Exploration of the Clinical Utility of High Risk Medication Regimens

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Dedication

This dissertation is dedicated to my family – particularly my husband and children; to women and girls aspiring toward education and careers in STEM; and to Bonnie Westra and the team of mentors and researchers at the University of Minnesota who supported me to the finish line.

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Introduction

1. Background

Avoidable hospital readmissions have become a common and much-publicized issue in American health care, with research estimating that they waste billions of dollars every year.(National Quality Forum, 2010a) A 2009 study by Jencks et al. focused attention to the problem when it found that one-fifth of hospitalized Medicare patients were readmitted within 30 days, and that 90 percent of those readmissions were unplanned.(Jencks, Williams, & Coleman, 2009) Hospital groups have subsequently made them a top priority in their quality improvement efforts (HealthEast Care System, 2010; Rennke et al., 2013; Schwartz, 2013) and the federal Medicare program has sought to reduce hospitalizations by issuing penalties to hospitals with unacceptable 30-day readmission rates.(Abelson, 2013; Rau, 2013) Medication problems have emerged in research as a driver of readmissions and a target for hospitals seeking to improve the quality of their care.(Bonnet-Zamponi et al., 2013; Kansagara et al., 2011; Morrissey, Morrissey, McElnay, Scott, & McConnell, 2003) Four of five elderly patients leaving Yale-New Haven Hospital experienced medication problems, according to a survey of 377 patients, because they didn't understand their revised prescription regimens, or because doctors prescribed the wrong drugs or doses or took their patients off drugs that were still needed.(Ziaeian, Araujo, Van Ness, & Horwitz, 2012) Patients' struggles with managing their new prescription regimens have been associated with readmissions along with confusion among doctors in reconciling their patients' new prescription regimens with the drugs they took before they were hospitalized.(Agency for Healthcare Research and Quality, 2012; National Quality Forum, 2010b) A lack of access to affordable

medication has similarly been cited as a cause of adverse-drug events in patients that pushes them back into hospital care.(Silow-Carroll, Edwards, & Lashbrook, 2011) Estimates vary in terms of how many readmissions are due to medication issues, but one study found nearly one in five readmissions of elderly patients was due to adverse drug reactions, which are defined as "noxious and unintended" consequences of normal medication usage.(Teymoorian, Dutcher, & Woods, 2011) Another study found nearly one in four of these adverse reactions prompted hospital readmissions when only looking at seniors 80 and older.(M. Zhang et al., 2009) Examining the broader concept of "medication-related problems," which includes not only adverse reactions but other issues such as drug overuse, another study associated these problems with nearly 4 in 10 rehospitalizations in a sample population of elderly patients.(Bonnet-Zamponi et al., 2013)

Hospitals over the past decade have been encouraged by groups such as the Joint Commission to create medication reconciliation processes to make sure that changes in prescriptions during admissions don't leave patients with harmful, inadequate or confusing drug regimens when they are discharged home or to another care setting.(Agency for Healthcare Research and Quality, 2012) Pharmacists have been engaged at more hospitals in discharge planning as well – often with the primary goal of reducing avoidable readmissions.(Anderegg, Wilkinson, Couldry, Grauer, & Howser, 2014; Fera, Anderson, Kanel, & Ramusivich, 2014; Kirkham, Clark, Paynter, Lewis, & Duncan, 2014; Pal, Babbott, & Wilkinson, 2013) Patient interviews have made it apparent that a pamphlet or 15 minutes of instructions when they are about to be

discharged from hospital care aren't enough.(Robert Wood Johnson Foundation, 2013) While home visits by nurses(HealthEast Care System, 2010) and even firefighters(Smetanka, 2014) might be effective alternatives, these can be expensive and resource-intensive solutions. A challenge, as a result, is identifying which patients are at greatest risk of readmissions and would benefit most from these sorts of prevention strategies.(Kansagara et al., 2011; Morrissey et al., 2003; Walsh & Hripcsak, 2014) Therefore, there is a need to identify medication-related predictors of hospital readmissions.

Several medication measures have been studied in conjunction with hospital readmissions. One potential predictor of hospital readmission is polypharmacy, a simple count of the prescriptions in patients' regimens, and whether the number of drugs elevates readmission risk. Results of studies differ on whether polypharmacy is a risk factor, and studies that have found a problem have varied in terms of the number of drugs that separates patients into high- and low-risk groups.(Morandi et al., 2013; Sganga et al., 2014) Other studies have looked at the role of Potentially Inappropriate Medications (PIM) to determine if drugs with known risks in the elderly are driving readmissions. Findings so far have varied from finding an association,(Price, Holman, Sanfilippo, & Emery, 2014a) or no association,(Borenstein et al., 2013) or an association only in the context with polypharmacy.(Sehgal et al., 2013) A third target for research on medication-related readmission risks is the Medication Regimen Complexity Index (MRCI),(George, Phun, Bailey, Kong, & Stewart, 2004) a measure of patients' regimens based on the complexity of the drugs by their instructions, dosing or routes. At least one

study attempted an automated approach to scoring this measurement,(McDonald et al., 2013) while another found a relationship between MRCI and readmissions.(Willson, Greer, & Weeks, 2014)

Dierich hypothesized that a combination of all three measures (polypharmacy, PIM, and MRCI) could produce a more reliable indicator of readmission risk.(Dierich, 2010) Using factor analysis, she constructed a composite measure called High Risk Medication Regimen (HRMR) that utilized all three medication indicators, and tested its predictive power against the actual readmission histories of 911 adults from 15 Medicare-certified home health care agencies. A structural equation model using HRMR as a mediating variable was more predictive of readmissions than using comorbidity or any of the three components on their own as mediating variables. HRMR accounted for a unique variance of 10% in patients' readmission risks as well as 20% of the comorbidity effect of readmission.(Dierich, 2010)

A barrier to clinical utility of this discovery is the cumbersome, manual process used in the initial research to produce patient HRMR scores. The medications for the 911 patients were described in generic text descriptions, and not standardized in a way that could be used for data analysis and clinical decision support. Health care is gradually moving toward standardized electronic health records (EHRs), though, with $30 billion in federal funds helping hospitals and health systems achieve a basic level of competency known as "meaningful use."(Adler-Milstein et al., 2014) As of 2013, 59 percent of U.S. hospitals had achieved Stage 1 certification with their EHR systems, which requires them

to track patient medication lists and allow electronic prescription ordering.(Adler-Milstein et al., 2014)

2. Statement of Purpose

The overall purpose of this study was to transform the concept of HRMR into an automated tool that could potentially be used in clinical care to assess patients' medication-related rehospitalization risks. This was achieved by creating automated processes that convert non-standardized medication information into formatted data for analysis, and that calculate HRMR scores based on patients' standardized drug data. The rapidly expanding use of EHRs will greatly increase the potential for the automated calculation of HRMRs and its possible use as a clinical decision support tool.

3. Structure of Dissertation

Three publishable papers for this dissertation describe the steps in the process for transforming the concept of HRMR from a manual process to an automated process. The papers: (1) create an automated approach to deriving HRMR scores and testing its accuracy with the same home health care population Dierich used, (2) optimize the calculation of HRMR scores to maximize the algorithm's sensitivity to readmissions and ready it for clinical utility, and (3) identify clusters of patients to determine if HRMR-related readmission risks are more prevalent in certain demographic groups.

All three studies used Outcome and Assessment Information Set (OASIS) and medication records for 911 adults from 15 Medicare-certified home health care agencies

that were used in the original Dierich study. OASIS data were obtained from electronic health records for the patients, all of whom were at least 65 and were admitted from the hospital to home health care in 2004. The data included demographic, environmental, support system, health and functional status, and health service utilization information.(Centers for Medicare and Medicaid Services (CMS), 2012b) Medication data included the medication names, doses, dose forms, frequencies and special instructions.(Dierich, 2010)

The first study automated the algorithm by automatically mapping the medication data to RxNorm, a nomenclature created by the U.S. Library of Medicine (NLM) to match standardized drug terms with other commonly used names for drugs in medical records.(National Library of Medicine, 2013) HRMR scores were then calculated based on the standardized medication data. The automated algorithm was designed using RxNorm and NLM application programming interfaces, or APIs, for easy replication and application across different health care systems and databases. Results have been accepted for publication in the *Journal of Biomedical Informatics* and are available online.(Olson, Dierich, & Westra, 2014)

The second study used odds ratio analyses, literature reviews and clinical judgments to adjust the scoring of patients' HRMRs. Receiver Operating Characteristic (ROC) analysis evaluated whether these adjustments improved the predictive strength of the algorithm. The paper has been accepted and published in the *Journal of Applied Clinical Informatics*.(Olson, Dierich, Adam, & Westra, 2014)

The third study used unsupervised clustering to identify patient population subgroups. HRMR scores were then applied to these subgroups, and ROC and False Discovery Rate (FDR) analysis evaluated whether the predictive strength of the algorithm increased for a specific patient population subgroup. The paper has been formatted and submitted for publication in a peer-reviewed informatics journal.

All three manuscripts are included in the subsequent chapters for this dissertation, and the formats are consistent with the instructions of the respective journals to which they have been submitted. Chapter five includes a summary of major findings from this project along with a unified reference list for the introduction, the three papers and the conclusion.

Paper 1:

Automation of a High Risk Medication Regime Algorithm in a Home Health Care Population

Automation of a High Risk Medication Regime Algorithm in a Home Health Care Population

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Objective: Create an automated algorithm for predicting elderly patients' medication-related risks for readmission and validate it by comparing results with a manual analysis of the same patient population.

Materials and Methods: Outcome and Assessment Information Set (OASIS) and medication data were reused from a previous, manual study of 911 patients from 15 Medicare-certified home health care agencies. The medication data was converted into standardized drug codes using APIs managed by the National Library of Medicine (NLM), and then integrated in an automated algorithm that calculates patients' high risk medication regime scores (HRMRs). A comparison of the results between algorithm and manual process was conducted to determine how frequently the HRMR scores were derived which are predictive of readmission.

Results: HRMR scores are composed of polypharmacy (number of drugs), Potentially Inappropriate Medications (PIM) (drugs risky to the elderly), and Medication Regimen Complexity Index (MRCI) (complex dose forms, instructions or administration). The algorithm produced polypharmacy, PIM, and MRCI scores that matched with 99, 87 and 99 percent of the scores, respectively, from the manual analysis.

Discussion: Imperfect match rates resulted from discrepancies in how drugs were classified and coded by the manual analysis vs. the automated algorithm. HRMR rules lack clarity, resulting in clinical judgments for manual coding that were difficult to replicate in the automated analysis.

Conclusion: The high comparison rates for the three measures suggest that an automated clinical tool could use patients' medication records to predict their risks of avoidable readmissions.

Keywords: Rehospitalization, Avoidable Readmission, High Risk Medication Regimen, Home Health Care, Algorithm, RXNorm

1. Introduction

1.1. Background

Avoidable hospital readmissions are indicators of "wasteful" health care spending(National Quality Forum, 2010a) and of poor quality care and discharge planning for patients. A 2003-2004 claims analysis found that a fifth of Medicare patients were rehospitalized within 30 days of initial discharges, and that 90% of those readmissions were unplanned.(Jencks et al., 2009) The cost to Medicare in 2004 alone was $17.4 billion, the analysis found, and the readmissions were associated with longer follow-up hospital stays. Estimates vary widely in terms of how many unplanned readmissions are avoidable,(van Walraven, Bennett, Jennings, Austin, & Forster, 2011) but all hospital stays expose patients to risks of delirium, infections and iatrogenic consequences of tests and procedures.(Allegranzi, 2011; Inouye, Schlesinger, & Lydon, 1999) Identifying patients at greatest risk and offering them support to prevent readmissions has consequently become a top priority for hospitals – especially now that

the federal Medicare program financially penalizes hospitals with 30-day readmission rates deemed unacceptably high.(Abelson, 2013)

Some health systems and hospitals have reported early success in identifying patients at risk for potentially avoidable readmissions(Donze, Aujesky, Williams, & Schnipper, 2013) and providing these at-risk patients with post-discharge home visits and other preventive care services.(Bonnet-Zamponi et al., 2013; HealthEast Care System, 2010; Schwartz, 2013) However, one study concluded the evidence in favor of such post-discharge programs remains weak(Rennke et al., 2013) and another concluded that systems to identify patients at greatest risk for readmissions have "performed poorly."(Kansagara et al., 2011) Meanwhile, two-thirds of U.S. hospitals are paying federal penalties for having more readmissions than would be expected given their patient populations.(Rau, 2013)

In the search for a better way to reduce readmissions, focusing on medications would seem to offer a promising target. A survey of 377 elderly patients discharged from Yale-New Haven Hospital found 81.4% of elderly patients experienced medication problems after hospital discharges because they didn't understand changes to their drug regimens or because doctors erred in making prescriptions, setting doses, or telling patients to stop taking drugs they needed.(Ziaeian et al., 2012) Just the prescribing of medications with known risks that outweigh benefits for the elderly added an estimated $7 billion to U.S. healthcare expenditures in 2001.(Fu et al., 2007) Recent research has evaluated whether readmissions are associated with polypharmacy (patients who take multiple medications)(Morandi et al., 2013; Sehgal et al., 2013; Sganga et al., 2014);

Potentially Inappropriate Medication (PIM, drugs known to be risky to the elderly)(Sehgal et al., 2013); or medication regimen complexity (drugs with complex dose forms, instructions and administration)(Schoonover, 2011; Willson et al., 2014). While research has demonstrated an association between polypharmacy and avoidable readmissions, at least one study failed to find a relationship.(Mansur, Weiss, & Beloosesky, 2008) PIM alone has not emerged as a meaningful indicator.(Sehgal et al., 2013)

Dierich hypothesized that these variables did not consistently predict readmission on their own, and used factor analysis to construct a measure called high risk medication regimens (HRMRs) that combined all three.(Dierich, 2010) A structural equation model using HRMR as a mediating variable was more predictive of readmissions than using comorbidity or any of the three components on their own as mediating variables. HRMRs accounted for a unique variance of 10% in patients' readmission risks as well as 20% of the comorbidity effect of readmission.(Dierich, 2010)

However, the manual process of deriving HRMR scores for this study was tedious and limited the utility of this discovery. Automation of this process is necessary for follow-up research to verify the predictive power of HRMRs, and for the potential development of a clinical tool that uses prescription data from electronic health records to assess patients' readmission risks.

1.2. Objective

This study seeks to advance Dierich's discovery by developing an automated algorithm for determining HRMR scores – thereby determining which patients are at

greater risk for medication-related hospital readmissions and would benefit the most from medication management services. The specific aims are to: (1) map medication data automatically to RxNorm coding standards (2) create an automated algorithm that uses the coded medication data to calculate patient HRMR scores for easy replication and application across different health care systems and databases, and (3) test the algorithm's accuracy by seeing if it derived the same HRMR scores that Dierich calculated through her manual analysis.

2. Materials and Methods

2.1. Data Set

The data set developed in Dierich's study was utilized for this study. It contains Outcome and Assessment Information Set (OASIS) and medication data from 911 older adults from 15 Medicare-certified home health care agencies. Patients were 65 and older whose first episodes of home care took place after initial hospitalizations in 2004. Home care clinicians reviewed the medication records and validated their accuracy by observing the medications in patients' homes. Only patients with complete OASIS and medication records were included in the data set. OASIS is a comprehensive assessment tool completed by home care clinicians to track conditions of patients at admission, various points during their episodes of care, and discharge.(Dierich, 2010) It is used to calculate outcome and risk factors of patients in Medicare-certified home care agencies, and includes demographic, environmental, support system, health and functional status, and health service utilization information.(Centers for Medicare and Medicaid Services

(CMS), 2012a) The medication data includes all prescribed and over-the-counter medications and contained the medication name, dose, frequency, dose forms, frequencies and special instructions.

2.2. Coding Standard Definitions

RxNorm: A standardized nomenclature for clinical drugs that is produced by the National Library of Medicine (NLM).(National Library of Medicine, 2013) RxNorm's standardized naming conventions allow health systems, which might catalog drugs in different ways in their computer systems, to communicate efficiently and accurately.(Nelson, Zeng, Kilbourne, Powell, & Moore, 2011)

RXCUI: A unique numerical identifier for clinical drugs and their concepts. Medications with the same RXCUIs are considered the same drugs with the same ingredients, strengths and dose forms.

TTY: Term types (TTYs) are used along with RXCUIs to further identify generic and branded drug by their properties (ingredients, dose forms, etc.) Examples are shown in Table 1.

Table 1: RXCUI Examples with Corresponding TTY types

TTY	TTY Name	TTY Description[15]	RXCUI	RXCUI String
IN	Ingredient	A compound or moiety that gives the drug its distinctive clinical properties.	2541	Cimetidine
BN	Brand Name	A proprietary name for a family of products containing a specific active ingredient.	152402	Tagamet

MIN	Multiple Ingredients	Two or more ingredients appearing together in a single drug preparation, created from SCDF. In rare cases when IN/PIN or PIN/PIN combinations of the same base ingredient exist, created from SCD.	818150	alginic acid / Cimetidine
DF	Dose Form	Dose Form	316949	Injectable Solution
SCDF	Semantic Clinical Drug Form	Ingredient + Dose Form	371513	Cimetidine Injectable Solution
SCD	Semantic Clinical Drug	Ingredient + Strength + Dose Form	309296	Cimetidine 1.8 MG/ML Injectable Solution
SBD	Semantic Branded Drug	Ingredient + Strength + Dose Form + Brand Name	205746	Cimetidine 6 MG/ML Injectable Solution [Tagamet]

2.3. Tools used in Conjunction with Coding Standards

RXNORM APIs: Online tools that convert drug descriptions from datasets into normalized RxNorm drug codes for research and analysis.(National Library of Medicine, 2012) Examples from this study are in table 2.

Table 2: Example Mapping Local Medications to RXCUI Values

API Name	Description	Example API Calls	Example Record(s) Returned
approxMatch(term)	Search by name to find the	approxMatch(Cimetidine)	RXCUI: 2541 SCORE: 100 RANK: 1

	closest RxNorm concepts		RXCUI: 91215 SCORE: 100 RANK: 1
getRXConceptProperties(rxcui)	Return the concept's properties	getRXConceptProperties(2541)	STR:Cimetidine TTY: IN RXCUI: 2541
getAllRelatedInfo(rxcui)	Get all the related RxNorm concepts for a given RxNorm identifier	getAllRelatedInfo(2541)	STR: Tagamet TTY: BN RXCUI: 152402 STR: alginic acid / Cimetidin TTY: MIN RXCUI: 818150 STR: Cimetidine 6 MG/ML Injectable Solution [Tagamet] TTY: SBD RXCUI: 205746 STR: Cimetidine 1.8 MG/ML Injectable Solution TTY: SCD RXCUI: 309296
getAllConceptsByTTY(termtypes)	Return the RxNorm concepts for the specified term types	getAllConceptsByTTY(DF)	STR: Injectable Solution TTY: DF RXCUI: 316949 STR: Inhalant

			Powder TTY: DF RXCUI: 317000 STR: Ophthalmic Solution TTY: DF RXCUI: 7670

2.4. Methods

2.4.1. HHC Medication Record Data Converted to Coding Standards

In Dierich's study, medication record data was cleansed as follows:

- Medication names were converted to generic names.
- A patient's "likely disease" was derived from the medication's indication. (While the OASIS records contained ICD9 diagnostic values for a patient, the records were limited to one primary and five secondary diagnoses. In addition, medications were not linked to ICD9 codes, and could have been used for reasons for which there are no diagnostic codes.)
- Medication dose forms, frequencies and special instructions were manually derived by splitting the medication text into appropriate concepts.

To further prepare the data for this study, medication names were converted to RXCUI values with a TTY of IN or MIN. A SAS program was created that used

RXNORM APIs for this conversion (Figure 1). Dierich's medication dose forms were converted to RXCUI values with a TTY of DF using a RXNORM API. Dose forms that were not found by the API were converted to custom codes (Figure 2). In addition, a separate SAS program was created for future use to convert Medication RXCUI values with a TTY of SCD, SCDF, or SBD to Dose Form RXCUI values with a TTY of DF (Figure 3).

"Likely diseases" were manually converted to ICD9 values for each patient based on the expertise of the authors – a doctorally prepared informatician (Olson), a geriatric nurse practitioner (Dierich), and a nurse researcher with expertise in geriatrics and home health care data (Westra), and validated against the Charlson comorbidity index.(M. E. Charlson, Pompei, Ales, & MacKenzie, 1987) A separate record was created for each patient consisting solely of "likely diseases" and corresponding ICD9 values.

Lastly, medication frequencies and special directions were converted to custom codes from Dierich's manually derived values from her previous study. No standard was found for these values in the literature.

2.4.2. Polypharmacy Automated Algorithm

Dierich defined polypharmacy as a continuous count of all regularly taken medications (prescribed or over the counter) via any route listed in the first episode of care.(Dierich, 2010) Polypharmacy was also used as a categorical variable for descriptive analysis; patients with less than 9 medications were assigned a "0" and patients with 9 or more medications were assigned a "1". PRN medications (those used as needed), over-the-counter medications and medications with limited dosing time such as antibiotics

were included in the count. The count excluded certain items documented in the patients' medication records such as oxygen or saline used to dilute IV medications. Combination and variable dosed drugs were counted as one drug, rather than counting each active ingredient as a separate drug.

An automated algorithm was created to count medication records containing RXCUI values, and also count each medication record whether or not an RXCUI value was assigned using the same logic and cleansed data as Dierich used in her study.

2.4.3. Potentially Inappropriate Medications Automated Algorithm

The 2003 version of the Beers' criteria, a list of 48 drugs and 20 drug classes that the elderly should avoid, was used in Dierich's study to create PIM scores.(Fick et al., 2003) There is a newer version of the Beers criteria, but it was not available at the time of Dierich's study, hence the same version was used in this study for comparison of the manual process and algorithm. In the Beers' criteria, Fick et al. identified two categories of inappropriate drugs: PIM Table 1 includes those inappropriate for older adults no matter their diagnosis and PIM Table 2 includes medications that could be inappropriate depending on the diagnosis. The criteria also differentiated drugs by whether or not they posed risks of severe adverse outcomes (Appendix A).

Fick et al did not assign scores to medications; hence, based on clinical judgment, Dierich operationalized the PIM criteria by assigning a score of 2.5 to each medication that was considered always inappropriate, and a score of 2 for each medication with a lower severity ranking. For medications with risks related to specific diseases, the assigned scores were 1.5 for medications with the highest risks and 1.0 for medications

with lower risks. A drug may have more than one score, and the highest score was kept for each drug. The medication scores were then summed to provide a total risk level score for each patient.

2.4.3.1. PIM Table 1 Automated Algorithm

A SAS program was created to generate a crosswalk that maps drug names from PIM Table 1 to RXCUI values with TTY types of IN, MIN, BN, SCD, SCDF and SBD. The program used RXNORM APIs to generate the RXCUI values. It also assigned Dierich's score to each medication record (Figure 4). Another SAS program matched RXCUI crosswalk information and patient medication records to produce PIM Table 1 scores (Figure 5).

2.4.3.2. PIM Table 2 Automated Algorithm

A SAS program was created to generate a crosswalk that maps medication names to RXCUI values, and medication classes to medication names to RXCUI values. The NLM Drug portal was used to map medication classes to medication names. A standard was not used for the drug class, and the medication class from PIM Table 2 was manually typed into the web portal which then displayed all medications for that drug class. A SAS program then converted the medication names to RXCUI values using RXNORM APIs. Clinical judgment was used to manually map diagnoses to ICD9 values. The ICD9 values were then assigned to each entry of the crosswalk along with Dierich's score (Figure 6). Another SAS program combined medication records, patients' likely diseases, and PIM Table 2 crosswalk data to produce patients' PIM Table 2 scores (Figure 7).

2.4.4. Medication Regimen Complexity Automated Algorithm

Dierich used a modified version of the Medication Regimen Complexity Index (MRCI) developed by George et al, because at the time it was "the only validated and reliable non-disease specific measure addressing medication complexity in the published literature."(George et al., 2004) The index utilizes weighted scores in three subscales – by the complexity of their route (MRCI Table A), their dosing frequency (MRCI Table B), and their directions or preparation (MRCI Table C) – and then combines the subscale scores into a summary score (Appendix B). George et al. did not provide a cut point for highly complex regimens. Dierich used a continuous score in her structural equation modeling, and a cut point of 20 or above in her categorical data analysis as an indication of high medication regimen complexity.

2.4.4.1. MRCI Table "A" Automated Algorithm

A SAS program was created to generate a crosswalk that maps the dose forms from MRCI Table A to RXCUI values with a TTY type of DF using a RXNORM API. Dose forms that were not found with the API were converted to custom codes (Figure 8). Similar to its use in PIM scoring, a SAS program generated patients' MRCI Table A scores through the input of medication records and MRCI Table A crosswalk data (Figure 9).

2.4.4.2. MRCI Table "B" and "C" Automated Algorithm

SAS programs were created to generate a crosswalk that maps custom codes for dosing frequency and special directions to MRCI Table B and C. Two other SAS programs were created to then generate patients' MRCI Table B and C scores. The programs entered the medication records, and then MRCI Table B and Table C crosswalks, and produced the patients' MRCI Table B (Figure 10) and C scores (Figure 11).

3. Results

Results in this study include the percent of medications from Dierich's study that were automatically mapped to RXCUI values for both dose forms and medication names, as well as the polypharmacy, PIM and MRCI patient scores that were produced through this conversion of drug names.

3.1. Mapping Results

Overall, 99% of drugs in the medication data set were converted to RXCUI values. Initially, without any manipulation of Dierich's data, 82% of the drug names were converted to RXCUI values. The 82% consisted of exact generic drug names that were recognized by the API. After adjusting the data to redefine combination drugs with multiple ingredients into the naming formats that the NLM API expected, the match rate increased to 90%. (Dierich used "And" instead of "/" in the names for multi-ingredient drugs. So "aspirin and dipyridamole" was reformatted to "aspirin / dipyridamole".) Another 9% of the drug records were then converted, either by using the brand names in Dierich's data to find the active ingredient(s) RXCUI types of "IN" or "MIN," or by

correcting misspellings in generic drug names. In the end, 1% of drug records could not be converted; they lacked specific generic or brand names. Rather, the medication terms represented broad medication categories such as "Laxative" or "Sports Cream".

Lastly, 80% of the dose forms in Dierich's study were converted to RXCUI values. Custom codes were created for irrigant, g-tube, intravesicle, dressing, nebulizer and peg tube values. After adding custom codes, 100% mapping of dose forms was achieved.

3.2. Polypharmacy Results

Polypharmacy was calculated two ways: by counting medication records containing RXCUI values, and by counting each medication record whether or not an RXCUI value was assigned. The count of all medication records for patients produced a 100% match to Dierich's data. The count of records with RXCUI values per patient produced a 99% match to Dierich's data.

3.3. PIM Table Results

The match between the automation of patients' PIM scores and Dierich's manual PIM counts was 87%. PIM Table 1 consists of potentially inappropriate medications independent of patients' diagnoses. PIM Table 2 consists of potentially inappropriate medications that were linked to diagnoses. Medications could have more than one score between PIM Table 1 and PIM Table 2; the highest score was assigned to the medication.

In order to reach 87%, the manual calculations and logic in the automated design were adjusted (Table 3). The manual count, for example, included all long acting NSAIDs, such as diclofenac, whereas the automated count only included specific drugs in

PIM Table 1. These missing drugs from the manual count were added to the PIM Table 1 crosswalk to be included in patients' scores and to increase the match rate. The automation for PIM Table 2 found more drugs in diagnosis-specific drug classes than the manual scoring. More muscle relaxants such as quinine, for example, were found by the automated search of patients' medication records. These drugs were removed from the PIM Table 2 crosswalk so they would not be included in the patients' automated scores. The automation also caught mistakes made in the manual review, such as not applying medications consistently across all patients' records. The correction of these errors resulted in modest changes to the manually derived PIM scores.

Table 3: Adjustments to Automated and Manual Logic

Discrepancy with Manual Approach	Resolution
Automation only included dose amount for drugs which included amount guidelines such as ferrous sulfate >325 mg/d	Automation adjusted to include dose and frequency.
Automation only considered specific drugs in PIM Table 1, even when a drug class was identified in combination with specific drugs.	Automation adjusted to consider all drugs for muscle relaxants and antispasmodics, gastrointestinal antispasmodic drugs, anticholinergics and antihistamines.
Automation did not identify tegaserod and scopolamine as anticholinergic.	Tegaserod and scopolamine added to PIM Table 2 crosswalk.
Automation did not identify all benzodiazepines.	Lorazepam, oxazepam, temazepam, alprazolam, and clonazepam added to PIM Table 1 & 2 crosswalks.
Automation did not identify all stimulant laxatives.	Senna and magnesium hydroxide added to PIM

	Table 1 crosswalk.
Automation did not exclude coxibs from NSAID drug Class.	Rofecoxib and celecoxib removed from PIM Table 2 crosswalk.
Automated approach included quinine as a muscle relaxant.	Quinine removed from PIM Table 2 crosswalk.

The 13% that did not match included drugs that were obscured by the conversion of all drug names to their generic forms and to RXCUI values. For example, there is only one RXCUI value for the generic nifedipine. The manual calculations used the brand names and differentiated between long- and short-acting formulations of this medication. The automated design did not, because it utilized the single RXCUI value from the generic conversion. The drugs that did not match also included those with dose or form considerations such as Estrogen which were considered in the manual calculations but not the automated design. Future adjustments to the automated design could allow it to account for these considerations (Table 4).

Table 4: Future Adjustments

Drug/Drug Class	Issue	Future Resolution
Short acting nifedipine (Procardia and Adalat)	Identifying short vs. long acting nifedipine	The automated algorithm used the generic RXCUI value of 7531 (TTY = IN), because the medication data was stored with generic RXCUI values. Only RXCUI values related to short acting Nifedipine should be included in the PIM Table 1 crosswalk. The crosswalk may then be used with medication data stored with RXCUI formats which include the short acting specification. Examples below: 491072 (TTY = SBDF): Nifedipine Extended Release Tablet [Adalat]

		198034 (TTY = SCD): 24 HR Nifedipine 30 MG Extended Release Tablet 672918 (TTY = SBD): 24 HR Nifedipine 90 MG Extended Release Tablet [Adalat]
Muscle relaxants and antispasmodics: Do not consider the extended-release Ditropan XL	Identifying extended release Ditropan XL	The automated algorithm used the generic RXCUI value of 32675 (TTY = IN) for oxybutynin. Exclusion criteria may be identified with RXCUI values stored in a format which includes the extended release specification. Examples below: 863622 (TTY = SBD): 24 HR Oxybutynin chloride 10 MG Extended Release Tablet [Ditropan] 863621 (TTY = SBDF): Oxybutynin Extended Release Tablet [Ditropan] 863619 (TTY= SCD): 24 HR Oxybutynin chloride 10 MG Extended Release Tablet
Estrogen (Oral)	Identifying oral dose form	The automated algorithm used the generic RXCUI value of 4099 (TTY = IN) for estrogen. Only RXCUI values for Oral Estrogen should be defined in the PIM Table 1 crosswalk. The crosswalk may then be used with medication data stored with RXCUI formats which include the oral dose form specification. Examples below: 1441737 (TTY = SBDF): bazedoxifene / Estrogens, Conjugated (USP) Oral Tablet [Duavee] 197662 (TTY = SCD): Estrogens, Conjugated (USP) 1.25 MG Oral Tablet 1441740(TTY = SBD): bazedoxifene 20 MG / Estrogens, Conjugated (USP) 0.45 MG Oral Tablet [Duavee]

3.4. MRCI Table A Results

MRCI Table A consisted of complex dose forms and a corresponding weighting assigned to each entry of the table. The following results were produced for MRCI Table A:

- When the automation ran against a crosswalk that converted MRCI Table A dose forms to RXCUI dose form values, the match was 80% to Dierich's manual calculations.
- When the automation ran against a crosswalk that converted MRCI Table A dose forms to RXCUI dose form values, and included custom values for irrigant, g-tube, intravesicle, dressing, nebulizer and peg tube, the match was 99% to Dierich's manual calculations.

3.5. MRCI Table B & MRCI Table C Results

MRCI Table B consisted of complex dose frequencies and a corresponding weighting assigned to each entry of the table. MRCI Table C consisted of complex special instructions and a corresponding weighting assigned to each entry of the table. The automation of patients' MRCI Table B and MRCI Table C scores produced a 99% match.

4. Discussion

Automated analysis of clinical data is rapidly emerging as a way for health care providers to predict patient needs and risks for a variety of disorders and adverse events.(Deleger et al., 2013; Overby et al., 2013) McDonald et al in 2012 created a successful approach to determining MCRI scores of patients in post-acute home care settings through an algorithm using medication data from their electronic health records.(McDonald et al., 2013) Medication data presents unique challenges in this

pursuit, though, because of the heterogeneous nature of prescription recordkeeping by different health care providers and the lack of standards for drug data coding and entry.(Richesson, 2014) RxNorm is viewed as an "ideal standard" for standardizing prescription data,(Richesson, Smith, Malloy, & Krischer, 2010) and making it available across health care systems for secondary analysis.(Rea et al., 2012) This study provides further validation of the utility of RxNorm and of automated algorithms for secondary analysis, and takes an important next step in applying this approach to the scoring of HRMRs, which Dierich showed have unique potential to assess medication-related risks for hospital readmissions. Automating HRMR calculations was a step that Dierich found necessary for further study in this area in order to "greatly improve the quality of research, the accuracy of findings, and the speed of release of findings."(Dierich, 2010)

4.1. Limitations

The absence of coding standards from the data used in the original Dierich study created several limitations in terms of the ability to truly automate the process of assembling HRMR scores and analyzing patient readmission risks. If a medication record had a misspelling for a dose or medication name, an RXCUI value was not automatically found for that record, and manual editing was needed to clean up the database.

For PIM Table 2, the NLM drug portal was used to find all the medication names associated with a medication class. This was not a truly automated process, and drug class coding standards were not used. Medication classes were typed into the portal to find associated medication names, and a SAS program was created to map the medication names to RXCUI values using RxNorm APIs. In addition, ICD9 values were manually

mapped to a patient's likely disease. This study would have benefited from automation and tools to convert diagnosis text to ICD9 codes, just as this study utilized NLM APIs to convert medication names to RXCUI values.

For MRCI Table A, the SAS program created to generate dose form RXCUI values, based on medication RXCUI values, was created for future use and was not validated with Dierich's data. The data did not consist of medication records that were stored by Semantic Clinical Drug (SCD), Semantic Clinical Drug Dose Form Group (SCDG) or Semantic Clinical Drug Form (SCDF).For MRCI Tables B and C, informatics standards were not used, and custom codes were created for dose frequency and special instructions.

The rapid expansion of electronic health records with common or relatable terminologies – increased by federal meaningful use financial incentives for hospitals and clinics(Heisey-Grove, Danehy, Consolazio, Lynch, & Mostashari, 2014) – would address some of the limitations experienced in this study. The standardization of prescription information is necessary so that physicians can review the safety of drug regimens with patients who transition out of hospitals or to new levels of care. A secondary benefit beyond this process of medication reconciliation is more consistency in the format of prescription information for data preparation and analysis. Federally funded projects such as SHARPn also are developing open source tools that extract clinical text from disparate EHRs and "normalize" it for secondary analysis.(Rea et al., 2012) An attempt at using the HRMR algorithm in this study with a dataset prepared under today's EHR conditions and requirements would likely result in fewer setup problems.

5. Conclusion

The tool developed in this study is a novel approach for assessing medication-related readmission risks that can be replicated and applied across hospital and health care recordkeeping systems. The APIs available through the NLM website, and the crosswalks generated, allow the algorithm to be adapted and adjusted in other systems for future clinical analysis and research. An important next step is to adjust criteria in the automated algorithm to determine optimal cut-points that separate patients at higher risk of hospitalization from patients who have lower risk based on their high risk medication regime scores. The scores of 2.5, 2, 1.5 and 1 that Dierich used for PIM calculations were arbitrary based on clinical judgment. Future users could determine that greater scoring weight should be given to certain medications, such as those presenting the greatest risks of severe adverse outcomes. Using the algorithm to identify the most sensitive scores and cut-points will hasten the use of HRMR as a meaningful source of patient information in clinical, hospital and home health care systems.

Figure 1

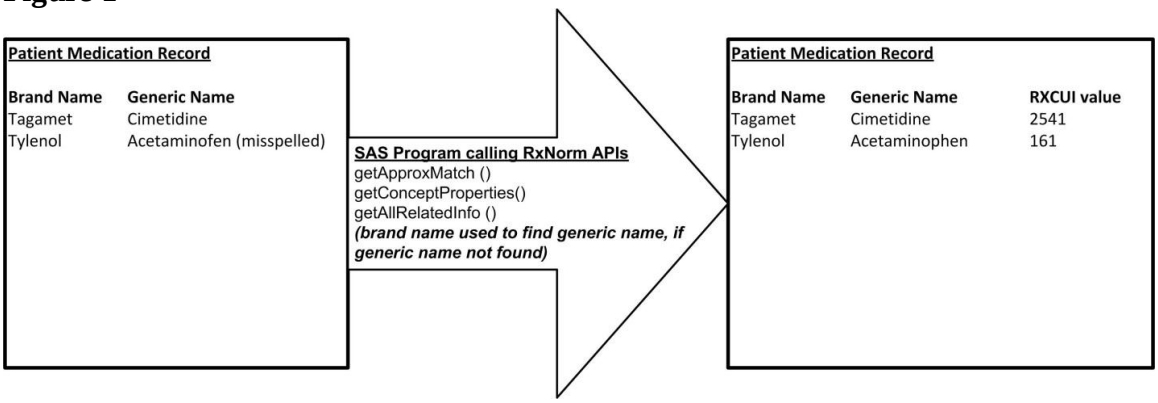


Figure 2

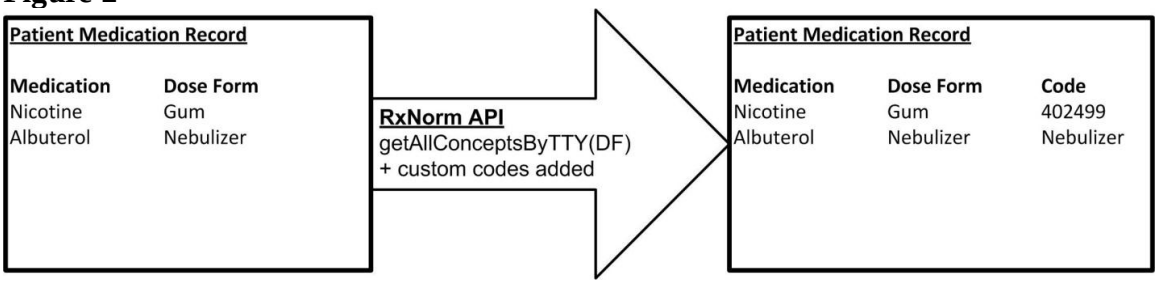


Figure 3

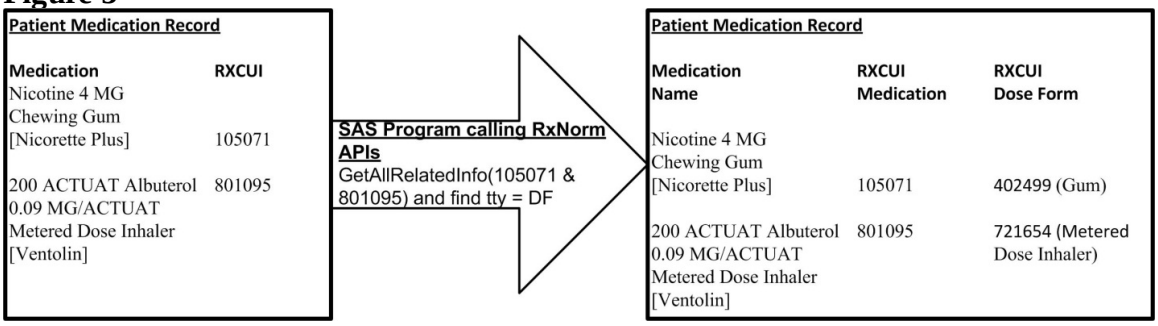


Figure 4

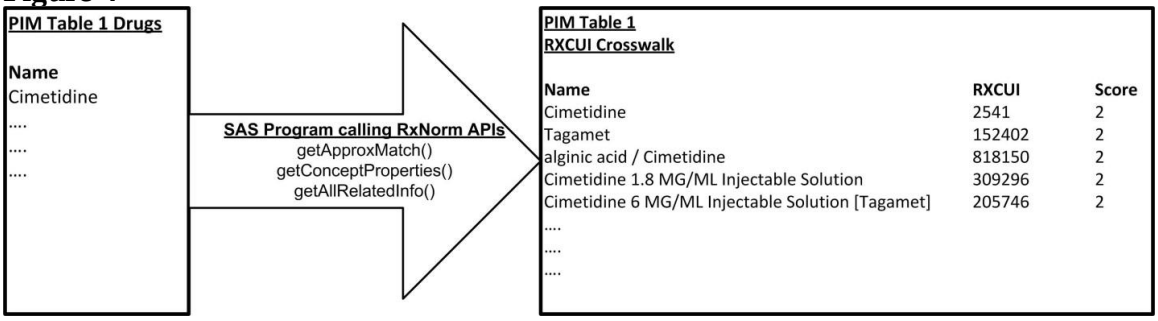


Figure 5

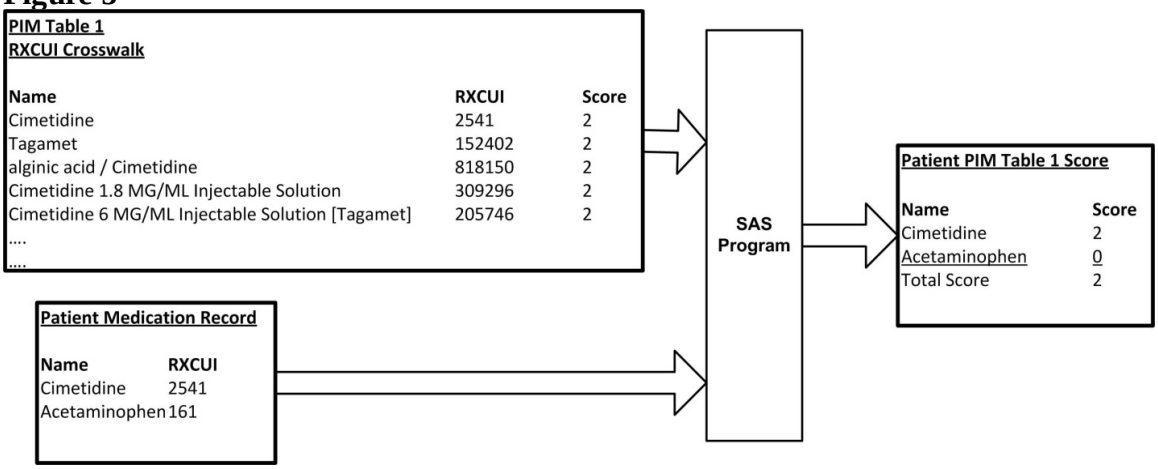


Figure 6

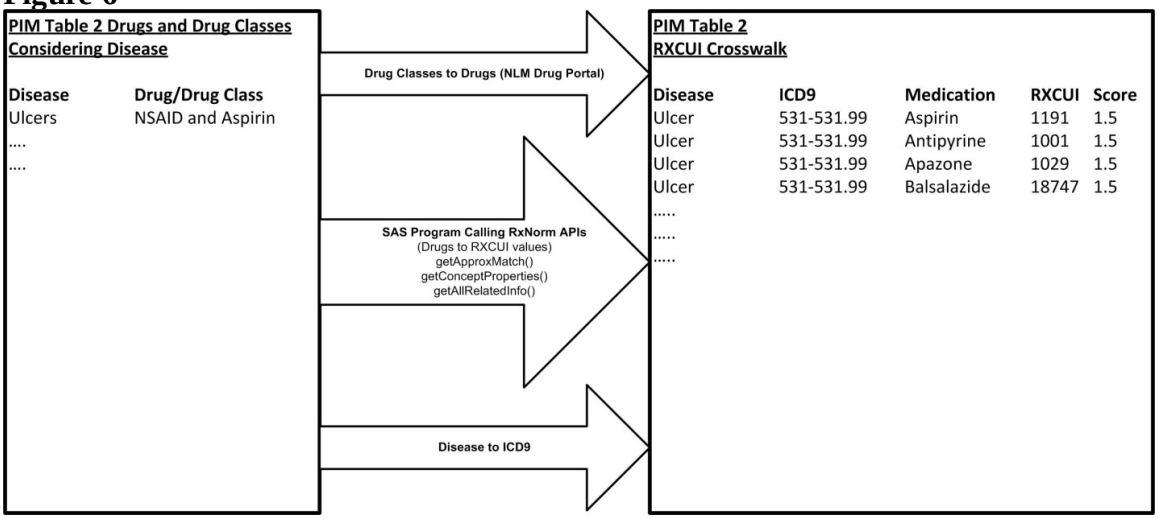


Figure 7

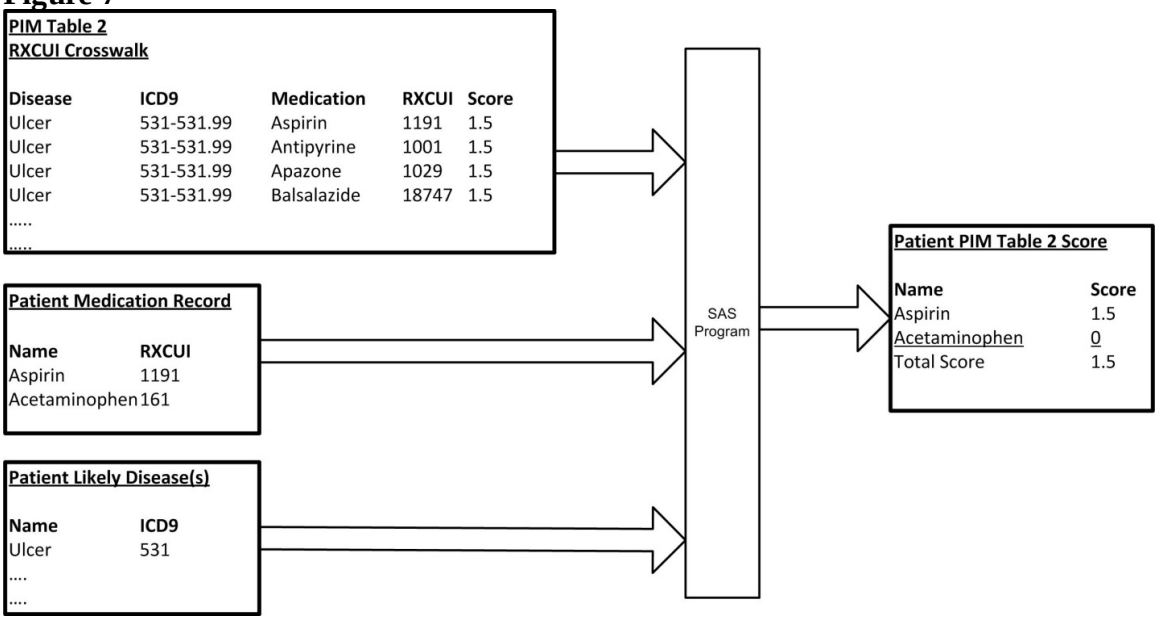


Figure 8

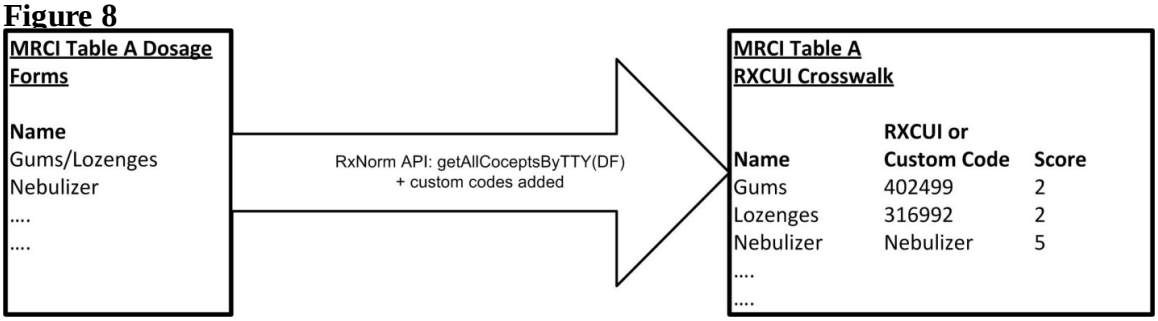


Figure 9

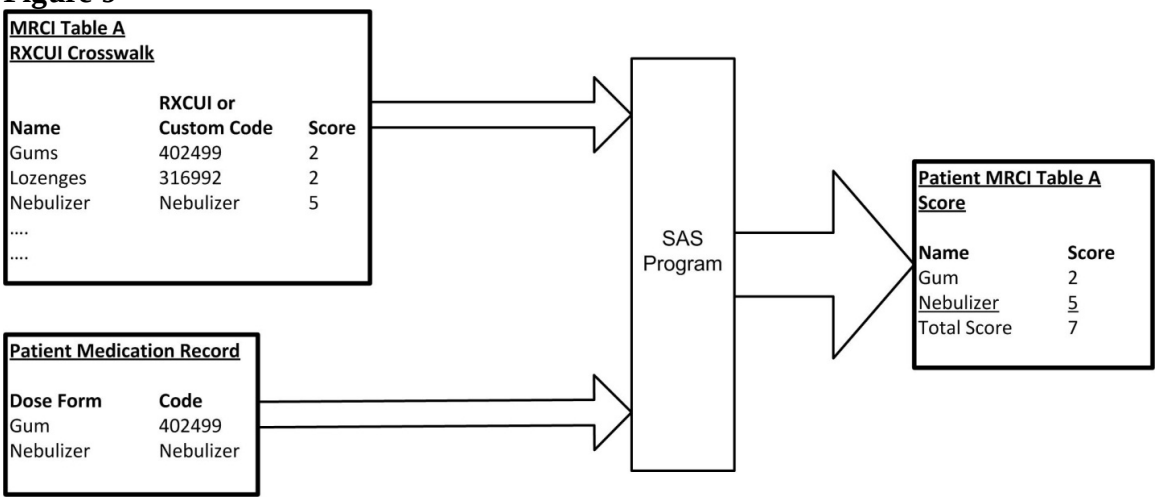


Figure 10

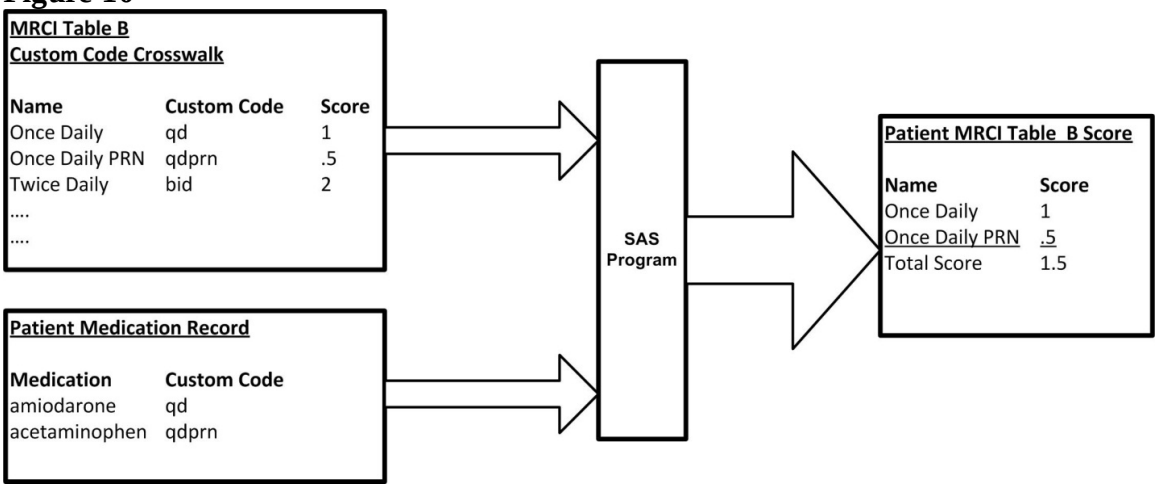
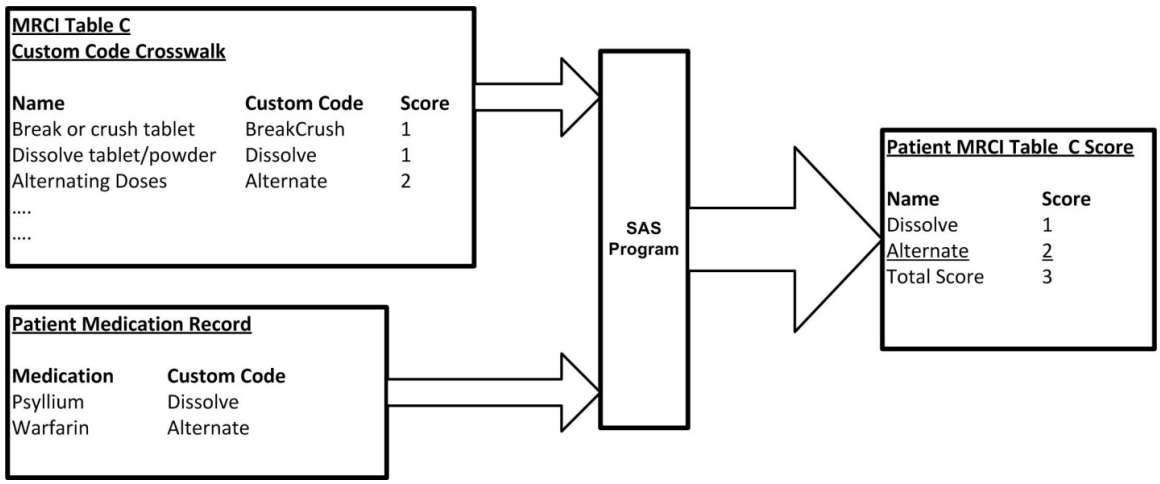


Figure 11


MRCI Table C
Custom Code Crosswalk
Name
Custom Code
Score
Break or crush tablet
BreakCrush
1
Dissolve tablet/powder
Dissolve
1
Alternating Doses
Alternate
2
....
....
Patient Medication Record
Medication
Custom Code
Psyllium
Dissolve
Warfarin
Alternate
SAS Program
Patient MRCI Table C Score
Name
Score
Dissolve
1
Alternate
2
Total Score
3

Paper 2:

Optimization of Decision Support Tool using Medication Regimens to Assess Rehospitalization Risks

Optimization of Decision Support Tool using Medication Regimens to Assess Rehospitalization Risks

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Background: Unnecessary hospital readmissions are costly for the U.S. health care system. An automated algorithm was developed to target this problem and proven to predict elderly patients at greater risk of rehospitalization based on their medication regimens.

Objective: Improve the algorithm for predicting elderly patients' risks for readmission by optimizing the sensitivity of its medication criteria.

Methods: Outcome and Assessment Information Set (OASIS) and medication data were reused from a study that defined and tested an algorithm for assessing rehospitalization risks of 911 patients from 15 Medicare-certified home health care agencies. Odds Ratio analyses, literature reviews and clinical judgments were used to adjust the scoring of patients' High Risk Medication Regimens (HRMRs). Receiver Operating Characteristic (ROC) analysis evaluated whether these adjustments improved the predictive strength of the algorithm's components.

Results: HRMR scores are composed of polypharmacy (number of drugs), potentially inappropriate medications (PIM) (drugs risky to the elderly), and Medication Regimen Complexity Index (MRCI) (complex dose forms, dose frequency, instructions or administration). Strongest ROC results for the HRMR components were Areas Under the Curve (AUC) of .68 for polypharmacy when excluding supplements; and .60 for PIM and .69 for MRCI using the original HRMR criteria. The "cut point" identifying MRCI scores as indicative of medication-related readmission risk was increased from 20 to 33.

Conclusion: The automated algorithm can predict elderly patients at risk of hospital readmissions and its underlying criteria is improved by a modification to its polypharmacy definition and MRCI cut point.

Keywords: Patient readmission, Polypharmacy, Medication Adherence, Home Care Agencies, ROC Curve.

1. Introduction

Medications can both enhance health and cause adverse events, particularly for older adults, whose prescription regimens increase with age and chronic health problems.(Hung, Ross, Boockvar, & Siu, 2011) Nine in ten older adults take at least one prescription medication and most take more than five.(Qato et al., 2008) The combination of health conditions and chemical ingredients in medications can increase older adults' risk of adverse events and need for emergency medical care.(Centers for Disease Control and Prevention (CDC), 2012) Avoidable readmissions to hospitals have been linked to problems with medication usage,(Freund et al., 2013; Kripalani, Theobald, Anctil, & Vasilevskis, 2013) but efforts to identify and predict which patients suffer this adverse event have been mixed. Studies have explored a connection between readmissions and the numbers of drugs patients take (polypharmacy)(Morandi et al., 2013; Sganga et al., 2014), their use of potentially inappropriate medications (PIM)(Price et al., 2014a; Price, Holman, Sanfilippo, & Emery, 2014b; Sehgal et al., 2013), and the complexities of the doses or forms of their medications (Medication Complexity Index (MRCI))(Willson et

al., 2014; Wimmer et al., 2014). Mary Dierich theorized that limitations of these individual medication measurements might be addressed by constructing them into a combined measurement, the High Risk Medication Regimen (HRMR). In an initial study of 911 elderly home health care patients, HRMRs accounted for 10 percent of the variance in hospital readmissions, making them more predictive than comorbidity. (Dierich, 2010)

The potential utility of HRMR as a clinical decision support tool to prevent avoidable readmissions – which can now result in federal Medicare penalties if hospitals report too many of them(Abelson, 2013) – was tempered by the labor-intensive process in the original study for calculating the scores. Further research subsequently developed an automated tool that maps medication data to RxNorm coding standards and created an algorithm with the coded medication data to calculate patients' HRMR scores.(Olson et al., 2014) The standardized format of the coded data addressed some of the practical challenges of using HRMR for clinical decision support, and also made the algorithm potentially useable across different electronic health record (EHR) systems and health care organizations. Automating the calculation also allowed for more rapid testing of the criteria underlying this new combined measurement and the "cut points," which were manually selected based on the researchers' clinical expertise and literature review, that distinguish patients at high and low risk of rehospitalization. This study sought to take advantage of that advancement by testing adjustments to the HRMR criteria and to the cut points to determine the optimal calculation for predicting medication-related rehospitalizations of elderly home health care patients.

1.1 Objectives

The objective of this study was to improve the automated algorithm for predicting hospital readmissions by optimizing the underlying criteria within the algorithm and determining the optimal cut points for HRMR scores. Optimizing the algorithm's criteria is a key next step in advancing the HRMR concept toward clinical utility.

2. Methods

2.1. Data Set

This study used Outcome and Assessment Information Set (OASIS) and medication records for 911 adults from 15 Medicare-certified home health care agencies that were used in previous studies.(Dierich, 2010; Olson et al., 2014) The medication records included both prescription and over-the-counter medications taken by patients in their homes and recorded by home care clinicians in their EHRs. Medication data included the medication names, doses, dose forms, frequencies and special instructions. OASIS data for the patients, all of whom were at least 65 and were admitted from the hospital to the home health care agencies in 2004, included demographic, environmental, support system, health and functional status, and health service utilization information.(Centers for Medicare and Medicaid Services (CMS), 2012a)

2.2. Data Analysis

Dierich operationalized the medication data by first calculating polypharmacy, PIM and MRCI scores based on patients' drug regimens, and then using summative

factor analysis to construct those weighted scores into a combined HRMR measurement.(Dierich, 2010) The original HRMR research defined polypharmacy as nine or more medications. Scores of "0" were assigned for patients with fewer than 9 medications, and "1" for patients with 9 or more medications.

Scores for PIM were based on the 2003 version of the Beers' criteria, a list of 48 drugs and 20 drug classes that the elderly should avoid. In defining the Beers' criteria, Fick et al. (Fick et al., 2003) differentiated drugs by whether or not they posed risks of severe adverse outcomes, and whether they were inappropriate for older adults regardless of diagnosis (PIM schedule 1) or inappropriate depending on the diagnosis (PIM schedule 2). The initial HRMR research assigned weighted scores of 2.5 to medications that were always inappropriate and carried the greatest risks, 2 for medications with lower risks of severe outcomes, 1.5 for medications with the highest risks for certain diagnoses, and 1.0 for medications with lower risks for certain diagnoses. (Drugs that met multiple criteria received the higher score.) The medication scores were then summed to provide a total PIM risk level score for each patient.

The original HRMR research used a modified version of the Medication Regimen Complexity Index developed by George et al. (George et al., 2004) that weighted drugs by three subscales – by the complexity of their route (MRCI Schedule A), their dosing frequency (MRCI Schedule B), and the complexity of their directions or preparation (MRCI Schedule C) – and then combined the subscale scores into a summary score (Figure IV). A summary score cut point of 20 or above was set in the original HRMR

research as an indication of high medication regimen complexity, though it was an "arbitrary" distinction due to the lack of prior research.(Dierich, 2010)

This method of assigning weighted scores to predictive variables is similar to what was used in the development of the Charlson index of comorbidity for predicting mortality risks,(M. Charlson, Szatrowski, Peterson, & Gold, 1994) and another recent analysis that identified factors for predicting early and preventable rehospitalizations after kidney transplants.(Harhay et al., 2013)

2.2.1. ROC Analysis. Receiver Operating Characteristic (ROC) curves were used in this study to evaluate optimization of the algorithm and determine optimal cut points for the HRMR components (Polypharmacy, PIM, and MRCI) associated with rehospitalization. The ability to identify cut points is considered an advantage of ROC analysis.(Hajian-Tilaki, 2013) The area under the ROC curves (AUC) can be interpreted in this study as the probability of correctly predicting rehospitalization, based on sensitivity and specificity. The closer the AUC is to 1, the better the measure. An AUC resultabove .7 is considered meaningful by one generic value scale(Tape,), but studies have characterized results between .6 and .7 as "moderate" or "good."(Akyuz, Alpsoy, Akkoyun, Degirmenci, & Guler, 2014; Cheung, 2014; Heng et al., 2014; Hiersch et al., 2014; Malik, Banning, & Gershlick, 2014) ROC curves are frequently used to assess the value of predictive measures, and have been used to optimize the analysis of patients who had poor outcomes after hospitalization for inflammatory pelvic disease,(Terao et al., 2013) and to create a prognostic index of patient mortality after intensive care.(Cardoso & Chiavone, 2013)

In using the ROC results to select cut points for the HRMR components, the authors reviewed common mathematical approaches such as the Youden index(Greiner, Pfeiffer, & Smith, 2000) but opted on a customized approach in an attempt to account for the prevalence of hospital readmissions and also the expense of testing overall and of false positive results. The authors had to fundamentally decide whether to err in the selection of cut points on the side of sensitivity (the ability of a test to correctly identify people with a medical condition) or on specificity (the ability to rule out people who don't have a particular disease or medical problem). The dilemma has been described, respectively, as whether a test should "rule in" patients for further consideration of a medical issue, or "rule out" their risks.(Florkowski, 2008) A "rule in" approach was adopted here, with the presumption that clinicians would use an HRMR screening to evaluate patients at risk and then conduct further clinical assessments of their needs. This favored cut points weighing more heavily on sensitivity, at the expense of specificity and a higher rate of false positive results. An initial target of .75 for sensitivity and .50 for specificity was chosen for the revision of cut points for the HRMR components.

2.2.2. Odds Ratio. Odds ratio (OR) computations were used to test the strength of the relationship between HRMR and rehospitalization risks and compare the original scoring criteria with newly derived HRMR scoring criteria using ORs. Odds ratios indicated whether the relative odds of the occurrence of rehospitalization were different for each of the independent variables that make up PIM (disease and medication class, and medications) and MRCI (dose form, instructions, and frequency). The intent was for the relative odds of the independent variables to be applied to the HRMR algorithm to see

if they generated better AUC curve results and more optimal cut points for predicting rehospitalization rather than the original scoring criteria.

2.3. Data Transformations

Adjustments to the original HRMR scoring criteria were made based on clinical observations and expertise of the authors – a doctorally prepared informatician, a geriatric nurse practitioner, a nurse researcher with expertise in geriatrics and home health care data, and a physician who is also a clinical pharmacist. These transformations were attempted to optimize the criteria of the algorithm and the HRMR cut points, and the methodologies behind them are described below:

2.3.1. Polypharmacy

PRN medications (taken as needed), over-the-counter medications, and medications with limited dosing time such as antibiotics were included in the original HRMR research, while other more benign items such as oxygen or saline to dilute IV medications were excluded. Combination and variable dosed drugs were counted as one drug.

Based on clinical judgment and polypharmacy criteria in other recent publications,(Abdulraheem, 2013; Beloosesky, Nenaydenko, Gross Nevo, Adunsky, & Weiss, 2013) this study modified the polypharmacy scoring for HRMR calculations by excluding acetaminophen, vitamins, supplements, and PRN medications from the medication count. ROC curves were used to compare the predictive strength of the original HRMR scoring with these modified scores.

2.3.2. Potentially Inappropriate Medications

This analysis modified the PIM scoring criteria, based on clinical observation and a review of recent publications regarding adverse drug events related to certain drug classes.Two additional higher-risk categories were created for selected drugs in PIM schedule 1 (those always inappropriate regardless of diagnosis) and assigning them greater scoring weights (Table 1).

- Highest (assigned weight of 10) included antispasmodics and long-acting benzodiazepines due to adverse central nervous system effects and dementia and increased sensitivity with age. Antispasmodics also have uncertain effectiveness and are highly anticholinergic while the benzodiazepines present an elevated risk of falls.(American Geriatrics Society 2012 Beers Criteria Update Expert Panel, 2012)
- Medium (assigned weight of 5) included digoxin due to potential toxic effects and nitrofurantoin and thioridazine due to known risks and the availability of safer alternatives for the treatments, respectively of infections and psychosis.
- Remaining PIM schedule 1 drugs retained their assigned weights (2.5 and 2) from the original analysis as did schedule 2 drugs (1.5 and 1).

Odds ratio analysis also was applied to PIM schedules 1 and 2 using the independent variables of high-risk medications and medications with disease-specific risks in the elderly. The intent of this analysis was to apply the relative odds of

rehospitalization for each of the independent variables to the algorithm to determine if they were stronger than the weighted scores in the original HRMR research.

ROC analysis then was used to see if either of the modified PIM scoring criteria – one derived from clinical judgment and literature review, the other from the OR analysis – were better at identifying patients needing rehospitalization than the original scoring criteria.

2.3.3 Medication Regimen Complexity Index (MRCI).

ROC analysis then compared the predictive strength of MRCI in identifying patients who will be rehospitalized against modified criteria, including MRCI schedules A, B and C individually; and schedules A and C together only. The latter was done to address a theory that schedule B (dosing frequency) might be redundant with polypharmacy.

In addition, odds ratio analyses were applied to schedules A, B, and C using independent variables of dose form, frequency and special dosing instructions to understand the relative odds of rehospitalization. The intent of this analysis was to apply the relative odds of rehospitalization for each of the independent variables to the algorithm instead of George's original weighted scores. ROC analysis was again used to test the independent variables and whether they optimized the algorithm.

3. Results

Table 2 summarizes results of the ROC analyses.

3.1 Polypharmacy

Removing vitamins and supplements from the medication counts improved the AUC slightly (.66 vs. .68) (Figure I). Removing PRN medications did not improve the AUC (.66) and removing acetaminophen caused the AUC to decrease (.64). Using the criteria that produced an AUC of .68 (the analysis in which vitamins and supplements were removed), the optimal cut point remained 9. This was based on a true positive rate of .77 and a false positive rate of .53.

3.2 Potentially Inappropriate medications (PIM)

The original automated PIM algorithm produced an AUC curve of .6 (Figure II). When weights based on clinical observation were applied to the algorithm, there was no improvement to the original HRMR weights, producing a curve of .59.

When the odds ratio analysis was applied to each independent variable (risky medications) in PIM schedule 1 (Table III) and each independent variable (risky medications considering diagnosis) in PIM schedule 2 (Table IV), the resulting models produced confidence intervals which contained one for each independent variable, meaning the model was not valid.

Therefore, there was no support of an independent PIM effect on the odds of the outcome (rehospitalization)). As a result, adjusted weights based on odds ratio analysis were not applied to the algorithm to improve the AUC curve of .60.

3.3. Medication Complexity Index (MRCI)

MRCI schedules A, B, and C, when calculated separately, showed similar results (.68, .68, .69) as when all MRCI schedules were calculated together (.69). (Figure III) A cut point of 33, higher than the original 20, produced a true positive rate of .76 and a false positive rate of .49 – meeting the goal in the study for establishing HRMR as a rule-in test for readmission risks. When the odds ratio analysis was run on each component of schedule A, B, and C, the only schedule which produced a statistically valid model was C. Schedules A and B produced models in which each of the independent variables had confidence intervals which contained 1. Therefore, dose form and frequency were not supported to have an independent effect on the relative odds of the outcome (rehospitalization). Schedule C's model produced valid confidence intervals for 7 of 10 independent variables. (Table V) The other three variables were removed from the model as their confidence intervals also were weak.

Rounding to the nearest whole number, each point estimate is identical to George's original weights for the MRCI variables. (Figure IV) The only exception is the variable for "multiple units at one time"; the odds ratio analysis gave that a greater rounded weight (2 points) than George's original analysis (1 point). After rerunning the ROC curve for MRCI with these modified weights, the AUC remained unchanged at .69. Using the actual results from the Odds Ratio analysis, instead of rounding to match George's methodology, produced a slightly stronger .7 AUC result for schedule C's influence on rehospitalization risks.

4. Discussion

This study determined optimal criteria for an algorithm using HRMR scores to predict elderly patients at risk for rehospitalization, and contributed to an acceleration of research in the area of medications and hospital readmissions. Two other studies both attributed hospital readmissions in the elderly to polypharmacy(Morandi et al., 2013; Sganga et al., 2014) – though they used different criteria – while a third concluded that both polypharmacy and PIM are "under recognized causes of readmissions to the hospital."(Sehgal et al., 2013) But while the components of HRMR draw increasing research interest, there has been little follow-up to the initial discovery that HRMR is uniquely associated with hospital readmission risks.(Dierich, 2010) This could owe to the fact that HRMR and the MRCI component itself are relatively new to medical research. PubMed shows only 33 studies referring to MRCI, with one associating it with hospital readmissions in the elderly.(Willson et al., 2014)

The ROC analysis supported that polypharmacy is a strong component of the HRMR model, and was slightly more predictive of rehospitalizations when vitamins and supplements were removed from patients' drug counts. This exclusion mimics approaches used in other studies(Beloosesky et al., 2013) and argues in favor of removing vitamins and supplements from future studies linking polypharmacy to rehospitalization and related outcomes. Supplements are not risk-free for seniors,(Mursu, Robien, Harnack, Park, & Jacobs, 2011) but they are widely taken for general health.(Kaufman, Kelly, Rosenberg, Anderson, & Mitchell, 2002) Removing them might have sharpened the algorithm's ability to identify rehospitalizations by focusing on sicker

patients whose high polypharmacy counts consisted of more prescription medications. The results were weakened by the removal of acetaminophen, which also is taken broadly by seniors for general pain relief,(Kaufman et al., 2002) but has documented risks such as drug-induced liver injury(Leise, Poterucha, & Talwalkar, 2014; Yuan & Kaplowitz, 2013) that could make it more relevant to this HRMR analysis.

An ancillary benefit of the study is its contribution to the global definition of polypharmacy. The original HRMR cut point for polypharmacy was 9 or more drugs, one that is commonly but not exclusively used in research, and further analysis showed a polypharmacy cut point of 9 optimized the algorithm and the prediction of patients at risk for rehospitalization. This could serve as a guide for future research.

Results for PIM schedules showed they were weaker components of the HRMR calculation in estimating patient rehospitalization risks. PIM in other studies has had a dependent relationship with polypharmacy, in that the more drugs elderly patients have, the more likely they are to have inappropriate prescriptions in their regimens.(Vieira de Lima, Garbin, Garbin, Sumida, & Saliba, 2013; Weng et al., 2013). Attempts to strengthen PIM by revising cut points were unsuccessful in this study as the AUC curves produced were only slightly better than chance. While at least one study has associated PIM with readmissions,(Price et al., 2014a) our findings agree with other studies that have found PIM alone to be predictive of other problems, such as inpatient falls, but not rehospitalization.(Borenstein et al., 2013) Despite its weak relationship to rehospitalizations on its own, PIM nonetheless appears an important component of the HRMR construct. Dierich's original study found HRMR to be "more than the sum of its

parts" and that PIM played a role in its predictive strength.The original MRCI scoring weights from George's research also proved optimal, though adjustments based on an odds ratio analysis did modestly improve the predictive strength of schedule C (drugs with special instructions). ROC results for both HRMR components approached .7, which is a statistical threshold. This analysis also adjusted the cut point that distinguishes patients at greater risk of rehospitalization to 33 for MRCI (the original cut point in the HRMR calculation was 20). This is one of the first attempts in research literature at establishing such a cut point for the use of MRCI in predictive tests.

This study suggests a need for more targeted research on HRMR scores and whether they can predict adverse outcomes among the elderly in ways that other measures of medications and medication regimens cannot.

4.1 Limitations

Odds ratio and ROC analysis are common validation tools in medical research for the development of predictive tools and indexes, but they are ultimately dependent upon the criteria and information selected for analysis. Medical researchers have not arrived on a common definition for polypharmacy, with cut points often ranging from 2 to 9,(Hajjar, Cafiero, & Hanlon, 2007) and have varied in their inclusion of over-the-counter medications. This study used a PubMed literature search and clinical judgments of its authors to decide which medications and medication classes to exclude from the weighted scoring of both polypharmacy and PIM in the calculations of HRMR scores. Due to the broad number of drug inclusion and exclusion combinations, it is possible that relevant adjustments to the weighted scores were not tested and identified in this research. For

continuity with Dierich's original HRMR research, it was necessary to use the original 2003 Beers criteria, though a significant update was produced in 2012.(American Geriatrics Society 2012 Beers Criteria Update Expert Panel, 2012) Although the two lists have "substantial agreement,"(Baldoni et al., 2013) nineteen classes of drugs were removed in the latest update – in some cases because the drugs were removed from the U.S. market – while other common medications such as atypical antipsychotics were added. Further research using the updated criteria and its inclusion of antipsychotics and other medications could alter how PIM counts contribute to research involving HRMRs and to the strength of HRMRs in predicting readmission risks.

5. Conclusion

HRMR calculations are optimized by adjusting the underlying criteria of polypharmacy to exclude supplements and vitamins from the count of medications, and by increasing the MRCI cut point that distinguishes patients by their medication-related risks for hospital readmissions. While modest, the changes strengthen the case for an HRMR algorithm that clinicians can use to assess elderly patients' risks for avoidable readmissions.Next steps include testing the automated HRMR algorithm with the prescription and OASIS data of different populations to see if can be optimized further.

Clinical Relevance Statement

This report is the next step in operationalizing for clinicians and researchers an automated algorithm which has proven to predict elderly home care patients at risk for unnecessary hospital readmissions.

Conflict of Interest

The authors report no conflicts of interest in the production of this paper.

Human Subjects Protections

This study was reviewed by a university Institutional Review Board and meets the human protections criteria set forth by the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects.

Tables

Table 1: Potentially Inappropriate Medications: Independent of Diagnoses or Conditions, from Fick et al. (2003, p. 2719), used with permission.
New Scoring: **Highest (10), *Medium (5)
Note: Remaining PIM Table 1 drugs retained their assigned weights (2.5 and 2).

Drug/Drug Combinations with the Active Ingredient	Low Risk	High Risk
Propoxyphene (Darvon)	X	
Indomethacin (Indocin)		X
Pentazocine (Talwin)		X
**Muscle relaxants and antispasmodics: methocarbamol (Robaxin), carisoprodol (Soma), chlorzoxazone (Paraflex), metaxalone (Skelaxin), cyclobenzaprine (Flexeril), and oxybutynin (Ditropan). Do not consider the extended-release Ditropan XL.		X
**Flurazepam (Dalmane)		X
**Amitriptyline (Elavil), chlordiazepoxide-amitriptyline (Limbitrol), and perphenazine-amitriptyline (Triavil)		X
Doxepin (Sinequan)		X
Meprobamate (Miltown and Equanil)		X
Doses of short-acting benzodiazepines: doses greater than lorazepam (Ativan), 3 mg; oxazepam (Serax), 60 mg; alprazolam (Xanax), 2 mg; temazepam (Restoril), 15 mg; and triazolam (Halcion), 0.25 mg		X
**Long-acting benzodiazepines: chlordiazepoxide (Librium), chlordiazepoxide-amitriptyline (Limbitrol), clidinium-chlordiazepoxide (Librax), diazepam (Valium), quazepam (Doral), halazepam (Paxipam), and chlorazepate (Tranxene)		X
Disopyramide (Norpace and Norpace CR)		X
*Digoxin (Lanoxin) (should not exceed _0.125 mg/d except when treating atrial arrhythmias)	X	
Short-acting dipyridamole (Persantine). Do not consider the long-acting dipyridamole (which has better properties than the short-acting in older adults) except with patients with artificial heart valves	X	

Methyldopa (Aldomet) and methyldopa-hydrochlorothiazide (Aldoril)		X
Reserpine at doses > 0.25 mg	X	
Chlorpropamide (Diabinese)		X
*Gastrointestinal antispasmodic drugs: dicyclomine (Bentyl), hyoscyamine (Levsin and Levsinex), propantheline (Pro-Banthine), belladonna alkaloids (Donnatal and others), and clidinium-chlordiazepoxide (Librax)		X
**Anticholinergics and antihistamines: chlorpheniramine (Chlor-Trimeton), diphenhydramine (Benadryl), hydroxyzine (Vistaril and Atarax), cyproheptadine (Periactin), promethazine (Phenergan), tripelennamine, dexchlorpheniramine (Polaramine)		X
**Diphenhydramine (Benadryl)		X
Ergot mesyloids (Hydergine) and cyclandelate (Cyclospasmol)	X	
Ferrous sulfate >325 mg/d	X	
**All barbiturates (except phenobarbital) except when used to control seizures		X
**Meperidine (Demerol)		X
Ticlopidine (Ticlid)		X
**Ketorolac (Toradol)		X
**Amphetamines and anorexic agents		X
Long-term use of full-dosage, longer half-life, non–COX-selective NSAIDs: naproxen (Naprosyn, Avaprox, and Aleve), oxaprozin (Daypro), and piroxicam (Feldene)		X
Daily fluoxetine (Prozac)		X
Long-term use of stimulant laxatives: bisacodyl (Dulcolax), cascara sagrada, and Neoloid except in the presence of opiate analgesic use		X
*Amiodarone (Cordarone)		X
Orphenadrine (Norflex)		X
Guanethidine (Ismelin)		X

Guanadrel (Hylorel)		X
Cyclandelate (Cyclospasmol)	X	
Isoxsurpine (Vasodilan)	X	
*Nitrofurantoin (Macrodantin)		X
*Doxazosin (Cardura)	X	
Methyltestosterone (Android, Virilon, and Testrad)		X
*Thioridazine (Mellaril)		X
Mesoridazine (Serentil)		X
Short acting nifedipine (Procardia and Adalat)		X
Clonidine (Catapres)	X	
Mineral oil		X
Cimetidine (Tagamet)	X	
Ethacrynic acid (Edecrin)	X	
Desiccated thyroid		X
Amphetamines (excluding methylphenidate hydrochloride and anorexics)		X
Estrogens only (oral)	X	

Table 2: Summary Results – ROC Analysis

Polypharmacy	**AUC**
Original Dierich - Manual & Automated	0.66
PRN Medications Only	0.65
All Medications except PRN	0.64
All Medications except acetaminophen	0.66
All Medications except vitamins and supplements	0.68
PIM	**AUC**
Original PIM Manual	0.6
Original PIM Automated	0.59
Clinical Expertise - Modified 4 Scale	0.59
MRCI	**AUC**
Original Dierich	0.69
Table A&C Only	0.69
Table A	0.68
Table B	0.68
Table C	0.69
Odds Ratio	0.69

Table 3: PIM Table 1- Sample Odds Ratio Analysis Results

Odds Ratio Estimates			
Effect	Point Estimate	95% Wald Confidence Limits	
Alprazolam	0.90	0.29	2.75
amitriptyline	0.51	0.18	1.47
Bisacodyl	1.42	0.81	2.49

Table 4: PIM Table 2- Sample Odds Ratio Analysis Results

Odds Ratio Estimates			
Effect	Point Estimate	95% Wald Confidence Limits	
Chronic Constipation and CCB	0.91	0.68	1.22
Clot Disorder and NSAID	0.78	0.48	1.25
Parkinson's and Antipsychotics	2.93	0.59	14.53

Table 5: MRCI Odds ratio analysis for Table C

Odds Ratio Estimates			
Effect	Point Estimate	95% Wald Confidence Limits	
Variable dose	1.34	1.09	1.65
Take/use at specified time/s	1.33	1.11	1.58
Tapering/increasing dose	2.52	2.27	2.79
Alternating dose	1.69	1.31	2.18
Take/use as directed	2.39	2.19	2.60
Relation to food	1.51	1.35	1.70
Multiple units at one time	1.85	1.56	2.20
Dissolve tablet/powder**	1.29	0.83	1.99
Break or crush tablet**	1.23	0.84	1.81
Take with specific fluid**	1.75	0.32	9.54

**Variables removed from model due to weak confidence intervals.

Figures

Figure 1: ROC Curves for Polypharmacy

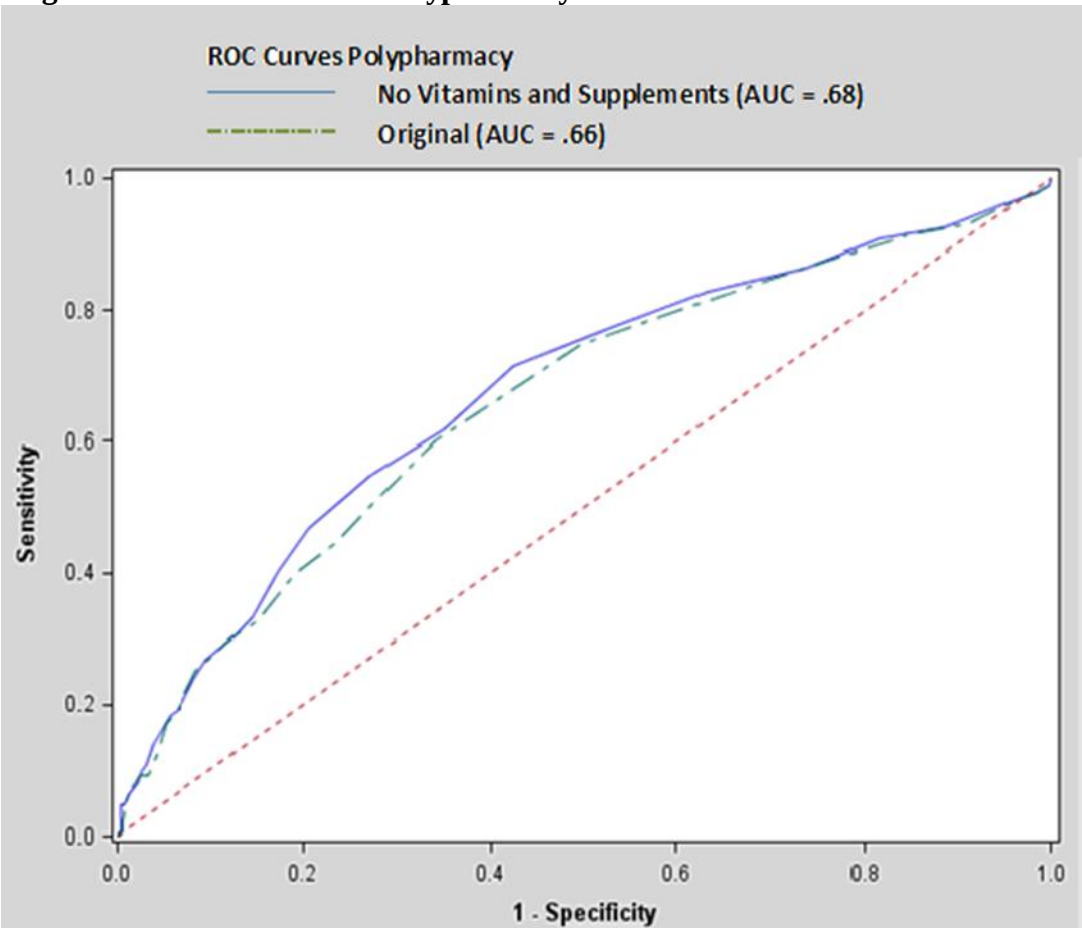


Figure 2: ROC Curve for PIM

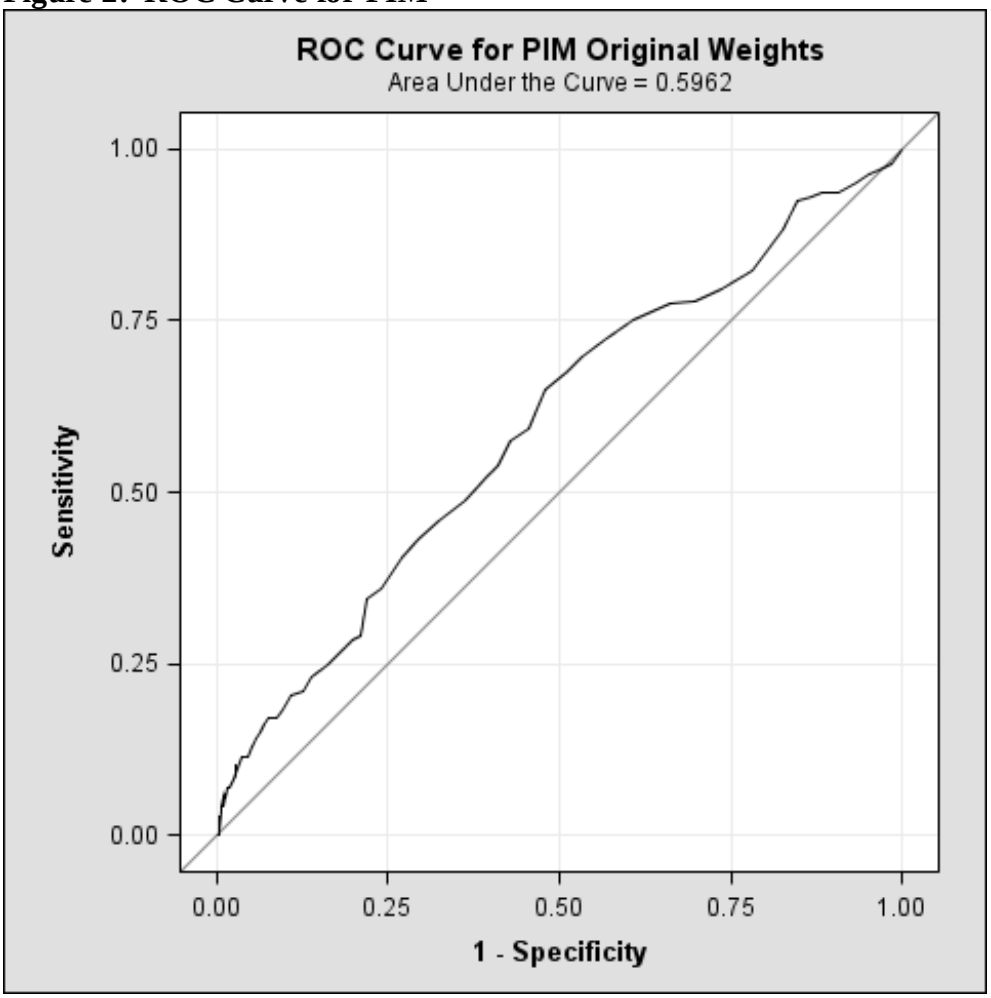
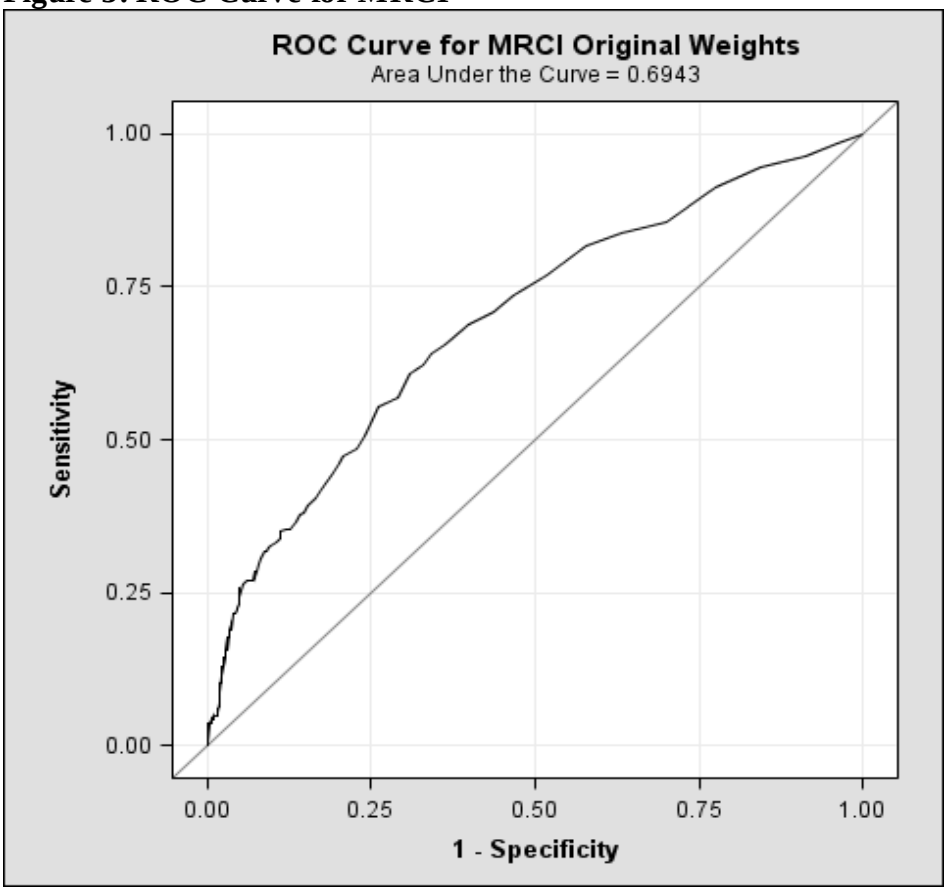


Figure 3: ROC Curve for MRCI



Paper 3:

Clustering of Elderly Patient Subgroups to Identify Medication-Related Readmission Risks

Clustering of Elderly Patient Subgroups to Identify Medication-Related Readmission Risks

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Introduction: High Risk Medication Regimen (HRMR) scores are weakly predictive of hospital readmissions for elderly home health care patients. One possibility is that HRMR scores are more predictive for demographic subgroups of elderly patients. HRMR is composed of three elements related to drug risks: polypharmacy (number of medications); Potentially Inappropriate Medications (PIM) known to be harmful to the elderly; and the Medication Regimen Complexity Index (MRCI) that weighs drugs by the complexity of their dosing and instructions. This study used Outcome and Assessment Information Set (OASIS) variables to identify subgroups of patients for whom the HRMR measures appeared more predictive for hospital readmissions.

Methods: OASIS and medication data were reused from a study of 911 patients from 15 Medicare-certified home health care agencies that established the relationship between HRMR and hospital readmissions. Hierarchical agglomerative clustering using the Jaccard distance measure and average-link method identified patient subgroups based on the OASIS data. Receiver operating curve (ROC) analyses evaluated the predictive strength of the HRMR variables for each subgroup. Additional False Discovery Rate (FDR) analyses assessed whether the clustered relationships were chance.

Results: Clustering of OASIS data for 911 patients identified six subgroups (patients with good functional status, females with moderate to severe pain, patients with poor prognosis needing functional status assistance, patients with poor functional status, males with adult children as caregiver, adults living alone with spouses as primary caregiver.) ROC results relating these subgroups to HRMR risks were strongest for males with adult children as caregivers (AUC: polypharmacy, .73; PIM, .64; MRCI, .77). The

findings for this subgroup also met the FDR analysis threshold (<=.20).

Conclusions: A risk of medication-related readmissions in elderly men with adult children as caregivers is consistent with research showing problems in medication adherence when seniors are supported by informal caregivers. The results from clustering analysis present a hypothesis for research on HRMR and on the relationship between adult caregivers and their fathers.

Keywords: Patient Readmission, Caregiver, Cluster Analysis, home healthcare, High Risk Medication Regimen

1. Introduction

Reducing hospital readmissions has become a focus for U.S. hospitals and health care systems following research showing that a substantial number of them are unplanned(Jencks et al., 2009) and preventable(Kripalani et al., 2013), and that they result in as much as $25 billion each year in "wasteful" health care spending.(National Quality Forum, 2010a) Beyond the costs, preventing readmissions is a patient safety issue because hospital care in general exposes patients to risks, including adverse drug events, infections, delirium and cognitive decline.(Donze, Lipsitz, Bates, & Schnipper, 2013) While transitional and home health care strategies have been developed to prevent patients from needing readmissions,(Berry et al., 2011; Hunter, Nelson, & Birmingham, 2013; Markley, Sabharwal, Wang, Bigbee, & Whitmire, 2012) they are costly interventions if provided universally to patients upon their discharges.(Donze et al., 2013)

Identifying patients at greatest risk for hospital readmission has consequently become a priority. Medication usage by elderly homecare patients has emerged as an important indicator of hospital readmission risk (Morrissey et al., 2003; National Quality Forum, 2010a) with one study finding a composite measure of High Risk Medication Regimens (HRMR) more strongly associated with hospital readmissions than the presence of comorbid conditions.(Dierich, 2010) This was a substantial finding given the number of studies linking comorbidity to avoidable readmissions.(Donze et al., 2013; Librero, Peiro, & Ordinana, 1999; Zekry et al., 2012) Further analysis found these HRMR calculations could be automated and potentially integrated into clinical information systems to identify at-risk patients for hospital readmission and provide them with supportive and preventive services.(Olson et al., 2014) Opportunities to further identify the patients at greatest risk of HRMR-related hospital readmissions are possible due to home healthcare providers implementing electronic health record (EHR) systems and the development of data mining tools that can be used to find patterns within the EHR data. Data mining techniques have already been used to identify home healthcare patients that are more adaptive to assistive technology(S. Zhang et al., 2014) and those able to show greater improvement from incontinence(Westra et al., 2011). The purpose of this study was to apply data mining techniques to determine if certain clusters of patients were more likely to have high-risk drug regimens and consequently be at greater risk of hospital readmissions. The results could prove instructive to the hospitals and health systems trying to reduce their readmission rates – both to improve patient care and avoid new Medicare penalties for having more readmissions than expected of patients treated for

pneumonia, heart failure or acute myocardial infarction.(Abelson, 2013)

1.1. Objective

This study sought to (1) optimize the utility of the automated HRMR algorithm by using data mining to determine if specific patient populations were more at risk for medication-related hospital readmissions, and (2) use the data from the federal Outcome and Assessment Information Set (OASIS) to characterize and group patients for the assessment of risk for medication-related hospital readmissions.

2. Materials and Methods

This study used EHR data from a previous study consisting of OASIS home healthcare records and medication records for 911 adults from 15 Medicare-certified home health care agencies.(Dierich, 2010; Olson et al., 2014) OASIS data for the patients, all of whom were 65 or older and admitted from hospitals to home healthcare, were from 2004 and included demographic, environmental, support system, health and functional status, and health service utilization information.(Centers for Medicare and Medicaid Services (CMS), 2012a) The medication records included both prescription and over-the-counter medications taken by patients in their homes and recorded by home care clinicians in their EHRs. Medication data included the medication names, doses, dose forms, frequencies and special instructions.

2.1. Data Pre-Processing

HRMR scores were calculated for home healthcare patients based on three criteria that make up the composite measure: polypharmacy (the number of drugs they take),

Potentially Inappropriate Medications (PIM), and the Medication Regimen Complex Index (MRCI) that weighs drugs by the complexity of their dose forms or instructions. A separate study optimized the algorithm for calculating these criteria scores, primarily by adjusting the definition of polypharmacy to make it more sensitive to HRMR-related readmission risks. (Olson et al., 2014)

The OASIS data was pre-processed for the purpose of data mining following the same model and rules as a mobility outcome study that consisted of OASIS data for 283,193 patients from 581 Medicare-certified home health care agencies.(Dey et al.,) Variables were removed if they had little or no variance or an excessive number of missing values. When two variables represented the same concept, such as the (1) presence and (2) number of Stage 1 pressure ulcers, only the less granular variable (presence of ulcer in this example) was retained. All data were transformed to binary variables where continuous variables were mapped to discrete categories, and ordinal variables were mapped to two discrete categories indicating little or no problems versus moderate to severe problems. For example, the continuous variable for age was transformed to three age categories for patients ages 65 to 74, 75 to 85, and older than 85. An example of discretizing an ordinal value was a patient's pain frequency, which is normally logged in OASIS code M0420 on a 0-3 scale. For this research, it was mapped to two binary categories: (0) little or no pain, and (1) moderate to severe pain.

2.2. Methods

The pre-processed OASIS data was sorted into unsupervised clusters using the hierarchical agglomerative approach, which treats data points as individual clusters and

continuously merges them into larger clusters based on their similarity.(Blei, 2008) The Jaccard distance measure was used to determine the similarity of data points, and the average-linkage method was selected to create clusters based on the average distance of their data points from one another. Three other clustering techniques that analyze binary data were tested and applied to the OASIS data (hierarchical clustering using the complete-linkage method, and flat clustering use the *k*-means Hamming and *k*-means cosine methods) but ruled out for further analysis. A hierarchical approach can be less efficient and require more computations, but can produce more informative and interpretable results by creating a hierarchical structure that identifies relationships among the obtained clusters as well as the underlying data variables.(Manning, Raghavan, & Schutze, 2009) This was viewed as an appropriate choice for the study of a relatively small OASIS dataset, because hierarchical clustering can uncover relationships in patient characteristics that are novel but still relatable to clinicians in terms of what they see in their real-life home health care populations. The average-link method is more complex, but was preferred because it isn't as crude as the complete-link method, which joins clusters by data points that are farthest apart. The complete method can fail to merge clusters that might have significant relationships(Blei, 2008; Milligan, 1980) due to being very conservative in computing the distance between the clusters, which results in many small clusters.(Pang-Ting, Steinbach, & Kumar, 2006)

Receiver Operating Characteristic (ROC) analysis was then applied to the patient subgroups produced by unsupervised clustering to determine if the HRMR algorithm is predictive of their rehospitalizations. ROC curves were generated for each of the HRMR

components (polypharmacy, PIM, and MRCI) for each subgroup. The area under the ROC curves (AUC) can be interpreted in this study as the probability of correctly predicting hospital readmission, based on sensitivity and specificity. The closer the AUC is to 1, the better the measure. An AUC curve between .7 and .9 is considered meaningful.(Tape,) Results from the subgroups were then compared with the results for the overall population of 911 patients in the study group.

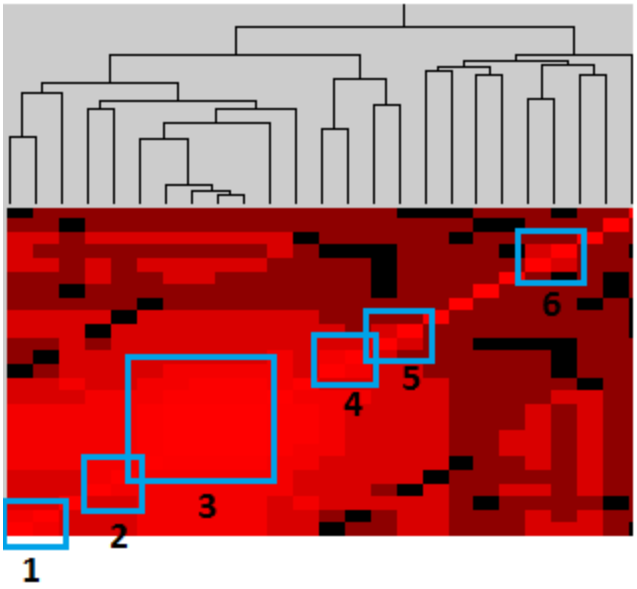
A test using the False Discovery Rate (FDR), a method of accounting for false positives in multiple-hypothesis research (Genovese, 2004), was then conducted to check the possibility that the subgroups' AUC results were due to chance. Randomizing the headings of the demographic variables for the original OASIS patient data, 1,000 dummy patient groupings were created for each subgroup produced by unsupervised clustering. The patient numbers in each dummy group matched the number of patients in the actual clusters. ROC curves were then calculated for each dummy group in relation to the HRMR components, and used to estimate the probability that the results from the actual subgroups are false positives. For this study's domain of a home healthcare patient population at medication-related risk for rehospitalization, an FDR rate of <.20 was pre-selected to control the probability of false positives in the HRMR risk data. A literature review supported an FDR rate at this level as a threshold.(Charchar et al., 2012; Subramanian et al., 2005)

3. Results

A heat map review of the hierarchical clustering results revealed six clusters of home healthcare patient groupings. The symmetrical map plotted the OASIS data on both

the vertical and horizontal axis and created a diagonal line across the map where data variables were compared with themselves. Color coding of the map identified the size and strength of data clusters along the diagonal. (Figure 1) The dendrogram at the top of the map shows how agglomerative clustering merged characteristics of the 911 patients in the OASIS study group from the bottom up.

Figure 1: Hierarchical Clustering Results for OASIS Study Population.
Six blooms show clusters of patients formed from hierarchical analysis of their health status and demographic data in home health records. Names assigned by the authors to these clusters are below along with the OASIS data items that form the clusters.



1: Good Functional Status
OASIS codes: M0640-M0710 </= 7; M0720-M0770 </= 9

2: Females in Moderate to Severe Pain
OASIS codes: M0069 = 2; M0420-M0430 >/= 2

3: Poor Prognosis Needing Functional Status Help
OASIS codes: M0140 = 6; M0150 = 1 or 2; M0260 = 0; M0200 = 1; M0380 = 1 and 2

4: Poor Functional Status
OASIS codes: M0640-M0710 >/= 8; M0720-M0770 >/= 10

5: Males with Adult Children as Caregiver
OASIS codes: M0069 = 1; M0360 = 2

6: Living Alone with Spouse as Primary Caregiver
OASIS codes: M0360 = 1; M0340 = 1

Two of the clusters related solely to functional status, which is measured in the

OASIS data by patients' relative abilities to complete activities of daily living (ADL), which include self-care tasks such as dressing or bathing, and instrumental activities of daily living (iADL), which include tasks for living independently such as housework and shopping.

- Cluster 1, labeled Good Functional Status, reflected patients whose composite ADL scores (OASIS codes M0640-M0710) were lower than eight, and whose iADL scores (OASIS codes M0720-M0770) were lower than 10. Lower scores indicate that home health patients have more independent living skills.
- Cluster 4 was labeled Poor Functional Status because it merged the opposite – patients with ADL scores of eight or higher, and iADL scores of 10 or higher – meaning they were in need of more assistance.
- Cluster 2 produced a relationship between female home health patients (M0069 = 2) and those with moderate to high levels of pain. Pain level was determined by a composite score of 2 or greater for OASIS fields M0420 and M0430, which measure the frequency of pain and the presence of intractable pain, respectively.
- Cluster 3 was the largest, merging the variables of patients who were white (M0140 = 6), received Medicare as their primary payer source (M0150 = 1 or 2), received assistance for ADLs and iADLs (M0360 = 1 and 2), received a change in treatment plan with 14 days of OASIS assessment (M0200 = 1), and was diagnosed with a poor prognosis

(M0260 = 0).

- Cluster 5 identified a relationship between home health patients who were male (M0069 = 1) and whose designated home health caregivers were their children (M0360 = 2).
- Cluster 6 paradoxically associated home health care patients who live alone (M0340 = 1) with having their spouses as primary caregivers (M0360 = 1).

Overall hospital readmission rates varied by cluster; the highest rate was 41 percent in the Poor Functional Status group. Results also varied for how closely readmissions were tied to medication issues, as measured by the ROC curve analysis. (Table 1)

Table 1: Patient Cluster Relationships to HRMR Components
The rate of hospital readmissions among the clusters varied, as did the ROC analysis results indicating whether the clusters had relationships with medication-related predictors of readmission.

Cluster ID	Description	Size	% Readmitted	Polypharmacy AUC	PIM AUC	MRCI AUC
1	Good Functional Status	382	20%	0.68	0.58	0.69
2	Females with Moderate to Severe Pain	354	22%	0.7	0.64	0.68
3	Poor Prognosis Needing Functional Status Help	419	18%	0.68	0.59	0.68
4	Poor Functional Status	287	41%	0.65	0.56	0.67
5	Males with Adult Children as Caregiver	197	27%	0.73	0.64	0.77
6	Lives Alone with Spouse as Primary Caregiver (cluster does not make sense)	206	3%	0.7	0.58	0.69

	**Entire OASIS Study Population	911	20%	0.68	0.59	0.69

AUC results for all three medication-related components of HRMR were strongest for Cluster 5 – 197 men with adult children as caregivers – when compared to the results for the overall patient group. AUC curves of .73 and .78 for polypharmacy and MRCI, respectively, suggested these measurements were meaningful predictors of hospital readmissions within this patient subgroup. PIM had a weak predictive value (.64) for this patient cluster, but the AUC result was nonetheless stronger than it was for the overall patient population (.59). Cluster 5 also had the second-highest rate of patients who were readmitted to hospitals (27 percent).

Using FDR analysis, AUC results for the six groups produced by unsupervised clustering were compared to AUC results for randomized sample populations of the same sizes. (Table 2) The size of the clusters resulted in variations in FDR results, even when AUC results for the clusters were identical. This analysis supports the hypothesis that the males with adult children caregivers cluster was more strongly associated with HRMR-related hospital readmissions. FDR rates in this subgroup met the study criteria of <=.20, indicating a hypothesis for future study. AUC results similarly improved when comparing medication-related readmission risks for the cluster of females with moderate to severe pain to the risks for the overall population of 911 home health care patients. However, the FDR results did not verify a strong relationship between this cluster and readmission risks.

Table 2: False Discovery Rate Analysis of Cluster Relationships to HRMR Components

Testing whether the relationships between OASIS patient clusters and HRMR components were significant or possibly due to chance, the analysis validated the strength of the relationship for cluster 5.

Cluster ID	Description	Polypharmacy FDR	PIM FDR	MRCI FDR
1	Good Functional Status	0.41	0.5	0.43
2	Females with Moderate to Severe Pain	0.30	0.22	0.50
3	Poor Prognosis Needing Functional Status Help	0.24	0.3	0.25
4	Poor Functional Status	0.59	0.63	0.57
5	Males with Adult Children as Caregiver	0.19	0.20	0.15
6	Lives Alone with Spouse as Primary Caregiver (cluster does not make sense)	0.28	0.54	0.44

4. Discussion

A challenge of unsupervised clustering and data mining in general is deciding which groups are meaningful. Human reasoning and theory-based interpretation can help but are limited because there is no statistical validation of these processes. This study used a valid test for finding clusters and determining through ROC and FDR analysis which ones met the threshold for interpretation. It also demonstrated that cluster analysis of OASIS data can identify subgroups of home healthcare patients, and that HRMR scores vary by clusters of patients compared to the overall population.

Only one group met the threshold for having a statistical correlation with medication-related hospital readmissions, and for further analysis and interpretation in this study. The

finding that a medication-related hospital readmission risk might be greater among elderly men with adult children as caregivers is novel, though other studies have found broader relationships between informal caregivers and medication-related problems. For example, changes or inconsistencies in the levels of care provided by informal caregivers, including adult children caring for their parents, can lead to difficulties in complying with prescription regimens and following complex dosing schedules and instructions.(Gillespie, Mullan, & Harrison, 2013) Further, struggles with medication compliance are linked with a high-percentage of medication-related visits to emergency departments,(Orwig, Brandt, & Gruber-Baldini, 2006) and hospitalizations among elderly adults whose assistance at home is insufficient.(Kuzuya et al., 2008)

There are several potential explanations for the relationship between HRMR scores and rehospitalizations for elderly men receiving assistance from their children. Adult children might find it difficult to manage medications for parents who want to maintain their autonomy, or create confusion as part-time caregivers if they oversee parents' medications on some days, but not others. The latter would seem especially relevant in an era in which adult Baby Boomers do not view caring for their aging parents as a "natural" responsibility or one they can easily manage amid their own parenting and careers.(Guberman, Lavoie, Blein, & Olazabal, 2012) Caregiving situations in which siblings are caring for parents could also confuse the roles and responsibilities of medication management.

It is unclear whether informal caregiving itself is a cause of medication problems. One study found overdoses or missed doses were more common among elderly people

receiving informal medication support at home, but didn't determine whether this support increased the risk of medication non-adherence or was merely associated with it.(Thiruchselvam et al., 2012) Another study found informal caregiving to have a positive relationship with adherence, as spouses or adult children helped people with chronic obstructive pulmonary disease stick to medication regimens and potentially avoid hospital readmissions.(Trivedi, Bryson, Udris, & Au, 2012)

Unsupervised clustering to identify patient groups by symptom combinations is emerging in literature. (Lee et al., 2010; Lewandowski, Sperry, Cohen, & Ongur, 2014; Moser et al., 2014; Wardenaar et al., 2014) Applying this approach specifically to OASIS data to identify patient subgroups by their demographic and health status information was novel, though not unprecedented.(Westra et al., 2011) The results suggested problems among specific subgroups of patients and informal caregivers that either aren't well-studied in research literature or have been studied inconclusively. The role of gender in medication issues such as non-adherence, for example, has been evaluated with varying results.(Granger et al., 2009; Holt et al., 2013; Pasina et al., 2014)

Our results suggested promising targets for future research: (1) identifying characteristics of adult children who are less reliable in helping their parents with medication management, and (2) uncovering risk factors that make elderly fathers more likely to experience medication-related hospital readmissions than mothers. More targeted research could also address whether a cause-and-effect relationship exists between family caregiving and an increased risk of medication-related hospital readmissions. With at least 75 percent of long-term care provided by family caregivers –

at an estimated value of $375 billion in unpaid labor(Gibson & Houser, 2007) – there is a great need to address their strengths and weaknesses and the dynamics of family caregiving that could lead to medication problems and hospital readmissions.

4.1. Limitations

There are several limitations that should be considered in interpretation of this study. FDR's broad handling of false positives and error rates allow for the discovery of associations that otherwise might go unseen. The FDR threshold in this study of .20 was supported by literature, but nonetheless was a judgment made by the researchers. Interpretations about medication management from a patient group in 2004 also need to be considered in light of health care reforms in the subsequent decade, including federal medication reconciliation requirements for hospitals to have electronic processes for verifying the safety and accuracy of patients' prescription regimens. OASIS data interpretation could also affect the results of this study, as evidenced by the cluster of people paradoxically listed in the data as living alone at home but receiving care from spouses. More research using other methodologies is needed to verify the strength of the results.

5. Conclusion

The unsupervised clustering combined with comparable literature results present an intriguing hypothesis that elderly men receiving care at home from their adult children are at elevated risk of medication-related hospital readmissions. The results also further research into HRMRs and their potential use in clinical systems to identify patients at risk

for avoidable readmissions. Future research opportunities presented by this study include exploration of the role of informal caregivers in managing or contributing to medication adherence issues, and further evaluation of HRMR in a different patient population to demonstrate its potential use as a clinical tool. More broadly, the success in one of the first attempts to apply clustering to OASIS data suggests other researchers could use this rich dataset to identify patterns in elderly patient care and health.

Discussion and Conclusion

1. Discussion

The three studies in this dissertation demonstrated that HRMR can be automated and potentially developed into a clinical support tool to predict hospital readmissions and identify patients who would benefit from support services that prevent readmissions. The algorithm for calculating HRMR scores from patients' medication data was automated(Olson et al., 2014) and then optimized to improve its predictive accuracy and enhance its clinical utility.(Olson et al., 2014) Clustering analysis then identified a patient subgroup that had a greater HRMR-related risk for hospital readmission, presenting a hypothesis for future study and contributing to the emerging field of data mining using patient demographic and health care utilization databases.

1.1 Contributions to Informatics & Gaps in Literature

While increasing studies have individually investigated the concepts of polypharmacy,(Abdulraheem, 2013; Arnet, Abraham, Messerli, & Hersberger, 2013; Beloosesky et al., 2013; Hajjar et al., 2007; Morandi et al., 2013; Pasina et al., 2014; Sehgal et al., 2013; Sganga et al., 2014) PIM, (Baldoni et al., 2013; Bao, Shao, Bishop, Schackman, & Bruce, 2012; Fu et al., 2007; Price et al., 2014a; Price et al., 2014b; Sehgal et al., 2013; Vieira de Lima et al., 2013; Weng et al., 2013; Zhan et al., 2001) and MRCI(George et al., 2004; McDonald et al., 2013; Schoonover, 2011; Willson et al., 2014; Wimmer et al., 2014), there has been no focus in published literature on the combination of these three drug-related indicators since an original HRMR study showed that these concepts together identify home health care patients who are at elevated risk of

hospital readmissions.(Dierich, 2010) All three studies produced as part of this dissertation are novel and address gaps in the health care literature in that they focus on this untested concept of the HRMR. The first study demonstrated that the manual concept of calculating HRMR could be automated, the second fine-tuned the underlying criteria for HRMR to optimize its predictive relationship with hospital readmissions, and the third used clustering techniques to examine subgroups in the sample population most susceptible to medication-related readmission risks. Beyond the results, the methods used to achieve them also contributed to the field of informatics by demonstrating their effectiveness as research tools.

The first study converted medication data into common RxNorm terminology, using crosswalks generated by APIs available on the National Library of Medicine web site, and was a key step in the proof of concept for HRMRs. The heterogeneous nature of medication records and prescription systems is a barrier to research and clinical analysis across health care systems.(Richesson, 2014) The standardization with RxNorm, which is considered "ideal" for such purposes,(Richesson et al., 2010) expedited the conversion of drug data into HRMR scores. This conversion made it possible for this novel approach of assessing readmission risks to be replicated by other clinicians or researchers. The APIs and crosswalks also allow researchers and clinicians to adapt and adjust the HRMR algorithm for future analysis and research.

However, while the conversion was ultimately successful, only 82 percent of the drug names were converted to RXCUI values without any manipulation of the data set that was used.(Olson et al., 2014) Conversion of 99 percent of the drug names required

some manual manipulation of the drug data due to misspellings or confusion over multi-ingredient drugs. Analysis of drug data will be greatly enhanced and expedited by the continued adaptation of medication standards in EHR by hospitals and health systems.

The second study optimized the automated algorithm by using ROC curve analysis to test modified HRMR criteria against the original criteria used by Dierich.(Dierich, 2010) The original manual HRMR study was based on clinical judgments, so the automation of the data presented an opportunity to test those judgments and determine if adjustments to HRMR scoring could improve the prediction of readmission risks. This further enhanced the clinical utility of the algorithm by improving its sensitivity to hospital readmission risks. The primary change from the optimization was the exclusion of vitamins and supplements for polypharmacy counts.(Olson et al., 2014) Other tests, such as removing acetaminophen from the algorithm, did not improve the ROC results. Widespread variations exist in the polypharmacy cut point used in previous studies(Hajjar et al., 2007) to distinguish patients with a low number of drugs versus those with a high number of drugs that puts them at risk for problems such as readmissions. This current study verified a cut point of 9 drugs as most effective in distinguishing patients' hospital readmission risks. It also supported previous studies showing little to no correlation between readmissions and PIM medications alone.(Borenstein et al., 2013; Sehgal et al., 2013) The lack of any such connection is surprising, as it would seem intuitive that any elderly patients with drugs known to be risky would be at risk for complications that would require their returns to hospital care. The original MRCI criteria (George et al., 2004) from George et al. proved optimal for

predicting patients' readmission risks, though adjustments based on an odds ratio analysis did modestly improve the predictive strength of Table C (drugs with special instructions). However, the MRCI cut point for separating patients by their readmission risk was increased to 33 from the original cut point of 20 used in the initial HRMR study.(Olson et al., 2014) Cut points produced by the analysis of the automated data could prove instructive as future researchers use these drug-related measurements.

The focus of the third study was on identifying patient subgroups that could potentially benefit from the clinical utility of the HRMR model. In theory, an EHR could identify patients by their characteristics – such as elderly males with adult child as caregivers – and flag clinicians of potential readmission risks. The results from the unsupervised clustering also offered a hypothesis that contributed to the literature showing the challenges of adult children and other informal caregivers caring for the elderly and managing their medications.(Gillespie et al., 2013; Kuzuya et al., 2008; Thiruchselvam et al., 2012) The results contributed to the evidence base for clinicians, who could discuss the potential for medication problems with informal caregivers and also consider this subgroup of elderly males with adult children as caregivers as candidates for additional support and home health services. The paper also reflects the novel and successful use of clustering to identify these patient groups within OASIS data. This rich dataset for home health patients could now be attractive to other researchers seeking to identify subgroups of patients by the demographics or health care utilization status.

2. Limitations

While providing proof of concept for HRMR and its potential utility as a clinical support tool, these studies could only go as far as one relatively small data set could carry them. The conversion of drug data into RxNorm terminology was necessitated by the older and somewhat crude methods of recording medication data. The data set lacked clear information about the 911 patients' diagnoses. Authors reconstructed the most likely diagnoses of the patients based on the indications of the medications they were taking. While diagnoses were only relevant in analysis of PIM medications – to differentiate whether patients were taking drugs that had side effects related to certain conditions – the authors' interpretations could have led to some errors in the results. Lastly, the lack of standards for special instructions and dose frequency resulted in limited automation from informatics coding standards to compute MRCI values.

Finally, the connection established between HRMR readmission risks and elderly patients with adult children as caregivers was validated using an FDR statistical method that is more liberal and is intended for the purpose of hypothesis generation. While there was research literature to suggest the connection was plausible, additional analysis is needed to prove it.

3. Future Implications

The increasing adoption of EHRs – expedited in the last few years by government grants and mandates – has created new datasets and opportunities to analyze patient care trends and predict what types of patients are most likely to experience complications or adverse events. Research has grown rapidly in the area of analyzing secondary EHR data for patient care such as predicting the diagnosis of depression by mining diagnosis and

medication and clinical progress notes,(Huang et al., 2014) or earlier identification of heart failure patients through mining of signs and systems documented on encounter notes.(Vijayakrishnan et al., 2014) Analysis of patient medication data has been expedited by RxNorm, which is viewed as "ideal" for standardizing prescription data,(Richesson et al., 2010) and was used successfully to convert non-standardized medication records for the calculation of HRMR scores.(Olson et al., 2014) RxNorm is being adopted directly by EHRs to support live recording of patients' medication histories(Bennett, 2012). This presents opportunities for rapid calculation of patient HRMR scores and other medication metrics using EHR systems without any prior "normalization" of the medication data they contain. The construction of the HRMR model, and the ability to automate its calculation, present further opportunities for research, particularly with different patient populations and datasets to demonstrate the potential of HRMR as a clinical tool. Those opportunities include:

- Larger and more recent OASIS and medication datasets. The original HRMR automation study was based on a home health care population of 911 patients. The tools and techniques, such as utilizing RxNorm APIs with SAS implementation, need to be tested on a larger dataset to determine if they remain efficient and effective at preparing medication data for analysis. Analyzing a larger patient population is also important to verify whether the relationship between HRMRs and hospital readmissions exists beyond the one population in the original study. The finding that a cluster of men with adult children as caregivers was more susceptible to medication-related readmission risks also

could be verified. And perhaps new clusters of clinically relevant home health care populations could emerge from data mining of a larger OASIS dataset.

- Other clinical EHR datasets. While OASIS is valuable for the clinical and demographic information it contains, it is limited to the population of home healthcare patients. As EHR datasets become more robust and formatted for secondary research, the opportunity arises to test the predictive power of HRMR on a broader range of ages and demographics. Testing the automated HRMR algorithm on a broader population is important, because it is possible that HRMR only has a predictive quality for hospital readmissions in the home health care or elderly population. It is also possible that the cut points for the HRMR components such as polypharmacy (the number of drugs that separate patients by their risk levels) will be different in a broader population. As a result, HRMR might be clinically useful but will need to be adjusted based on demographic factors to assess hospital readmission risks. And just as data mining found a unique subgroup of patients within an OASIS dataset, this same clustering research might identify high-risk groups within the broader population. Studies, for example, already point to medication adherence and mental illness as indicators of readmission.(Haddad, Brain, & Scott, 2014) Other variables that might be analyzed within an EHR dataset include social history (tobacco use, illegal drug use, sexual activity, etc.), vitals (height, weight, BMI, blood pressure), allergies, immunizations, orders (lab, radiology, etc.) and problem lists. EHRs are currently used to flag clinicians when patients appear at risk of

depression and heart failure; it is certainly possible that HRMR tracking could be integrated into these systems to similarly flag clinicians about patients with medication-related risks for hospital readmissions.

- Medical and Pharmacy Claims data. Similarly, follow-up studies could explore whether claims databases could efficiently and effectively yield HRMR scores of patients. The size of public or private insurance claims databases – spanning across health care providers and systems – could help provide important validation for the relationship between HRMR and hospital readmission risk. Claims databases could also expand the analysis of HRMRs to determine whether they are more likely among patients with higher personal costs of care, or among patients with different types of health insurance (HMO, PPO, etc.) They could also allow for comparisons in terms of the net cost of patients – comparing those who meet the threshold for HRMRs and those who do not. Given that patients with high risk medication regimens are more likely to be rehospitalized, it would seem possible that they would cost more than patients with lower medication usage who don't meet that threshold. Applying the automated HRMR calculations to claims databases could prove or disprove that assumption.

4. Conclusion

Applying the automated algorithm to diverse datasets is crucial to validating and optimizing the clinical utility of HRMR calculations, and to identifying the types of patients for whom HRMR is a more meaningful predictor of hospital readmissions. The overall goal of the study demonstrated that HRMR can be automated as a clinical support

tool to enhance patient care – and demonstrates ripple effects that point to new directions for research.

A valid, automated method for deriving HRMR scores from EHRs could compel other researchers to use the method and to further evaluate using these scores as clinical tools. Secondary analysis has the potential – as revealed by the third study – to uncover multiple relationships between patients' HRMR scores and their health outcomes as measured by the OASIS and EHR data. The clustering analysis offered new targets for researchers to explore further in their efforts to understand the linked roles of medication, medical interventions and the health and outcomes.

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Appendix A

Potentially Inappropriate Medications
Potentially Inappropriate Medications: Independent of Diagnoses or Conditions, from Fick et al. (2003, p. 2719), used with permission.

Drug/Drug Combinations with the Active Ingredient	Low Risk	High Risk
Propoxyphene (Darvon)	X	
Indomethacin (Indocin)		X
Pentazocine (Talwin)		X
Muscle relaxants and antispasmodics: methocarbamol (Robaxin), carisoprodol (Soma), chlorzoxazone (Paraflex), metaxalone (Skelaxin), cyclobenzaprine (Flexeril), and oxybutynin (Ditropan). Do not consider the extended-release Ditropan XL.		X
Flurazepam (Dalmane)		X
Amitriptyline (Elavil), chlordiazepoxide-amitriptyline (Limbitrol), and perphenazine-amitriptyline (Triavil)		X
Doxepin (Sinequan)		X
Meprobamate (Miltown and Equanil)		X
Doses of short-acting benzodiazepines: doses greater than lorazepam (Ativan), 3 mg; oxazepam (Serax), 60 mg; alprazolam (Xanax), 2 mg; temazepam (Restoril), 15 mg; and triazolam (Halcion), 0.25 mg		X
Long-acting benzodiazepines: chlordiazepoxide (Librium), chlordiazepoxide-amitriptyline (Limbitrol), clidinium-chlordiazepoxide (Librax), diazepam (Valium), quazepam (Doral),		X

halazepam (Paxipam), and chlorazepate (Tranxene)		
Disopyramide (Norpace and Norpace CR)		X
Digoxin (Lanoxin) (should not exceed _0.125 mg/d except when treating atrial arrhythmias)	X	
Short-acting dipyridamole (Persantine). Do not consider the long-acting dipyridamole (which has better properties than the short-acting in older adults) except with patients with artificial heart valves	X	
Methyldopa (Aldomet) and methyldopa-hydrochlorothiazide (Aldoril)		X
Reserpine at doses > 0.25 mg	X	
Chlorpropamide (Diabinese)		X
Gastrointestinal antispasmodic drugs: dicyclomine (Bentyl), hyoscyamine (Levsin and Levsinex), propantheline (Pro-Banthine), belladonna alkaloids (Donnatal and others), and clidinium-chlordiazepoxide (Librax)		X
Anticholinergics and antihistamines: chlorpheniramine (Chlor-Trimeton), diphenhydramine (Benadryl), hydroxyzine (Vistaril and Atarax), cyproheptadine (Periactin), promethazine (Phenergan), tripelennamine, dexchlorpheniramine (Polaramine)		X
Diphenhydramine (Benadryl)		X
Ergot mesyloids (Hydergine) and cyclandelate (Cyclospasmol)	X	
Ferrous sulfate >325 mg/d	X	

All barbiturates (except phenobarbital) except when used to control seizures		X
Meperidine (Demerol)		X
Ticlopidine (Ticlid)		X
Ketorolac (Toradol)		X
Amphetamines and anorexic agents		X
Long-term use of full-dosage, longer half-life, non–COX-selective NSAIDs: naproxen (Naprosyn, Avaprox, and Aleve), oxaprozin (Daypro), and piroxicam (Feldene)		X
Daily fluoxetine (Prozac)		X
Long-term use of stimulant laxatives: bisacodyl (Dulcolax), cascara sagrada, and Neoloid except in the presence of opiate analgesic use		X
Amiodarone (Cordarone)		X
Orphenadrine (Norflex)		X
Guanethidine (Ismelin)		X
Guanadrel (Hylorel)		X
Cyclandelate (Cyclospasmol)	X	
Isoxsurpine (Vasodilan)	X	
Nitrofurantoin (Macrodantin)		X
Doxazosin (Cardura)	X	
Methyltestosterone (Android, Virilon, and Testrad)		X

Thioridazine (Mellaril)		X
Mesoridazine (Serentil)		X
Short acting nifedipine (Procardia and Adalat)		X
Clonidine (Catapres)	X	
Mineral oil		X
Cimetidine (Tagamet)	X	
Ethacrynic acid (Edecrin)	X	
Desiccated thyroid		X
Amphetamines (excluding methylphenidate hydrochloride and anorexics)		X
Estrogens only (oral)	X	

Appendix B

Medication Regimen Complexity Index

The Medication Regimen Complexity Index, Section A (George et al., 2004, p. 1374), used with permission.

MEDICATION REGIMEN COMPLEXITY INDEX

Patient ID: ----------

Total no. of medications (including prn/sos medications): ----------

Instructions

1. MRCI applies only to prescribed medications. All entries are to be made only based on information on the label or drug chart (at the time of dispensing or discharge). No assumptions are to be made based on clinical judgement.
2. There are three sections in the scale. Complete each section before proceeding to the next. At the end, add the scores for the three sections to give the MRCI.
3. If the same medication (same brand and same dosage form) is present more than once in different strengths in a regimen (e.g. Marevan 5mg, 3mg and 1 mg mdu), it is still considered as one medication.
4. In cases where the dosage is optional, choose the dosing instruction with the smallest dose/frequency. (e.g. Ventolin MDI 1-2 puffs, 2-3 times daily will get weightings for 'metered dose inhalers', 'variable dose' and 'twice daily'; but not for 'multiple units at one time')
5. In certain cases the dosing frequency needs to be calculated (e.g. Ranitidine 1mane and 1nocte is 1twice daily)
6. It is possible that with certain 'use as directed' instructions, the regimen will not get a score under dosing frequency (e.g. Prednisolone 5mg mdu)
7. If there is more than one dosing frequency direction, they should be scored for all the dosing frequency directions (e.g. Ventolin MDI 2 puffs bd and prn, will get scores for 'metered dose inhalers', 'multiple units at one time', 'twice daily' as well as 'prn')
8. Instances where two or more medications are mutually exclusive, they need to be scored twice or more as prn with the recommended dosing frequency (e.g. Ventolin MDI or Ventolin nebuliser twice daily will get scores for both 'metered dose inhalers' and 'nebuliser' under dosage forms, but needs to be scored two times for 'twice daily prn')
9. In cases where there is no matching option, choose the closest option (e.g. six times daily could be considered as 'q4h')

A) Circle the weighting corresponding to each dosage form (ONCE ONLY) present in the regimen.

Dosage Forms		Weighting
ORAL	Capsules/Tablets	1
	Gargles/Mouthwashes	2
	Gums/Lozenges	2
	Liquids	2
	Powders/Granules	2
	Sublingual sprays/tabs	2
TOPICAL	Creams/Gels/Ointments	2
	Dressings	3
	Paints/Solutions	2
	Pastes	3
	Patches	2
	Sprays	1
EAR, EYE & NOSE	Ear drops/creams/ointments	3
	Eye drops	3
	Eye gels/ointments	3
	Nasal drops/cream/ointment	3
	Nasal spray	2
INHALATION	Accuhalers	3
	Aerolizers	3
	Metered dose inhalers	4
	Nebuliser	5
	Oxygen/Concentrator	3
	Turbuhalers	3
	Other DPIs	3
OTHERS	Dialysate	5
	Enemas	2
	Injections: Prefilled	3
	Ampoules/Vials	4
	Pessaries	3
	Patient controlled analgesia	2
	Suppositories	2
	Vaginal creams	2
	Total for Section A	

DPI = dry-powder inhaler; MDI = metered-dose inhaler.

(continued on page 1375)

The Medication Regimen Complexity Index, Sections B and C (George et al., 2004, p. 1375), used with permission.

Appendix II. Medication Regimen Complexity Index (MRCI) (continued)

B) For each medication in the regimen tick a box [√] corresponding to the dosing frequency. Then, add the no. of [√] in each category and multiply by the assigned weighting. In cases where there is no exact option, choose the best option.

Dosing Frequency	Medications	Total	Weighting	Weighting × No. of medications
Once daily			1	
Once daily prn			0.5	
Twice daily			2	
Twice daily prn			1	
Three times daily			3	
Three times daily prn			1.5	
Four times daily			4	
Four times daily prn			2	
q 12h			2.5	
q 12h prn			1.5	
q 8h			3.5	
q 8h prn			2	
q 6h			4.5	
q 6h prn			2.5	
q 4h			6.5	
q 4h prn			3.5	
q 2h			12.5	
q 2h prn			6.5	
prn/sos			0.5	
On alternate days or less frequently			2	
Oxygen prn			1	
Oxygen <15hrs			2	
Oxygen >15hrs			3	
			Total for Section B	

C) Tick a box [√] corresponding to the additional directions, if present in the regimen. Then, add the no. of [√] in each category and multiply by the assigned weighting.

Additional Directions	Medications	Total	Weighting	Weighting × No. of medications
Break or crush tablet			1	
Dissolve tablet/powder			1	
Multiple units at one time (e.g. 2 tabs, 2 puffs)			1	
Variable dose (e.g. 1-2 caps, 2-3 puffs)			1	
Take/use at specified time/s (e.g. mane, nocte, 8 AM)			1	
Relation to food (e.g. pc, ac, with food)			1	
Take with specific fluid			1	
Take/use as directed			2	
Tapering/increasing dose			2	
Alternating dose (e.g. one mane & two nocte, one/ two on alternate days)			2	
			Total for Section C	

Medication Regimen Complexity = Total (A) + Total (B) + Total (C)=

DPI = dry-powder inhaler; MDI = metered-dose inhaler.