their attention divided, as suggested by the theory of competing demands, making more complicated patients less likely to get certain treatments.^{115, 116} Individual patient circumstances may also influence decision-making⁹⁵ and receptiveness to certain interventions,¹¹⁷ which is why this study analyzes patient factors as well as provider factors. In some cases, providers may doubt the credibility or applicability of guidelines, particularly with proscriptive guidelines,¹¹⁸ and perhaps with

good reason, as many guidelines have little evidence for an effect on patient outcomes.¹¹² However, even good evidence and good source credibility do not ensure adherence.²⁷

To maximize adherence to guidelines, a few recommendations have been made. As advised for effective clinical support,³⁸ and in general for all behavioral change,¹¹⁹ having guidelines customized to the situation and available at the time of ordering could increase adherence; for example, when antibiotic guidelines were made available electronically at the time of computerized ordering, but no requirement to follow them was made, non-conformity with guidelines decreased.¹²⁰ Tiering electronic alerts, with more severe interruptions for more dangerous actions, also increases physician adherence to alerts,¹²¹ suggesting that perhaps stronger evidence could affect behavior, though again, this has not always been the case in the past.

Other factors contributing to adherence are addressed below, including the level of available evidence and provider specialty.

ii. Levels of Evidence

Past research has rarely addressed the question of provider factors associated with ordering of monitoring tests. However, physician adherence to guidelines overall and to black box warnings in particular has been examined. Another study on black box warnings concluded in multivariate analysis that older patients, healthier patients, and patients at a hospital-based clinic were prescribed medications in violation of BBW at a higher rate than others.⁹⁶ Our results somewhat differed. We did not find a strong association between the number of prescriptions and number of BBW prescriptions. However, we found the odds ratios for ordering to be significantly higher for BBW in

both older patients and sicker patients, often across groups, and in those patients on more medications. Thus while ordering rates for BBW drug-test combinations are certainly not high enough, we also need to consider the recommendations with less evidence and determine whether those testing need to be targeted for increase or whether better evidence needs to be gathered to support the guidelines.

As in previous studies,⁸⁸ we found a large amount of variation for adherence between guidelines and a large portion of the variation could be attributed to variation among physicians, greater than that attributable to the variation among patients.

iii. Volume

Surgical literature has long shown an association between procedure volume and outcomes. Recent work on quality indicators also suggests an association between frequency of prescribing or treating and associated quality indicators.¹²² Generally, volume is associated with better adherence,¹²³ though in some studies, increased provider volume has shown decreased adherence to surveillance guidelines.¹²⁴ Our results show a relationship between number of patients and frequency of prescribing and ordering rates, suggesting familiarity with a medication increases adherence to testing guidelines, with providers with the top quartile of patients 3.4 times as likely to order a test as those in the bottom quartile ($p=.003$). Whether measured by patient panel size, prescription number, or frequency of prescribing a specific drug, those providers in the top quartile were 2.4-7 times as likely to order a test in the unadjusted models ($p<.001$ for each of these variables) and as high as 5 times as likely ($p<.001$) in the adjusted models. Thus volume plays a major role in test ordering.

iv. Specialists versus Generalists

Past research has found that specialists showed greater adherence to expert guidelines⁸⁷ and has suggested better care among specialists as compared to generalists, though the effects on outcomes were stronger in the hospital setting as compared to the ambulatory setting.^{85, 86, 125} We found a relationship between frequency of prescribing a medication and ordering rate.

However, our findings also show that when primary care providers prescribed medications, they were actually more likely to have tests ordered, and when factors such as volume were included in the model, this difference disappeared, suggesting familiarity with the medication because of frequency of prescribing was a main factor affecting this result. However, when stratified by evidence level, specialists were more likely to order tests in those drug-test pairs with stronger warnings (BBW), suggesting that for those drug-test pairs, which are prescribed more often by specialists, those providers are more likely to follow the guidelines. This may be related to prescribing frequency as well.

v. Strengths

A major strength of this study is its data source: the electronic nature of the records allowed us to track a medication from prescription through test ordering (and in another paper, we will also examine test completion). As noted in the literature, combining laboratory and medication data allows for evaluating the quality of treatment, studying adverse events, and investigating drug-test interference.^{18, 19} Furthermore, because we have information about both providers and patients in an electronic system, we have been able to study associations with test ordering that have not been previously

reported, such as provider specialty, provider volume, and years of practice. As we noted earlier, even in places with electronic ordering of tests, it is often difficult to track which tests are completed.³³ We were able to directly link providers with their prescriptions and their patients along with orders and their completion through a single electronic system.

vi. Limitations

As previously noted, the patients receiving care from Fallon Clinic are representative of the population of central Massachusetts. However, although Fallon Clinic is similar to many similar healthcare provider groups across the US and its patient population is broadly representative, it is different in that it is an integrated health care system and it is one of the early providers to have full implementation of electronic medical records and computerized physician order entry. Similarly, Fallon Clinic providers represent a range of experience and specialties, but employees of a multispecialty group practice may differ from private practitioners and hospital-based providers. Furthermore, we had detailed information about specialty and years of experience for Fallon Clinic providers, but for providers who have submitted orders through the Fallon EMR but are not Fallon Clinic providers, we did not have the same extensive data. For our analysis, we included as much information as we had. Providers from outside Fallon Clinic may differ in some ways from Fallon clinic providers.

As in Chapter III, we may have missed monitoring that was done at a hospital, and we were unable to confirm patient adherence to drugs or patients who did not complete tests because they were no longer using the medication for whatever reason.

Also, we chose to use claims data because of the potential bias of including prescriptions from the electronic record that patients were not taking or had not even filled. Many prescriptions are not “discontinued” when patients cease to take them, even when the provider is informed, making the EMR somewhat unreliable for current medications. Claims data, in contrast, only reflect prescriptions that have been filled. However, claims data also have their shortcomings, as they do not include the increasing number of medications for which patients are paying in cash through special discount programs at large pharmacy chains. However, we would rather underestimate medication use than overestimate medication use.

vii. Implications for Practice

While electronic interventions have not been consistently successful in improving monitoring rates thus far,²³ the potential for such tools to be effective at increasing safety²¹ and improving patient outcomes¹²⁶ remains. Much depends on how these interventions are designed¹²⁶ and analyzed,²³ however, and many reminders have had less of effect on provider behavior than expected or hoped.¹²⁷

Variation in adherence even to BBW shown in our results and elsewhere emphasize the importance of having guidelines based on strong evidence, easily accessible, and, ideally, in a computerized format to maximize adherence.¹²⁰ At the same time, we should be less concerned about providers following guidelines that don't have good evidence. Therefore, while providers should continue to be encouraged to follow evidence-based guidelines, researchers, professional societies, and other leaders in

medication guidance and safety should continue to pursue strong evidence for those guidelines as well as making them clear enough to not require interpretation.

Also, as recommended elsewhere,^{27, 95} guidelines and warnings should be more specific and frequently updated so providers will be able to follow them and to rely on them.

Interviews with providers suggest they are open to computerized reminders²⁶ and to clinical decision support in general if it is designed well, not too sensitive, and minimally interruptive.¹²⁸⁻¹³⁰ Primary care providers said that they can comply better with guidelines given electronic clinical reminders (79% in one survey¹³¹) although they may be less likely to do so when behind or when managing complicated patients.¹³² Another study, however, showed physicians were more inclined to use an electronic prescribing system for patients who used more medication, made more emergency department visits, had more prescribing physicians, and had lower continuity of care.¹¹⁷ Our study had similar findings as this study on prescribing, with sicker patients receiving more appropriate test orders.

Thus we see: 1) the importance of having data electronically so as to be able to separate ordering and completion and actually report ordering accurately; 2) the importance of having evidence-based recommendations for quality of care as well as for adherence; and 3) the power of technology to facilitate guideline delivery to the right person at the right place and time. While providers are open to these interventions, other systems factors may impact laboratory monitoring, such as accuracy of medication lists,

ease of ordering, communication among providers, and of course, patient completion, which we address in the next chapter.

viii. Future Research

Because patients with fewer interactions with the health care system have fewer tests ordered, research involving contacting patients directly about unordered tests could be a path to increased testing ordering.

It must also be noted that ordering differences between provider types may have to do with the quality of communication between specialists and generalists, with specialists expecting generalists to order monitoring for medications the specialists prescribed: a secondary analysis, to be pursued in more depth in the future, will look at the cases where the provider who ordered the test is not the same provider as the one who prescribed the medication.

Similarly, in some cases, a test was ordered appropriately for a patient by someone other than the prescribing provider. Patients often have more than one provider (15% of our population had prescriptions for study drugs from at least two providers) and of course providers generally had more than one patient, even in this limited dataset (mean of 132 patients for whom each provider in the study wrote a study prescription), so our data contained multiple patient-provider relationships. This slightly complicated the question of giving a provider credit when a test was ordered. Future research will examine the role of the prescriber separately from that of the orderer. However, past research suggests that it is reasonable to hold a provider accountable for a quality event if the patient had a visit with this physician during a time frame during which the provider

could have fulfilled this requirement,¹²² which is the case for our prescribers. This applies to laboratory monitoring as well as to other quality indicators.

ix. Conclusion

This study had novel findings in factors associated with test ordering for ambulatory patients taking high-risk medications. Older and sicker patients and those with more interactions with the health care system were more likely to have testing ordered, as were tests for drug-test combinations with black box warnings. This higher rate for BBW combinations indicates that these warnings have permeated provider consciousness and suggests a role for provider education and reminders in improving test ordering.

Further research should use electronic data and should focus on interventions on targets with the greatest potential for improvement, like younger and healthier patients, on medications with evidence of harm, even when not as well established, and for providers who have less familiarity prescribing a given medication. Patients with less interaction with the health care system are also at risk of not having tests ordered and perhaps should be reminded and scheduled for laboratory testing to ensure completion. Lastly, guidelines should be clarified, consistent, and frequently updated so that providers can follow the best evidence in treating their patients.

CHAPTER V

FACTORS ASSOCIATED WITH COMPLETION OF MONITORING FOR HIGH-RISK MEDICATIONS

A. Abstract

Purpose

To determine patient factors that contribute to completion of ordered monitoring tests for high-risk medications. We hypothesized that sicker patients, patients with psychiatric illnesses, younger patients, and patients with tests ordered for a date in the future rather than the same day would be less likely to complete an ordered test after adjusted for provider characteristics such as specialty.

Design, Participants, Measures, and Data Analysis

As in Chapter IV, we performed a cross-sectional analysis of the administrative claims and electronic medical records of patients prescribed a high-risk medication requiring laboratory monitoring in a large multispecialty group practice between January 1, 2008 and December 31, 2008. For this analysis, we only included patients for whom a monitoring test for one of these medications was ordered. The outcome was patient completion of the ordered monitoring test. Key predictor variables were patient

characteristics such as age, gender, and comorbidities. Potential confounders include provider characteristics such as specialty and drug-test characteristics. We used multivariable logistic regression to identify the independent association of patient characteristics with completion of laboratory tests, after controlling for potential confounders. We used robust standard errors to account for clustering of patients within providers.

Results

Patient completion of ordered laboratory tests varied across drug-test pairs and ranged from 71% (Terbinafine–AST) to 100% (Cyclosporine–Cyclosporine level, all Quinidine tests, and a few other infrequent drug-test pairs). Completion rates were associated with patient age, number of drugs per patient, and visit frequency, though not with other comorbidity measures. Provider factors such as specialty did not affect completion. Highest risk drug-test pairs, measured by black box warning status, were associated with decreased odds of test completion.

Conclusions

Patients with more physician visits and higher medication burden were more likely to complete ordered laboratory monitoring for high-risk medications. Interventions targeting patients should be addressed to those subgroups with the greatest potential for improvement.

B. Background

It is established that prescription medications often cause injury,^{3, 57} and that failure to monitor high-risk medications is one of the leading factors contributing to adverse drug events (ADEs).³ While improvements in ordering rates by physicians could contribute to better monitoring, another major factor in low monitoring rates is patient non-completion of ordered tests.

However, as we demonstrated earlier, studies looking at laboratory monitoring generally do not measure both rates of ordering and rates of completion.²³ Most studies report only test completion rates,^{10-12, 24, 58} but without noting whether tests were ordered, it is difficult to attribute the non-testing to patient behavior. Furthermore, little research has been done on the patient factors that contribute to adherence to ordered laboratory monitoring.

Patient non-adherence to medications has been shown to contribute to preventable adverse drug events,³ and has been shown to be low in general, depending upon various factors including type of medication.²⁸ Visit frequency has been shown to be associated with medication adherence,¹³³ whether on its own or as a proxy for severity of illness; it is likely that it is also a factor in completion of ordered monitoring.

The actual reason for missing appointments has not been studied closely,²⁹ with only a few factors leading to non-attendance identified by patients, such as waiting time and the respect patients felt the health care system afforded them.^{67, 73} Some factors have been shown to correlate with appointment non-attendance: associated patient characteristics include being a young adult, having small children, lower socioeconomic

status, and longer time to appointment;⁶⁸ male sex, younger age, summer vacation, and a first time visit;⁶⁹ feeling better, transport problems, and, in contrast, short notice;⁶² male sex and higher disease burden;⁷⁰ poor past attendance;^{71, 72} and younger age, single status, being less disabled, being employed, living in an urban setting, lower education level, possibly lower socioeconomic status, and possibly accessibility.⁶¹ However, the factors associated with missing appointments may be different from those associated with laboratory completion.

We interviewed patients regarding missing monitoring, focusing on some of the factors identified for appointments, in the qualitative study described in Chapter III, but the small sample size there did not allow broad conclusions and did not include all of the data available in the electronic medical record.

Therefore, we conducted a large quantitative retrospective study to identify both patient and provider characteristics associated with patient completion of laboratory testing ordered for high-risk medications in the ambulatory setting.

The specific aims were to examine the association between the following factors: demographic information, including age and gender; number of currently prescribed study medications; frequency of medical appointments; and medical conditions, adjusting for provider factors affecting patient completion such as provider specialty training and frequency of prescribing this medication.

C. Methods

i. Study Design and Setting

This study was also conducted within the Fallon Clinic, a large multispecialty group practice closely aligned with the Fallon Community Health Plan, a non-profit, Central Massachusetts-based integrated health care delivery system, as described in Chapter III. The practice uses the EpicCare Ambulatory electronic medical record (EMR) system (Epic, Verona, WI, Spring 2007 IU3 at the time of the study).

For this analysis, we included patients if they received care from the multispecialty group practice, were 18 years or older, and had insurance coverage from the health plan between January 1, 2007, and December 31, 2008. Patients had to be continuously enrolled during the observation period and not residing in a long-term care facility. Patients additionally had to have an order for a monitoring test placed by a provider in the electronic record system within the time frame recommended for monitoring that drug-test pair.

ii. Selection of Study Medications

The medications included in this study, as in Chapters III and IV, were based on a list of high-risk medications with recommended laboratory monitoring tests developed for a clinical decision support system that was intended to be embedded in the EMR. The drug-test pair list is the same as in Chapter IV, Table 4.1.

As described in Chapter IV, each drug-test pair was additionally categorized based on the evidence basis for the test. In general, the level of evidence for medical

guidelines widely varies, with possibly half of guideline recommendations based on low-quality evidence.⁸⁹

iii. Medication Exposure

Data about medication exposure were derived from the prescription drug claims of the health plan, while data about laboratory test orders were derived from the multispecialty group practice electronic medical record. Use of claims data for medication exposure allowed for the measurement of medications actually filled at the pharmacy, avoiding possible exposure misclassification by using EMR prescribing data that may include prescriptions that were never filled or taken. In addition, the EMR includes “historical medications” which reflect over-the-counter medications and medications from outside providers but are inconsistently recorded across patients and providers. These medications are not included in the claims data and thus not included in this study, again meaning the possibility of not accounting for medications a patient is taking but also decreasing the risk of erroneously considering a patient to be taking a medication and thus underestimating appropriate testing. Completion of a test was also identified through the electronic record, using a field that uniquely identifies each ordered test and notes completion.

In cases where a patient had more than one new start of the same drug during the study time frame (no refills or prescriptions for 180 days and then a new prescription), we used the first prescription for that drug only.

iv. Provider Factors

Provider data were collected from an internal provider demographic database containing demographic information for past and present providers employed by the multi-specialty practice. As in Chapter IV, to maximize the dataset, we also included outside providers for whom we had specialty and gender. Provider and patient factors are described in Table 5.1.

v. Key Variables

As in Chapter IV, variables included in this analysis were selected based on Anderson's model of health services use which can be used to guide analyses of the association between patient factors, physician factors, and health service utilization (i.e., laboratory monitoring of prescription medications). This model generally looks at the behavior of patients and families, and it classifies predictors of behavior into three categories: *predisposing factors* refer to demographic factors like age and gender as well as family structure and health beliefs that affect service use; *enabling factors* include resources that promote or inhibit use like income and health insurance; and *needs factors*, which comprise the illness and circumstances that necessitate use.^{30, 31}

Outcome variable:

Completion of ordered monitoring tests, dichotomized for each patient-drug-test combination, was the outcome variable.

Key predictor variables:

Patient characteristics include age (continuous and by decade), gender, number of study prescriptions (categorized into two and three groups), health status using a Charlson score (score 0-16, index 0-2, and Romano variation), visit frequency (continuous and quartiles), and number of other study medications. Comorbidity was measured using the Charlson score using ICD-9 codes from encounter data in the EMR via a tool in STATA using ICD9 codes.⁹⁷ The Charlson score is correlated with 1-year mortality⁹⁸ and is the most widely used comorbidity index.⁹⁹ We examined both the weighted index (0-16) and a categorical three-point index (0-2) defined as a weighted Charlson of 0, 1, or ≥ 2 . The Romano adaptation of the Charlson score was also calculated in STATA from the disease-specific scores and also categorized into a dichotomous variable (Romano ≤ 2 vs. Romano ≥ 3).¹⁰⁰ The calculated variables were generated based on data in the EMR, including ICD-9 codes for diagnoses in the system.

Other variables:

Provider characteristics, including provider gender, age (continuous and by decade), and specialist versus primary care status, were included. Provider variables that were not in or calculable from the EMR (such as full-time status and year of hire and graduation) were captured, deidentified, from the practice's employment database.

As in Chapter IV, prescription characteristics, including drug, evidence for testing category (black box warning [BBW], other type of guideline, and testing for narrow therapeutic window category), whether the drug had single or multiple recommended tests, and testing frequency were included. The BBW category was identified by

individually checking whether a given test addresses a warning via online databases (labeling only relevant drug-test combinations as BBW, not by drug) with the caveat that even BBW status is reported differently in different locations.⁹⁴

For analysis, we categorized many continuous variables into quartiles to help account for possible non-linearity. For example, we calculated quartiles for visit number per patient, drug prescribing frequency for providers, prescription number per provider, and number of patients per provider. We categorized age by decade, starting with patients and providers below 40 and ending with providers >60 and patients >80, due to frequencies. We also categorized the number of drugs per patient (which ranged from 1 to 9) as a dichotomous variable (one or more than one), and into three categories, 1, 2-4, and 5-9, to enable comparison to similar studies.⁹⁶

vi. Data Analysis

As in Chapter IV, prescriptions, laboratory orders, and completion status of tests were extracted from the EMR for the time period in question. Each prescription, linked to scrambled IDs for both prescriber and patient, was then linked to laboratory orders for the patient in question during the relevant time period, as well as to completion data for those orders and to demographic and medical information for provider and patient.

We fit the data using a logistic regression models with a robust covariance estimator (sandwich estimator) to adjust standard errors for clustering. This approach provides conservative nonparametric estimates.¹⁰¹⁻¹⁰⁴ We first calculated robust standard errors based on clustering of medications within patient and separately performed calculations based on clustering within providers, ultimately clustering by provider for

more conservative estimates. Using this model, odds ratios (ORs) of factors associated with test completion were calculated.

Again, our modeling approach aimed to develop an explanatory model to identify factors that could be changed through intervention, rather than simply to obtain a best predictive model.¹⁰⁵ Therefore, unadjusted models examined relationships between each predictor and confounding variable with the outcome of test completion. Final multivariable models included factors hypothesized to be associated with test ordering *a priori*, and factors associated with test ordering at the $p < 0.20$ level in unadjusted analysis. We also calculated the c statistic, based on the area under the receiver operating characteristic (ROC) curve, to compare the multivariable logistic regression models.

Analyses were conducted in SAS 9.2 (SAS Institute, Cary, NC) and StataSE (Stata Statistical Software: Release 11.1, Stata Corporation, College Station, TX, USA).

D. Results

i. Patient Population and Use of Medications Requiring Laboratory Monitoring

Once ineligible patients, providers, and prescriptions were excluded and all prescriptions were linked to patients and prescribing providers, I then excluded drug-test pairs for which a test was not ordered. The dataset included 27,802 patients and 251 providers for a total of 55,592 drug-test pairs. As in the previous chapter, this included prescriptions for 34 high-risk medications or medication classes, some of which had multiple recommended tests, for a total of 60 drug-test combinations (Table 4.1).

Patients, with a mean age of 67, had on average 2 medications each (ranging from 1-9) as shown in Table 5.1 (not all information was available for all providers).

ii. Provider Characteristics

When including only ordered tests, the number of patients and providers were slightly smaller than in the ordering analysis, but the distribution was similar. Providers had an average of 20 years since graduation, were 41% female, were mostly physicians (84.9%), and slightly more than half were primary care providers. Three-quarters worked fulltime and the mean number of prescriptions they had in the study was 238.

Table 5.1: Summary of Provider and Patient Characteristics

Providers		N, of 251 providers
Mean age (years)	48.3	220
Female	41.0%	249
Physician vs. other kind of prescriber	84.9%	251
Primary care physician (PCP) vs. specialist	56.3%	222
Fulltime	76.4%	182
Years of experience (years since graduation)	20.4	220
Mean number of prescriptions in study	238	251
Patients		27,802
Mean age (years)	67.2	
Female	56.2%	
Study medications per patient	2.0	
Drug-test pairs		55,592
New vs. chronic use	35.7% new	
Black box warning	15.9%	

iii. Unadjusted Analysis

Many variables were significantly associated with rates of test completion (Table 5.2). Of particular interest were patient age (lower age associated with poorer completion, OR 2.33, $p < 0.001$ for those over 70 compared to those under 40, with an increasing trend by decade); patients with more visits or higher Charlson index scores were more likely to

complete tests, though the Romano score was not correlated with completion; taking more than one drug increased completion (OR 1.45, $p < 0.001$), being a new user of a prescription decreased completion (OR 0.36, $p < 0.001$); and black box warning status of the prescription decreased completion (OR 0.56, $p < 0.001$). Multiple tests for a drug increased completion for each test in that group (OR 1.48, $p < 0.001$). Provider characteristics did not seem to play a major role in completion rates except for prescribing frequency, which increased the odds a patient would complete a test (OR 1.95 for the highest quartile compared to the lowest). In addition, tests ordered by nurse practitioners (3% of the drug-test pairs) were associated with less completion (OR 0.73, $p < 0.05$) than those ordered by physicians (95% of the drug-test pairs).

Table 5.2: Unadjusted Characteristics Associated with Test Completion

Patient characteristics	Unadjusted Odds Ratio (OR) [95% Confidence Interval (CI)]
Patient gender	
Male	1 [Reference]
Female	1.06 [0.96 – 1.16]
Patient age	
<40 years old	1 [Reference]
40-50	1.14 [0.95 – 1.37]
50-60	1.39 [1.19 – 1.63]
60-70	1.90 [1.60 – 2.25]
70-80	2.34 [2.00 – 2.75]
≥80	2.32 [1.96 – 2.74]
Number of patient visits (quartiles)	
0-5 visits	1 [Reference]
6-10 visits	1.60 [1.44 – 1.79]
11-18 visits	1.84 [1.64 – 2.06]
≥19 visits	1.82 [1.65 – 2.02]
Charlson score	
Charlson score = 0	1 [Reference]
Charlson score = 1	1.19 [1.08 – 1.31]
Charlson score ≥ 2	1.31 [1.19 – 1.45]
Romano index	

<3	1 [Reference]
≥3	1.21 [1.10 – 1.34]
Specific diseases, compared to not present	
Heart disease	1.13 [1.03 – 1.23]
Dementia	1.31 [1.03 – 1.67]
Number of study drugs patient is taking	
Single drug	1 [Reference]
Multiple drugs	1.45 [1.33 – 1.58]
Number of study drugs patient is taking	
1 drug	1 [Reference]
2-4 drugs	1.49 [1.37 – 1.62]
>5 drugs	1.14 [0.96 – 1.35]
Provider characteristics	
Provider specialty	
Specialist	1 [Reference]
PCP	0.97 [0.79 – 1.19]
Provider type	
MD	1 [Reference]
NP	0.72 [0.59 – 0.89]
PA	0.94 [0.74 – 1.20]
Provider frequency of prescribing this drug	
First quartile (once)	1 [Reference]
Second quartile (2-5 times)	1.59 [1.08 – 2.34]
Third quartile (6-46 times)	1.73 [1.22 – 2.45]
Fourth quartile (≥47 times)	1.95 [1.35 – 2.81]
Prescription characteristics	
Evidence for test	
Not BBW	1 [Reference]
BBW	0.53 [0.47 – 0.59]
Test frequency	
Yearly	1 [Reference]
More frequent	0.82 [0.64 – 1.04]
Number of tests recommended for this medication	
Single	1 [Reference]
Multiple	1.48 [1.30 – 1.69]
Prescription type	
Chronic use	1 [Reference]
New use	0.36 [0.33 – 0.40]

Abbreviations: BBW, black box warning; MD, medical doctor; NP, nurse practitioner; PA, physician assistant; PCP, primary care provider.

iv. Multivariable Analysis

In the multivariable analysis, we included *a priori* patient age, gender, and health status. We also thought test frequency and black box warning status could contribute to patient completion rates, and we hypothesized that provider specialty would affect patient behavior. Other factors that were significant in the unadjusted analysis included provider type, number of drugs the patient was taking, new use versus chronic use, multiple versus single tests for a drug, and number of drugs per patient.

Associated factors were again the number of drugs a patient was taking (fewer drugs meant a patient was less likely to complete a test), patient health status (measured by visit frequency: healthier were less likely to complete), patient age (younger were less likely to complete), and to some extent, provider drug prescribing frequency (Table 5.3). Patient gender did not affect completion rates, and other provider factors we examined in the unadjusted model besides prescribing frequency were not associated with completion. Interestingly, when measured by Charlson index or Romano score rather than by visit frequency, patient health status was not associated with completion, perhaps due to the close interplay between age and Charlson index (when age was not accounted for, the lower Charlson score was associated with higher completion). When the number of patient drugs was categorized rather than dichotomized, the middle group (2-4 drugs) was more likely to complete tests (OR 1.3, $p < 0.001$), but those patients taking the most medications (≥ 5 drugs) were not significantly different in their completion rates than those taking only one. However, models including any of the proxies for health status had similar c statistics (0.68-0.69). Additionally, in all these models, BBW status, shown

elsewhere to be associated with higher ordering rates, was associated with lower rates of completion, between 0.52-0.54 ($p < 0.001$).

Table 5.3: Adjusted Model for Test Completion

Variable	N= 52407 Adjusted OR [95% CI]
Patient gender	
Male	1 [Reference]
Female	0.99 [0.90 – 1.08]
Patient age	
<40 years old	1 [Reference]
40-50	1.02 [0.84 – 1.24]
50-60	1.14 [0.96 – 1.37]
60-70	1.45 [1.19 – 1.75]
70-80	1.58 [1.33 – 1.89]
≥80	1.52 [1.27 – 1.83]
Number of patient visits (quartiles)	
0-5 visits	1 [Reference]
6-10 visits	1.37 [1.22 – 1.53]
11-18 visits	1.43 [1.27 – 1.60]
≥19 visits	1.41 [1.25 – 1.59]
Number of study drugs patient is taking	
Single drug	1 [Reference]
Multiple drugs	1.26 [1.15 – 1.37]
Provider specialty	
Specialist	1 [Reference]
PCP	0.85 [0.71 – 1.03]
Provider frequency of prescribing this drug	
First quartile (once)	1 [Reference]
Second quartile (2-5 times)	1.31 [0.84 – 2.05]
Third quartile (6-46 times)	1.58 [1.05 – 2.39]
Fourth quartile (≥47 times)	1.49 [0.97 – 2.28]
Evidence for test	
Recommended test	1 [Reference]
BBW	0.52 [0.46 – 0.60]
Guidelines	1.25 [1.07 – 1.46]
Test frequency	
Yearly	1 [Reference]
More frequent	1.01 [0.81 – 1.26]
Number of tests recommended for this medication	
Single	1 [Reference]
Multiple	1.46 [1.26 – 1.70]
Prescription type	

Chronic use	1 [Reference]
New use	0.39 [0.36 – 0.42]

Abbreviations: BBW, black box warning; CI, confidence interval; OR, odds ratio; PCP, primary care provider.

E. Discussion

As with test ordering (Chapter IV), completion of laboratory monitoring was associated with patient age and patient visits, with younger age and fewer visits associated with less test completion. Being on fewer medications or having fewer tests recommended for a given medication also decreased the odds of completion. As older, sicker patients have more contact with the health care system, they are more often in situations that make it easy to get one or more tests completed. Interestingly, however, black box warning status, a proxy for the seriousness of the potential adverse event caused by a drug, was associated with *decreased* completion, though it was associated with *increased* ordering. It is concerning that patients are less likely to complete testing for these higher-risk medications, particularly since we have shown that providers order the tests at higher rates. Interventions should target patients taking these medications.

We also found that new users of a medication were much less likely to complete ordered tests, perhaps due to lack of familiarity with the test process or the reasons behind the test. However, test frequency (more than yearly compared with yearly recommendations) was not associated with completion. This can be perhaps explained because this factor reflects the recommended frequency of testing, not the actual ordered frequency. The latter is more likely to affect patient behavior, but we only included one test per prescription. A follow-up study is underway which accounts for tests that need to be repeated on multiple occasions.

i. Adherence

Patient adherence poses challenges to ideal medical treatment in a number of ways. First of all, patients often do not take prescribed medications: depending on drug, one study showed variation between 36.8% (gout patients) to 72.3% (hypertension).²⁸ Our study showed relatively high completion rates, though still less than ideal, particularly given the large number of patients on some of these medications (for example, ordered AST tests for statins were not completed more than 10% of the time, thus affecting almost 1,400 patients in the one year in our dataset).

Just as improving medication adherence improves outcomes and reduces costs,¹³⁴ improving adherence to appointments and laboratory monitoring tests, as we have seen, has the potential for reducing adverse events, as well as reducing the costs associated with them.

Attendance at appointments has been shown to vary with factors associated with both patients and providers, with non-attendance ranging from 5-39% in the literature.^{71,}⁷² However, the provider factors tend to actually be system factors like waiting time and timing of appointment rather than actual provider characteristics,^{107, 135, 136} similar to our finding of limited association with provider factors.

As with attendance at appointments, we found that younger patients and healthier patients, as indicated by lower visit frequency or taking only one medication, were less likely to complete their testing. Thus interventions that have been successful in improving attendance at appointments^{70, 137-140} might also be effective at improving laboratory monitoring. However, an important distinction is that laboratory tests are

generally ordered for a time frame rather than for a specific time and date: sending reminders near the “due date” for the test (in our system, set up as an “expected completion date”) could improve completion.

Identifying early on these patients at risk for non-completion could allow for closer monitoring of their lab testing patterns and earlier intervention when a test is missed. Alerting provider regarding patient non-completion could also be effective, particularly for patients on medications with black box warnings, as the provider ordered a test and clearly considered it important.

ii. Tools to Improve Laboratory Monitoring

While use of EMRs, particularly in the ambulatory setting, is far from universal,¹⁴¹ the data stored in them allow for very targeted and scheduled interventions to be sent to patients, identifying targets for telephone, letter, or electronic communication. Furthermore, the increase in availability and patient use of personal health records (PHRs), often linked to institutional EMRs, allows patients to access the same data as their providers, including test results, upcoming scheduled appointments and tests, and overdue or missed events. These tools allow for targeting and intervention in a way impossible before. Furthermore, for identification and research, EMRs are central for distinguishing failure to order from failure to complete testing. However, simple presence of an EMR certainly does not guarantee better outcomes, at least on specific quality indicators,¹⁴² and it is even harder to make conclusions about overall quality and outcomes when severe adverse events, though relatively common, have low absolute frequencies, even for high-risk medications such as those included in this study,

and are often difficult to directly attribute to lack of monitoring; we would need an even larger sample size to study such outcomes.

We discussed the effectiveness of reminders to providers in Chapter IV. Interventions directed at improving test completion or those directed at patients have similarly inconsistent results. Reminders for outpatient appointments,¹⁴⁰ immunization,¹⁴³ and preventive screening,¹⁴⁴ have been found to be somewhat effective, depending on design. Telephone reminders in some cases were found to be most effective or most cost-effective.^{143, 144} Though most studies directed at patient attendance use letters or telephone calls to patients, including those specifically targeting laboratory testing,^{9, 13, 24} they increasingly rely on computers to customize those alerts and automate the intervention.

We recommend using the EMRs to identify patients for reminders, whether electronic, telephonic, or by letter, when a scheduled test is approaching its “expected completion date,” which should be a required field for the provider. Patients who have been using a PHR should be contacted that way. Patients who are younger or healthier, who are taking fewer medications, or who have missed a laboratory test should be prioritized for contact and should be contacted through their preferred modality and possibly through more than one.

Since these data were studied, we have initiated an automated calling system at our site, based on data in the EMR, that is currently being evaluated for effectiveness, with results to be reported in future publications.

iii. Strengths and Limitations

As above, the patients receiving care from our practice are representative of the population of central Massachusetts. Although the multi-specialty practice is similar to many similar healthcare provider groups across the US, it is different in that it is an integrated health care system and it is one of the early providers to have full implementation of electronic medical records and computerized physician order entry. As in Chapters III and IV, we may have missed monitoring that was done outside of the system, and we were unable to confirm patient adherence to drugs and were unable to identify patients who did not complete tests because they were no longer using the medication for whatever reason. Lastly, lack of completion may not be due to patient non-adherence. For example, patients may be told not to complete the test because of testing done elsewhere without the electronic record changed to reflect that through order cancellation (there is little motivation for a provider to cancel an pending order if the patient is not expected to complete it). However, the largest factor in completion is likely the patient, and therefore this model focuses on identifying patient characteristics that drive completion, as well as provider characteristics that have an effect. Lastly, this study only analyzes factors associated with completion of testing ordered for high-risk medications in the ambulatory setting. Patients may be more likely to complete testing for orders generated as a result of specific symptoms and this study does not analyze overall completion rates.

iv. Future Research

Already underway are interventions targeting patients by phone, by mail, and through electronic means to improve test completion. Though past interventions of this type have had varying effectiveness,²³ improved design and analysis of these types of interventions could have great impact.

Prior non-attendance has been shown to be associated with appointment non-attendance²⁹ and may be a helpful predictive factor in laboratory test non-completion; the population of patients who in the past have not shown up for ordered tests, using historical data to identify them, could be another target for future research.

v. Conclusion

Younger, healthier patients may be more at higher of not completing ordered laboratory tests, along with patients with medications that do not have black box warnings, which are considered particularly risky. Providing reminders to providers to order tests for high-risk medications is not on its own sufficient, as patients do not reliably complete ordered tests. Patients, particularly those at high risk of not completing tests, should be targeted directly for reminders or other interventions, ideally through a modality of their choice, in order to maximize adherence and prevent adverse drug events.

CHAPTER VI

DISCUSSION AND CONCLUSIONS

A. Summary of Research Findings

Little research has described factors contributing to patient completion of lab testing, and even less has focused on physician factors associated with ordering. This thesis has contributed to the literature with a number of new research findings.

In Chapter II, I reviewed the interventions that have been attempted thus far to improve laboratory monitoring in the ambulatory setting using health information technology. These attempts have had varied success and the best design for future interventions is not clear. However, focusing on the most important types of monitoring might make a difference.

In Chapter III, I presented a mixed-method study in which I found that completion rates significantly vary by drug-test pair, in this case for patients on chronic doses of frequently prescribed medications in the ambulatory setting, ranging from 37.90% (Valproic Acid-AST) to 96.84% (Niacin-AST). I showed that a part of non-completion could be attributed to provider non-ordering (rates varying from 1.1% in the Niacin-AST drug-test pair to 51.6% in the Valproic Acid-Valproic Acid level drug-test pair), while patient non-completion accounted for the rest (varying from 2.13% for Niacin-AST to

24.19% for Valproic Acid-AST). In structured interviews with patients, we found that most patients listed few barriers to completion, denying that various systems factors like transportation or convenience were barriers to completing tests. They generally attributed missing tests to forgetting. I concluded that well-timed reminders, customized by patient preference for delivery method, could increase attendance in populations like the one we interviewed. An intervention is now underway to test that hypothesis, with patients receiving phone calls before an ordered test is expected to be completed.

In Chapter IV, I reported results of an analysis examining factors associated with ordering of laboratory monitoring. The model suggested an association between lower ordering rates and the following factors: lower patient age, lower visit frequency, lack of black box status, and smaller provider panel size. Tests that are recommended for more frequent ordering were also associated with lower ordering rates. When stratified by black box status, specialists were much more likely to order a test for the higher-evidence drug-test combinations than primary care providers, a distinction not seen in the combinations without that level of evidence.

I then reported a similar analysis looking at factors associated with completion in Chapter V. For test completion, younger patients and those with fewer visits or fewer medications were again less likely to complete tests, but comorbidity was not associated with completion, and the evidence base was actually associated with a lower odds ratio for completion. No provider factors were significantly correlated with the outcome of test completion in multivariable analysis.

Overall, primary care doctors have larger patient panels (in this dataset, almost 10 times as many patients) and prescribe a greater number of different drugs (13 versus 5) than specialists on average. While this increased prescribing may improve familiarity and thus quality of care in some cases, the drug variety may also make it more difficult for primary care providers to be familiar with guidelines about every medication. In addition, older patients and those with more interaction with the health care system seem more likely to get recommended testing ordered and completed.

Another important finding is the quite different behavior for those drug-test combinations with black box warnings (BBWs) from the Food and Drug Administration. While adherence to these warnings is known to be variable and low and the level of evidence is uneven within the drug-test combinations with BBWs, we saw a strong association between these levels of warnings and higher testing rates, while we found less completion for drug-test combinations with BBWs.

These results should direct future interventions as we continue to work to improve laboratory monitoring for high-risk medications in the ambulatory setting and to improve medication safety for all patients.

B. Strengths and Limitations

The main limitation of this study is its lack of generalizability. Though we have shown that the population in our dataset is similar to the national population in many ways, and the multi-specialty practice from which we extracted the data is similar to many similar healthcare provider groups across the US, it is different in that it is an integrated health care system and it is one of the early providers to have full

implementation of electronic medical records and computerized physician order entry. Indeed, little research thus far has evaluated multifunctional commercially developed systems like Epic,²² and thus the applicability of our findings to smaller practices is unknown.

However, this dataset and study have many strengths. Using a fully integrated health care record, along with claims data, allowed us to achieve the linking of laboratory and pharmacy recommended to allow for quality improvement.¹⁹

Despite this integrated and relatively complete data source, I did encounter unexpected challenges using data not intended for research purposes. Some of these were true of all data not intended for research,¹⁷ while others were specific to this study. For example, in this electronic record system, orders are often duplicated when intended only once or not canceled when not intended to be completed; similarly, prescription orders are frequently duplicated and medications are often not appropriately discontinued in the system; patients or provider data is often incomplete, or identification is incorrect or confusing for research (such as cases where providers were listed in different places with different specialties because of certification in both); fields are defined in ways that may work clinically but can be limiting for research, such as allowing for free text; and many other problems. As always, human behavior is more complicated than the computer systems can account for: when a provider prescribes twice the dose so the patient can save money and take half a pill daily, it helps the patient but flummoxes researchers.

Challenges like this face anyone using data meant for administrative purposes for research, not just electronic or electronic medical record (EMR) data, and it required

extensive clarification and cleaning of the data. Furthermore, due to limitations in software, we were unable to correlate address information to get the socioeconomic status we were hoping for. Race and primary language information was not available.

We used claims data for prescriptions to overcome the problem of drugs prescribed but not ever filled at the pharmacy, but we had little recourse with some of the other data problems. For example, and importantly, laboratory tests are ordered without necessarily indicating the reason for the test. In some cases, a test that serves as a monitoring test for a specific medication may be ordered for another reason, such as symptoms or preparing for a procedure. These tests were not differentiated in our data from those done for monitoring.

However, the advantages were significant, as we were able to include various factors often not present in single datasets. Unlike other studies of laboratory monitoring, this thesis reports on work that was able to analyze both ordering rate and completion rates for a large population using electronic record data. By separating ordering from completion, as has rarely been done for this topic, I could identify specific associations for each behavior. Epic, one of the oldest and most popular electronic record systems in use in this country, has been used at this clinic for many years, allowing a longer timeframe for analysis than at institutions with recent electronic record implementation. The work was strengthened by a qualitative analysis of patient reasons for missing laboratory tests (Chapter III): for the first time, patients were directly asked why they had missed monitoring tests, identifying reasons beyond what was contained in the electronic record. Our interventions have now been directed at the causes for missing tests that were

identified by our patients, specifically aiming to remind patients regarding ordered testing when it is not associated with a specific appointment.

C. Future Directions

i. Changing Behavior

This work does not answer the difficult question of how to change provider practice or patient behavior. However, once the best target populations are identified, interventions to change behavior are the next step.

Potential impact of reminders to providers

Past research has shown dismal adherence to guidelines, with increases facilitated by some interventions,^{23, 88, 120, 145} though still not reaching ideal levels of adherence. Like patients, providers do not think they commit laboratory monitoring errors and “were surprised at the error rates reported in the literature.”²⁶ They are open to computerized alerts²⁶ and to clinical decision support in general if it is designed well, not too sensitive, and minimally interruptive.¹²⁸⁻¹³⁰ Primary care providers believe that they can comply better with guidelines given electronic clinical reminders (79% in one survey¹³¹) although they may be less likely to do so when behind or when managing complicated patients.¹³²

The reasons for provider non-adherence have been classified into five categories including concerns for a patient’s ability to adhere and concerns about side effects to patients of recommended treatment.¹¹⁴ To change provider behavior, however, the literature suggests there are five main strategies: “education, feedback, rationing, financial incentives, and penalties.”¹⁴⁶ However, few interventions have thus far been

shown to effectively improve ambulatory laboratory monitoring. Most interventions focus on the potential of reminders⁵⁰ particularly when presented at the right time,^{38, 120, 147}

However, we have seen the complication of the lack of evidence that guidelines actually improve patient outcomes, perhaps influencing provider behavior against certain interventions.¹¹² In some cases, there is explicit skepticism among providers about the evidence base of guidelines and their applicability, and even their motivation (cost containment rather than patient care).¹¹⁸ This is not unfounded skepticism: indeed, possibly more than half of guidelines are based on poor evidence.⁸⁹ Similarly, studies of clinical decision support systems that have shown change in provider behavior have not shown the same effect on patient outcomes.¹²⁶ Our data set was not large enough to demonstrate an impact on outcomes, but this kind of research—examining the impact of lack of test ordering and completion on hospitalizations and mortality—would greatly add to our understanding of not just how to promote guidelines but which are worth promoting.

Potential power of reminders to patients

Patients also stand to benefit from timely reminders. Some reminder programs have been shown to work. Regarding preventive care, for example, letters, phone calls, and enhanced reminders all effective at increasing mammography rates, with automated phone calls being most effective and low-cost.¹⁴⁴ Similarly, for immunizations, a recent review of 47 studies found that postcards, letters, telephone or auto-dialer calls were all

effective in improving immunization rates, though they found that phone calls were the most expensive.¹⁴³

Partly as a result of the findings of this thesis, our group has begun automated phone call reminders to patients as well as clinical decision support-based reminders to prescribers. We hope to report on the effectiveness of these interventions in the near future.

ii. Role of Health Information Technology (HIT)

A major challenge of this kind of research is, as noted elsewhere, that the evidence for laboratory monitoring is not consistently strong. Focusing on those drug-test combinations shown to be most important for safety will yield the largest benefit, but the current guidelines are often much broader. Thus better data collection is critical to determining the most important targets, and then intervening to improve monitoring focusing on those targets will be most effective.

HIT will play a central role in this data collection as well as in any interventions to improve laboratory monitoring. In the first chapter, I discussed the research that has been done so far on such HIT interventions. My systematic review,²³ reprinted here as Chapter II, suggested a promising role for these tools, limited by implementation as well as analysis of the interventions.

Overall, HIT has been shown to improve quality by increasing adherence to guidelines, improving disease surveillance, and decreasing medication errors.²² Another recent review showed predominantly positive results of health information technology.¹⁴⁸

However, the prevalence of electronic records in the United States is still quite low.^{141, 149,}

150

The first step in improving care is using the data we already have. The linking of laboratory data to pharmacy data is not at all universal, but it holds great potential for improved medical care as well as research, even before implementation of further alerts or other structured interventions.^{18, 19}

Once the data is available in an electronic medical record, research offers some guidance for the most promising interventions. Default settings are very powerful and can affect provider behavior.²¹ Tiered alerts¹²¹ and interruptive alerts¹⁵¹ have been shown to lead to better provider adherence in general. The computerized format also allows for further customizations, so that only certain providers can prescribe certain medications or order certain tests. Further work on laboratory monitoring-specific alerts is needed, however. Much of the research thus far on HIT and laboratory monitoring specifically and for these systems in general has come from only four large institutions, limiting generalizability to the broader setting.²² This suggests the need for testing more widely, especially in vendor systems.

Broader implementation of electronic records, which is occurring under the influence of the 2009 American Recovery and Reinvestment Act, will improve the nation's ability to track laboratory testing. We recommend tracking test orders and test completion separately and then reporting back to providers as well as institutions so that they are aware of their test ordering rates compared to the recommendations and perhaps compared to their colleagues. Orders and prescriptions should be clearly linked to

specific physicians, and future research should address the fact that the prescriber is not necessarily the person ordering the tests. When tests are ordered but not completed, ordering providers could be alerted in addition to sending alerts to patients,³³ though the effectiveness of such an intervention to affect completion is thus far unknown.

Contacting patients through their own selected modality (phone, email, personal health record) could also improve completion rates.

iii. Cost

No discussion of health care quality can ignore the issue of cost. With more than 16% of the United State's gross domestic product (GDP) going to health care as of 2008,¹⁵² cost of care should be considered in any health policy recommendation. This study did not measure the cost of adverse events resulting from inadequate testing nor did we examine the costs of unnecessary tests (though this is also a problem, more often in the inpatient setting,¹⁴⁶ with the potential for great savings¹⁵³). As we better identify the evidence supporting testing and the adverse events caused as a result of failure to do so, we will then be better able to assess the cost of under-monitoring as well as the waste involved in over-monitoring.

D. Final Conclusions

“Test non-completion decreases quality of care.”³³

Our data add to the knowledge about patients who miss laboratory tests and where along the prescribing-to-testing path interventions may be most promising and for whom.

We also identify the limitations of current data, with the hope that future systems will better gather data (including indications for testing and more detailed patient and provider information) to allow even more targeted work. We look forward to a healthcare system in which guidelines are supported by strong evidence and providers are given the tools to implement them consistently, while patients are supported to participate in their own care to achieve the best outcomes possible.

BIBLIOGRAPHY

1. Institute of Medicine. *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington, DC: National Academy Press;2001.
2. Institute of Medicine. *To Err is Human: Building a Safer Health System*. Washington, DC: National Academy Press;2000.
3. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA*. Mar 5 2003;289(9):1107-1116.
4. Raebel MA, Lyons EE, Andrade SE, et al. Laboratory monitoring of drugs at initiation of therapy in ambulatory care. *J Gen Intern Med*. Dec 2005;20(12):1120-1126.
5. Thomsen LA, Winterstein AG, Sondergaard B, Haugbolle LS, Melander A. Systematic review of the incidence and characteristics of preventable adverse drug events in ambulatory care. *Ann Pharmacother*. Sep 2007;41(9):1411-1426.
6. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. *JAMA*. Jul 5 1995;274(1):29-34.
7. Gandhi TK, Burstin HR, Cook EF, et al. Drug complications in outpatients. *J Gen Intern Med*. Mar 2000;15(3):149-154.
8. Kuperman GJ, Bobb A, Payne TH, et al. Medication-related clinical decision support in computerized provider order entry systems: a review. *J Am Med Inform Assoc*. Jan-Feb 2007;14(1):29-40.
9. Raebel MA, Lyons EE, Chester EA, et al. Improving laboratory monitoring at initiation of drug therapy in ambulatory care: a randomized trial. *Arch Intern Med*. Nov 14 2005;165(20):2395-2401.
10. Hoch I, Heymann AD, Kurman I, Valinsky LJ, Chodick G, Shalev V. Countrywide computer alerts to community physicians improve potassium testing in patients receiving diuretics. *J Am Med Inform Assoc*. Nov-Dec 2003;10(6):541-546.
11. Matheny ME, Sequist TD, Seger AC, et al. A randomized trial of electronic clinical reminders to improve medication laboratory monitoring. *J Am Med Inform Assoc*. Jul-Aug 2008;15(4):424-429.
12. Palen TE, Raebel M, Lyons E, Magid DM. Evaluation of laboratory monitoring alerts within a computerized physician order entry system for medication orders. *Am J Manag Care*. Jul 2006;12(7):389-395.
13. Raebel MA, Chester EA, Newsom EE, et al. Randomized trial to improve laboratory safety monitoring of ongoing drug therapy in ambulatory patients. *Pharmacotherapy*. May 2006;26(5):619-626.
14. Lo HG, Matheny ME, Seger DL, Bates DW, Gandhi TK. Impact of non-interruptive medication laboratory monitoring alerts in ambulatory care. *J Am Med Inform Assoc*. Jan-Feb 2009;16(1):66-71.

15. Steele AW, Eisert S, Witter J, et al. The effect of automated alerts on provider ordering behavior in an outpatient setting. *PLoS Med.* Sep 2005;2(9):e255.
16. Tjia J, Field TS, Garber LD, et al. Development and pilot testing of guidelines to monitor high-risk medications in the ambulatory setting. *Am J Manag Care.* Jul 2010;16(7):489-496.
17. Tjia J, Field TS, Fischer SH, et al. HEDIS Measurement Issues in the Meaningful Use of Electronic Health Records Era: Lessons from the Laboratory Monitoring of High-Risk Medications. *Submitted for publication.* 2011.
18. ten Berg MJ, Huisman A, van den Bemt PM, Schobben AF, Egberts AC, van Solinge WW. Linking laboratory and medication data: new opportunities for pharmacoepidemiological research. *Clin Chem Lab Med.* 2007;45(1):13-19.
19. Schiff GD, Klass D, Peterson J, Shah G, Bates DW. Linking laboratory and pharmacy: opportunities for reducing errors and improving care. *Arch Intern Med.* Apr 28 2003;163(8):893-900.
20. Agrawal A. Medication errors: prevention using information technology systems. *Br J Clin Pharmacol.* Jun 2009;67(6):681-686.
21. Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. *Arch Intern Med.* Jun 23 2003;163(12):1409-1416.
22. Chaudhry B, Wang J, Wu S, et al. Systematic review: impact of health information technology on quality, efficiency, and costs of medical care. *Ann Intern Med.* May 16 2006;144(10):742-752.
23. Fischer SH, Tjia J, Field TS. Impact of health information technology interventions to improve medication laboratory monitoring for ambulatory patients: a systematic review. *J Am Med Inform Assoc.* Nov 1 2010;17(6):631-636.
24. Feldstein AC, Smith DH, Perrin N, et al. Improved therapeutic monitoring with several interventions: a randomized trial. *Arch Intern Med.* Sep 25 2006;166(17):1848-1854.
25. Hayward GL, Parnes AJ, Simon SR. Using health information technology to improve drug monitoring: a systematic review. *Pharmacoepidemiol Drug Saf.* Dec 2009;18(12):1232-1237.
26. Goldman R, Soran C, Hayward G, Simon S. Doctors' perceptions of laboratory monitoring in office practice. *J Eval Clin Pract.* Dec 2010;16(6):1136-1141.
27. Leape LL, Weissman JS, Schneider EC, Piana RN, Gatsonis C, Epstein AM. Adherence to practice guidelines: the role of specialty society guidelines. *Am Heart J.* Jan 2003;145(1):19-26.
28. Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Comparison of drug adherence rates among patients with seven different medical conditions. *Pharmacotherapy.* Apr 2008;28(4):437-443.
29. George A, Rubin G. Non-attendance in general practice: a systematic review and its implications for access to primary health care. *Fam Pract.* Apr 2003;20(2):178-184.

30. Andersen RM. Revisiting the behavioral model and access to medical care: does it matter? *J Health Soc Behav.* Mar 1995;36(1):1-10.
31. Andersen R. A behavioral model of families' use of health services. Research Series No. 25. *Chicago: Center for Health Administration Studies, University of Chicago.* 1968.
32. Gandhi TK, Weingart SN, Seger AC, et al. Outpatient prescribing errors and the impact of computerized prescribing. *J Gen Intern Med.* Sep 2005;20(9):837-841.
33. Siegel LC, Housman D, Newmark L, Ungar J, Einbinder JS, Gandhi TK. Linking test ordering with order tracking: closing the loop in ambulatory care. *AMIA Annu Symp Proc.* 2008:1131.
34. Schiff GD, Kim S, Krosnjar N, et al. Missed hypothyroidism diagnosis uncovered by linking laboratory and pharmacy data. *Arch Intern Med.* Mar 14 2005;165(5):574-577.
35. Jha AK, Kuperman GJ, Teich JM, et al. Identifying adverse drug events: development of a computer-based monitor and comparison with chart review and stimulated voluntary report. *J Am Med Inform Assoc.* May-Jun 1998;5(3):305-314.
36. Classen DC, Pestotnik SL, Evans RS, Burke JP. Computerized surveillance of adverse drug events in hospital patients. *JAMA.* Nov 27 1991;266(20):2847-2851.
37. Dormann H, Muth-Selbach U, Krebs S, et al. Incidence and costs of adverse drug reactions during hospitalisation: computerised monitoring versus stimulated spontaneous reporting. *Drug Saf.* Feb 2000;22(2):161-168.
38. Bates DW, Kuperman GJ, Wang S, et al. Ten commandments for effective clinical decision support: making the practice of evidence-based medicine a reality. *J Am Med Inform Assoc.* Nov-Dec 2003;10(6):523-530.
39. Osheroff JA, Teich JM, Middleton B, Steen EB, Wright A, Detmer DE. A roadmap for national action on clinical decision support. *J Am Med Inform Assoc.* Mar-Apr 2007;14(2):141-145.
40. Stone CA, Palmer JH, Saxby PJ, Devaraj VS. Reducing non-attendance at outpatient clinics. *J R Soc Med.* Mar 1999;92(3):114-118.
41. Simon SR, Andrade SE, Ellis JL, et al. Baseline laboratory monitoring of cardiovascular medications in elderly health maintenance organization enrollees. *J Am Geriatr Soc.* Dec 2005;53(12):2165-2169.
42. Hurley JS, Roberts M, Solberg LI, et al. Laboratory safety monitoring of chronic medications in ambulatory care settings. *J Gen Intern Med.* Apr 2005;20(4):331-333.
43. Bates DW, Teich JM, Lee J, et al. The impact of computerized physician order entry on medication error prevention. *J Am Med Inform Assoc.* Jul-Aug 1999;6(4):313-321.
44. Rind DM, Safran C, Phillips RS, et al. Effect of computer-based alerts on the treatment and outcomes of hospitalized patients. *Arch Intern Med.* Jul 11 1994;154(13):1511-1517.

45. Pedersen CA, Schneider PJ, Scheckelhoff DJ. ASHP national survey of pharmacy practice in hospital settings: monitoring and patient education--2006. *Am J Health Syst Pharm*. Mar 1 2007;64(5):507-520.
46. Handler SM, Altman RL, Perera S, et al. A systematic review of the performance characteristics of clinical event monitor signals used to detect adverse drug events in the hospital setting. *J Am Med Inform Assoc*. Jul-Aug 2007;14(4):451-458.
47. Durieux P, Trinquart L, Colombet I, et al. Computerized advice on drug dosage to improve prescribing practice. *Cochrane Database Syst Rev*. 2008(3):CD002894.
48. Walton RT, Harvey E, Dovey S, Freemantle N. Computerised advice on drug dosage to improve prescribing practice. *Cochrane Database Syst Rev*. 2001(1):CD002894.
49. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. Jun 1998;52(6):377-384.
50. Grimshaw JM, Shirran L, Thomas R, et al. Changing provider behavior: an overview of systematic reviews of interventions. *Med Care*. Aug 2001;39(8 Suppl 2):II2-45.
51. Graham DJ, Drinkard CR, Shatin D, Tsong Y, Burgess MJ. Liver enzyme monitoring in patients treated with troglitazone. *JAMA*. Aug 15 2001;286(7):831-833.
52. Krall MA, Sittig DF. Clinician's assessments of outpatient electronic medical record alert and reminder usability and usefulness requirements. *Proc AMIA Symp*. 2002:400-404.
53. Majumdar SR, Soumerai SB. Why most interventions to improve physician prescribing do not seem to work. *CMAJ*. Jul 8 2003;169(1):30-31.
54. Wolfstadt JI, Gurwitz JH, Field TS, et al. The effect of computerized physician order entry with clinical decision support on the rates of adverse drug events: a systematic review. *J Gen Intern Med*. Apr 2008;23(4):451-458.
55. Ammenwerth E, Schnell-Inderst P, Machan C, Siebert U. The Effect of Electronic Prescribing on Medication Errors and Adverse Drug Events: A Systematic Review. *J Am Med Inform Assoc*. September-October 2008;15(5):585-600.
56. Elin RJ. Computer-assisted therapeutic drug monitoring. *Clin Lab Med*. Jun 1987;7(2):485-492.
57. Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. *N Engl J Med*. Apr 17 2003;348(16):1556-1564.
58. Raebel MA, Carroll NM, Andrade SE, et al. Monitoring of drugs with a narrow therapeutic range in ambulatory care. *Am J Manag Care*. May 2006;12(5):268-274.
59. Tang EO, Lai CS, Lee KK, Wong RS, Cheng G, Chan TY. Relationship between patients' warfarin knowledge and anticoagulation control. *Ann Pharmacother*. Jan 2003;37(1):34-39.
60. Lash S, Harding J. "Abandoned Prescriptions" A Quantitative Assessment of Their Cause. *J Managed Care Pharm*. 1995(1):193-199.

61. Canizares MJ, Penneys NS. The incidence of nonattendance at an urgent care dermatology clinic. *J Am Acad Dermatol*. Mar 2002;46(3):457-459.
62. Pal B, Taberner DA, Readman LP, Jones P. Why do outpatients fail to keep their clinic appointments? Results from a survey and recommended remedial actions. *Int J Clin Pract*. Sep 1998;52(6):436-437.
63. U.S. Census Bureau. *Census 2000 Summary File 1, Matrices P3, P4, PCT4, PCT5, PCT8, and PCT11*. 2000.
64. Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. *JAMA*. Oct 18 2006;296(15):1858-1866.
65. Shrank WH, Polinski JM, Avorn J. Quality indicators for medication use in vulnerable elders. *J Am Geriatr Soc*. Oct 2007;55 Suppl 2:S373-382.
66. Wagner AK, Chan KA, Dashevsky I, et al. FDA drug prescribing warnings: is the black box half empty or half full? *Pharmacoepidemiol Drug Saf*. Jun 2006;15(6):369-386.
67. Lacy NL, Paulman A, Reuter MD, Lovejoy B. Why we don't come: patient perceptions on no-shows. *Ann Fam Med*. Nov-Dec 2004;2(6):541-545.
68. Oppenheim GL, Bergman JJ, English EC. Failed appointments: a review. *J Fam Pract*. Apr 1979;8(4):789-796.
69. Rodriguez Pacheco R, Negro Alvarez JM, Campuzano Lopez FJ, et al. Non-compliance with appointments amongst patients attending an Allergology Clinic, after implementation of an improvement plan. *Allergol Immunopathol (Madr)*. Jul-Aug 2007;35(4):136-144.
70. Zailinawati AH, Ng CJ, Nik-Sherina H. Why do patients with chronic illnesses fail to keep their appointments? A telephone interview. *Asia Pac J Public Health*. 2006;18(1):10-15.
71. Simmons AV, Atkinson K, Atkinson P, Crosse B. Failure of patients to attend a medical outpatient clinic. *J R Coll Physicians Lond*. Jan-Feb 1997;31(1):70-73.
72. Collins J, Santamaria N, Clayton L. Why outpatients fail to attend their scheduled appointments: a prospective comparison of differences between attenders and non-attenders. *Aust Health Rev*. 2003;26(1):52-63.
73. Martin C, Perfect T, Mantle G. Non-attendance in primary care: the views of patients and practices on its causes, impact and solutions. *Fam Pract*. Dec 2005;22(6):638-643.
74. Glaser B, Strauss A. *Grounded Theory: The Discovery of Grounded Theory*. New York: de Gruyter; 1967.
75. Webb C, Kevern J. Focus groups as a research method: a critique of some aspects of their use in nursing research. *J Adv Nurs*. Mar 2001;33(6):798-805.
76. Guest G, Bunce A, Johnson L. How Many Interviews Are Enough?: An Experiment with Data Saturation and Variability. *Field Methods*. February 1, 2006 2006;18(1):59-82.
77. Higginbottom GM. Sampling issues in qualitative research. *Nurse Res*. 2004;12(1):7-19.

78. Marshall MN. Sampling for qualitative research. *Fam Pract*. Dec 1996;13(6):522-525.
79. Tang PC, Ralston M, Arrigotti MF, Qureshi L, Graham J. Comparison of methodologies for calculating quality measures based on administrative data versus clinical data from an electronic health record system: implications for performance measures. *J Am Med Inform Assoc*. Jan-Feb 2007;14(1):10-15.
80. Dam TN, Panizzon R, Jemec GB. Methotrexate use and monitoring in Switzerland and Denmark. *Dermatology*. 2005;210(3):253.
81. Haupt DW, Rosenblatt LC, Kim E, Baker RA, Whitehead R, Newcomer JW. Prevalence and predictors of lipid and glucose monitoring in commercially insured patients treated with second-generation antipsychotic agents. *Am J Psychiatry*. Mar 2009;166(3):345-353.
82. Boudourakis LD, Wang TS, Roman SA, Desai R, Sosa JA. Evolution of the surgeon-volume, patient-outcome relationship. *Ann Surg*. Jul 2009;250(1):159-165.
83. Rogers SO, Jr., Wolf RE, Zaslavsky AM, Wright WE, Ayanian JZ. Relation of surgeon and hospital volume to processes and outcomes of colorectal cancer surgery. *Ann Surg*. Dec 2006;244(6):1003-1011.
84. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med*. Apr 11 2002;346(15):1128-1137.
85. Go AS, Rao RK, Dauterman KW, Massie BM. A systematic review of the effects of physician specialty on the treatment of coronary disease and heart failure in the United States. *Am J Med*. Feb 15 2000;108(3):216-226.
86. Chin MH, Zhang JX, Merrell K. Specialty differences in the care of older patients with diabetes. *Med Care*. Feb 2000;38(2):131-140.
87. Harrold LR, Field TS, Gurwitz JH. Knowledge, patterns of care, and outcomes of care for generalists and specialists. *J Gen Intern Med*. Aug 1999;14(8):499-511.
88. Grol R. Successes and failures in the implementation of evidence-based guidelines for clinical practice. *Med Care*. Aug 2001;39(8 Suppl 2):II46-54.
89. Lee DH, Vielemeyer O. Analysis of overall level of evidence behind Infectious Diseases Society of America practice guidelines. *Arch Intern Med*. Jan 10 2011;171(1):18-22.
90. Fontanarosa PB, Rennie D, DeAngelis CD. Postmarketing surveillance--lack of vigilance, lack of trust. *JAMA*. Dec 1 2004;292(21):2647-2650.
91. Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. *JAMA*. Jul 28 2010;304(4):411-418.
92. Nissen SE, Wolski K. Rosiglitazone Revisited: An Updated Meta-analysis of Risk for Myocardial Infarction and Cardiovascular Mortality. *Arch Intern Med*. Jun 28 2010.
93. Harris G. F.D.A. to Restrict Avandia, Citing Heart Risk. *New York Times*. September 24, 2010, 2010: 1.

94. Wang LM, Wong M, Lightwood JM, Cheng CM. Black box warning contraindicated comedications: concordance among three major drug interaction screening programs. *Ann Pharmacother*. Jan 2010;44(1):28-34.
95. Lasser KE, Seger DL, Yu DT, et al. Adherence to black box warnings for prescription medications in outpatients. *Arch Intern Med*. Feb 13 2006;166(3):338-344.
96. Yu DT, Seger DL, Lasser KE, et al. Impact of implementing alerts about medication black-box warnings in electronic health records. *Pharmacoepidemiol Drug Saf*. Dec 28 2010.
97. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. Jun 1992;45(6):613-619.
98. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.
99. Chu YT, Ng YY, Wu SC. Comparison of different comorbidity measures for use with administrative data in predicting short- and long-term mortality. *BMC Health Serv Res*. 2010;10:140.
100. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. *J Clin Epidemiol*. Oct 1993;46(10):1075-1079; discussion 1081-1090.
101. Rogers WH. Regression standard errors in clustered samples. *Stata Technical Bulletin*. 1993;13:19-23.
102. Williams RL. A note on robust variance estimation for cluster-correlated data. *Biometrics*. Jun 2000;56(2):645-646.
103. Wooldridge JM. *Econometric Analysis of Cross Section and Panel Data*. Cambridge, MA: MIT Press; 2002.
104. Froot KA. Consistent covariance matrix estimation with cross-sectional dependence and heteroskedasticity in financial data. *Journal of Financial and Quantitative Analysis*. 1989;24:333-355.
105. Harrell FE. *Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis*: Springer Verlag; 2001.
106. Galanter WL, Didomenico RJ, Polikaitis A. A trial of automated decision support alerts for contraindicated medications using computerized physician order entry. *J Am Med Inform Assoc*. May-Jun 2005;12(3):269-274.
107. Dreiherr J, Froimovici M, Bibi Y, Vardy DA, Cicurel A, Cohen AD. Nonattendance in obstetrics and gynecology patients. *Gynecol Obstet Invest*. 2008;66(1):40-43.
108. Gurudu SR, Fry LC, Fleischer DE, Jones BH, Trunkenbolz MR, Leighton JA. Factors contributing to patient nonattendance at open-access endoscopy. *Dig Dis Sci*. Nov 2006;51(11):1942-1945.
109. Harrold LR, Yood RA, Mikuls TR, et al. Sex differences in gout epidemiology: evaluation and treatment. *Ann Rheum Dis*. Oct 2006;65(10):1368-1372.

110. van Luin M, Wit FW, Smit C, et al. Adherence to HIV Therapeutic Drug Monitoring Guidelines in The Netherlands. *Ther Drug Monit.* Dec 29.
111. Long CL, Raebel MA, Price DW, Magid DJ. Compliance with dosing guidelines in patients with chronic kidney disease. *Ann Pharmacother.* May 2004;38(5):853-858.
112. Worrall G, Chaulk P, Freake D. The effects of clinical practice guidelines on patient outcomes in primary care: a systematic review. *CMAJ.* Jun 15 1997;156(12):1705-1712.
113. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA.* Oct 20 1999;282(15):1458-1465.
114. Steinman MA, Patil S, Kamat P, Peterson C, Knight SJ. A taxonomy of reasons for not prescribing guideline-recommended medications for patients with heart failure. *Am J Geriatr Pharmacother.* Dec 2010;8(6):583-594.
115. Rost K, Nutting P, Smith J, Coyne JC, Cooper-Patrick L, Rubenstein L. The role of competing demands in the treatment provided primary care patients with major depression. *Arch Fam Med.* Feb 2000;9(2):150-154.
116. Jaen CR, Stange KC, Nutting PA. Competing demands of primary care: a model for the delivery of clinical preventive services. *J Fam Pract.* Feb 1994;38(2):166-171.
117. Tamblyn R, Huang A, Kawasumi Y, et al. The development and evaluation of an integrated electronic prescribing and drug management system for primary care. *J Am Med Inform Assoc.* Mar-Apr 2006;13(2):148-159.
118. Carlsen B, Glenton C, Pope C. Thou shalt versus thou shalt not: a meta-synthesis of GPs' attitudes to clinical practice guidelines. *Br J Gen Pract.* Dec 2007;57(545):971-978.
119. Krebs P, Prochaska JO, Rossi JS. A meta-analysis of computer-tailored interventions for health behavior change. *Prev Med.* Sep-Oct 2010;51(3-4):214-221.
120. Westphal JF, Jehl F, Javelot H, Nonnenmacher C. Enhanced physician adherence to antibiotic use guidelines through increased availability of guidelines at the time of drug ordering in hospital setting. *Pharmacoepidemiol Drug Saf.* Feb 2011;20(2):162-168.
121. Paterno MD, Maviglia SM, Gorman PN, et al. Tiering drug-drug interaction alerts by severity increases compliance rates. *J Am Med Inform Assoc.* Jan-Feb 2009;16(1):40-46.
122. Scholle SH, Roski J, Adams JL, et al. Benchmarking physician performance: reliability of individual and composite measures. *Am J Manag Care.* Dec 2008;14(12):833-838.
123. Holmboe ES, Wang Y, Tate JP, Meehan TP. The effects of patient volume on the quality of diabetic care for Medicare beneficiaries. *Med Care.* Dec 2006;44(12):1073-1077.

124. Turchin A, Shubina M, Pendergrass ML. Relationship of physician volume with process measures and outcomes in diabetes. *Diabetes Care*. Jun 2007;30(6):1442-1447.
125. Simon GE, Von Korff M, Rutter CM, Peterson DA. Treatment process and outcomes for managed care patients receiving new antidepressant prescriptions from psychiatrists and primary care physicians. *Arch Gen Psychiatry*. Apr 2001;58(4):395-401.
126. Garg AX, Adhikari NK, McDonald H, et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. *JAMA*. Mar 9 2005;293(10):1223-1238.
127. Shojania KG, Jennings A, Mayhew A, Ramsay C, Eccles M, Grimshaw J. Effect of point-of-care computer reminders on physician behaviour: a systematic review. *CMAJ*. Mar 23 2010;182(5):E216-225.
128. Weingart SN, Toth M, Sands DZ, Aronson MD, Davis RB, Phillips RS. Physicians' decisions to override computerized drug alerts in primary care. *Arch Intern Med*. Nov 24 2003;163(21):2625-2631.
129. Shah NR, Seger AC, Seger DL, et al. Improving acceptance of computerized prescribing alerts in ambulatory care. *J Am Med Inform Assoc*. Jan-Feb 2006;13(1):5-11.
130. Lapane KL, Waring ME, Schneider KL, Dube C, Quilliam BJ. A mixed method study of the merits of e-prescribing drug alerts in primary care. *J Gen Intern Med*. Apr 2008;23(4):442-446.
131. Murff HJ, Gandhi TK, Karson AK, et al. Primary care physician attitudes concerning follow-up of abnormal test results and ambulatory decision support systems. *Int J Med Inform*. Sep 2003;71(2-3):137-149.
132. Sittig DF, Krall MA, Dykstra RH, Russell A, Chin HL. A survey of factors affecting clinician acceptance of clinical decision support. *BMC Med Inform Decis Mak*. 2006;6:6.
133. Patel NC, Crismon ML, Miller AL, Johnsrud MT. Drug adherence: effects of decreased visit frequency on adherence to clozapine therapy. *Pharmacotherapy*. Sep 2005;25(9):1242-1247.
134. Roebuck MC, Liberman JN, Gemmill-Toyama M, Brennan TA. Medication adherence leads to lower health care use and costs despite increased drug spending. *Health Aff (Millwood)*. Jan 2011;30(1):91-99.
135. Cohen AD, Kaplan DM, Shapiro J, Levi I, Vardy DA. Health provider determinants of nonattendance in pediatric otolaryngology patients. *Laryngoscope*. Oct 2005;115(10):1804-1808.
136. Cohen AD, Goldbart AD, Levi I, Shapiro J, Vardy DA. Health provider factors associated with nonattendance in pediatric dermatology ambulatory patients. *Pediatr Dermatol*. Mar-Apr 2007;24(2):113-117.
137. Hardy KJ, O'Brien SV, Furlong NJ. Information given to patients before appointments and its effect on non-attendance rate. *BMJ*. Dec 1 2001;323(7324):1298-1300.

138. Lee CS, McCormick PA. Telephone reminders to reduce non-attendance rate for endoscopy. *J R Soc Med.* Nov 2003;96(11):547-548.
139. Oladipo A, Ogden S, Pugh S. Preclinic appointment telephone contact: an effective intervention for colonoscopy clinic nonattendance. *J Low Genit Tract Dis.* Jan 2007;11(1):35-38.
140. Jayaram M, Rattahalli RD, Kader I. Prompt letters to reduce non-attendance: applying evidence based practice. *BMC Psychiatry.* 2008;8:90.
141. DesRoches CM, Campbell EG, Rao SR, et al. Electronic health records in ambulatory care--a national survey of physicians. *N Engl J Med.* Jul 3 2008;359(1):50-60.
142. Romano MJ, Stafford RS. Electronic Health Records and Clinical Decision Support Systems: Impact on National Ambulatory Care Quality. *Arch Intern Med.* Jan 24 2011.
143. Jacobson VJ, Szilagyi P. Patient reminder and recall systems to improve immunization rates. *Cochrane Database of Systematic Reviews.* 2005(3). <http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD003941/frame.html>.
144. DeFrank JT, Rimer BK, Gierisch JM, Bowling JM, Farrell D, Skinner CS. Impact of mailed and automated telephone reminders on receipt of repeat mammograms: a randomized controlled trial. *Am J Prev Med.* Jun 2009;36(6):459-467.
145. Bates DW, Leape LL, Cullen DJ, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. *JAMA.* Oct 21 1998;280(15):1311-1316.
146. Bates DW. Improving the use of therapeutic drug monitoring. *Ther Drug Monit.* Oct 1998;20(5):550-555.
147. Chueh H, Barnett GO. "Just-in-time" clinical information. *Acad Med.* Jun 1997;72(6):512-517.
148. Buntin MB, Burke MF, Hoaglin MC, Blumenthal D. The benefits of health information technology: a review of the recent literature shows predominantly positive results. *Health Aff (Millwood).* Mar 2011;30(3):464-471.
149. Jha AK, Desroches CM, Kralovec PD, Joshi MS. A Progress Report On Electronic Health Records In U.S. Hospitals. *Health Aff (Millwood).* Aug 26 2010.
150. Simon SR, McCarthy ML, Kaushal R, et al. Electronic health records: which practices have them, and how are clinicians using them? *J Eval Clin Pract.* Feb 2008;14(1):43-47.
151. Litzelman DK, Dittus RS, Miller ME, Tierney WM. Requiring physicians to respond to computerized reminders improves their compliance with preventive care protocols. *J Gen Intern Med.* Jun 1993;8(6):311-317.
152. OECD. OECD Health Data 2010 - Version: October 2010. 2010; www.oecd.org/health/healthdata, 2011.
153. Larsson A, Palmer M, Hulten G, Tryding N. Large differences in laboratory utilisation between hospitals in Sweden. *Clin Chem Lab Med.* May 2000;38(5):383-389.