JEAN-FRANÇOIS RICCI
Improving Risk Adjustment Indices with Drug Exposure in Administrative Data
(Under the direction of BRADLEY C. MARTIN)

Risk adjustment is essential in any study comparing patients' outcomes such as mortality and effectiveness of care. Medicaid programs would also benefit from cost risk adjustment models, as they have been moving away from a traditional fee-for-service payment system toward a capitated managed care system. Very little research, however, has been published on risk adjustment specific to Medicaid populations. Most risk adjustment methods have been based on ICD-9-CM diagnosis codes, which present with some limitations in coding comorbidities in the context of longitudinal studies. Therefore, there exist opportunities to complement code-based measures with another source of comorbidity information. In this research, we developed and independently validated Medicaid-specific prospective cost and mortality risk adjustment models based on ICD-9-CM codes, drug exposure, and combined information. We modeled mortality and cost outcomes for three populations: ambulatory Medicaid recipients, patients with a first stroke event, and patients with an initial diagnosis of Alzheimer's dementia or related dementias (AD/D). Prospective models developed on the GA Medicaid population were validated by panels of clinicians, re-estimated, 'frozen', and tested on the independent population of North Carolina Medicaid recipients.

Either drug classes or ICD-9-CM codes can characterize the comorbidity burden of ambulatory, AD/D, and stroke patient populations independently, but used in conjunction with a hierarchical classification, the two sources of information increased the sensitivity to disease burden. Our prospective mortality risk adjustment models provide a tool to Medicaid programs and health service researchers to initially stratify or otherwise control for varying levels of disease severity and comorbid illnesses. A long-term goal for our prospective cost risk adjustment models is to forecast resources commensurate with actual needs of a large segment of the Medicaid population or for patient cohorts that will exact an increasing toll on Medicaid resources. However, further

refinements (re-calibration) and independent testing of our disease-specific cost models may be needed before they can accurately predict future levels of resource needs in Medicaid cohorts, whereas the combined ambulatory cost model achieved good external predictive power. Drug exposure represents a new venue of information that will help enhance the quality and performance of health service research studies.

INDEX WORDS: Risk adjustment indices, Drug exposure, Comorbidities, Stroke, Cerebrovascular diseases, Alzheimer's dementia, Ambulatory, Administrative data, Georgia Medicaid, North Carolina Medicaid.

# IMPROVING RISK ADJUSTMENT INDICES WITH DRUG EXPOSURE IN ADMINISTRATIVE DATA

by

JEAN-FRANÇOIS RICCI

Maîtrise, Université Claude Bernard, Lyon I, France, 1991

D.E.S.S, Université Jean Moulin, Lyon III, France, 1992

MBA, The University of Georgia, 1994

Diplôme d'Etat de Docteur en Pharmacie, Université Claude Bernard Lyon I, France, 1995

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of The University of Georgia in Partial Fulfillment of the

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JEAN-FRANÇOIS RICCI

Approved:

Major Professor: Bradley C. Martin

Committee: Jeffrey H. Dorfman
Susan C. Fagan
Jeffrey A. Kotzan
Jaxk H. Reeves

Electronic Version Approved:

Gordhan L. Patel
Dean of the Graduate School
The University of Georgia
December 2000

A Bouture, pour ta patience et ton amour

A nos deux soleils, Salomé et Céleste

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TABLE OF CONTENTS

Page

# CHAPTER ONE

# RISK ADJUSTMENT INDICES: INTRODUCTION AND LITERATURE REVIEW

Administrative data files are increasingly used for studying outcomes of medical care and have become the mainstay of an entire body of health services research studies.[1,2,3,4] To some extent, obtaining valid inferences from these databases depends on the ability of the researchers to stratify or otherwise control for varying levels of disease severity and comorbid illnesses.[5] Risk adjustment is essential in any study comparing patients' outcomes and effectiveness of care of new or established treatments, especially if patients are not randomly assigned to different treatment groups.[6] It is also essential at an institution level, when evaluating health plans and providers, or studying the impact of health care plans.[7] Comorbidities represent an important component of risk adjustment techniques because oftentimes patients with comorbid illnesses differ importantly from patients without these conditions.[8] Iezzoni provides an in-depth review of severity measures, their specificity, data requirements, methods of development, and vendors along with a complete list of references.[9]

## Role of Risk Adjustment Models

Health service researchers use risk adjustment methods and models to stratify or otherwise control for varying levels of disease severity and comorbid illnesses. Real world studies, as opposed to randomized controlled clinical trials, do not allow the investigator to control for potential biases (e.g., selection bias) by using a randomized assignment of individuals to treatment groups. Real world studies (i.e., ‘effectiveness’ as opposed to ‘efficacy’, ‘naturalistic’ as opposed to ‘controlled’ studies, etc.) can

strengthen their internal validity by using various statistical tools and methods. Risk adjustment models can be used to assess the effectiveness of a drug or intervention on patient survival or outcomes of care across different providers (patient profiling). The research investigator seeks to ensure that the patient group with the worse/best outcome was not sicker/healthier, so that the outcome is not confounded with patients' characteristics. Risk adjustment models allow the investigator to control for some of the patient characteristics through statistical techniques.[9]

Interest and research on risk adjustment models for cost outcomes grew when Medicare contracted health benefit for an increasing number of beneficiaries with Managed Care, and away from its then traditional fee-for-service system. Research on selection bias in the Medicare risk program and the need for more refined payment systems prompted a series of new models. The first payment system, the "adjusted average per capita cost" (AAPCC) was implemented by Medicare in 1985. AAPCC is based on an AAPCC county rate and a set of an enrollee's demographic factors.[10] Since then, several alternatives have been proposed to demographic-based risk adjusters (e.g., concurrent versus prospective models, models based on hospital encounters, on prior resource use, or on all encounters, etc.), as the equity and accuracy of AAPCC have been increasingly questioned. The overarching use of risk adjustment for providers who assume the financial risk for a population is to assess future health care costs. The objective for the party that contracts out the care is "to effectively predict costs while limiting the rewards for undesirable behavior with respect to either treatment or reporting" on the part of the provider.[11]

## Comorbidity-based Risk Adjustment Measures

To date, most comorbidity measures developed from administrative databases only use standard demographic data such as age and gender as well as diagnosis codes: ICD-9-CM and/or diagnosis-related groups (DRG).[12,13] Code-based measures have been defined for different types of populations. Most measures view acute care hospitalization

as the episode of illness.[9] In general, code-based measures target all hospitalized patients or adults broadly defined, e.g., the Acuity Index Method,[14] Diagnostic Cost Groups-Principal Inpatient,[15,16] and Risk Adjusted Mortality Index.[17] They sometimes also target patients diagnosed with a common indication for hospitalization such as congestive heart failure.[18] However, a few measures were developed for ambulatory patient populations (Ambulatory Care Groups (ACG), Diagnostic Cost Groups-Hierarchical Condition Category (DCG-HCC), Disability Payment System (DPS))[7,19,11,20,21] or were adapted to be used in longitudinal follow-up studies.[5] Code-based measures examined either implicit (expected resource use and length of hospital stay) or explicit definition of severity (mortality). They are often empirically derived, applicable to large populations, and easy to update. They do not necessitate a detailed and expensive abstraction of patient medical records, but more widely available computerized discharge abstract data and/or ambulatory care claims. On the other hand, these disease severity measures have mostly focused on hospitalized patients, thus quantifying risks of short-term. To the exception of the Charlson index[22], its later adaptations,[5,23] and the ACG,[7,19] DCG-HCC,[11,20] severity measures have not been developed for use in longitudinal studies. In addition, inpatient diagnoses may reflect the effect of a "built-in" incentive for the health care provider to beat the system and code for diagnoses that yield higher reimbursement rates. Moreover, inpatient discharge-based comorbidity measures reflect conditions diagnosed or treated during an entire admission, regardless of when they occurred during the hospital stay.[24] They can also code for conditions that are technically not diseases.[9] Furthermore, there is a potential for omission bias in coding comorbidities in the context of longitudinal studies. Doctors who treat patients for a given condition at a given time may not always code for that condition at every medical encounter. This threat might be more relevant with chronic and none life threatening conditions such as hypertension and hypercholesterolemia. Lastly, the comorbidity profile of ambulatory patients with no or few medical encounters might not be accurately represented when all comorbidity information is abstracted from administrative data

A team from the Agency for Health Care Policy and Research (AHCPR) center led by Elixhauser recently developed a comprehensive set of 30 comorbidities based on ICD-9-CM definitions for use with administrative data.[25] The Elixhauser team extended the method for classifying comorbidities proposed by Charlson (1987). Charlson initially worked on a cohort of patients admitted to the medical service of an acute care hospital[22] and developed a mapping algorithm based on ICD-9-CM codes. Later, Deyo,[5] and then Romano (Dartmouth-Manitoba index),[23] adapted the algorithm for use with ICD-9-CM coded in administrative databases.[26,27,28,29,30,31] Lacking information on prior use of health care, Elixhauser's team examined hospital discharge data on a large sample (n = 1.8 million). The sheer number of observations allowed them to assess a broad range of comorbidities for use on heterogeneous patient populations as well as on homogeneous diagnosis groups. Conversely, the Deyo's adaptation of the Charlson comorbidity index was based on a smaller number of patients but addressed the needs of longitudinal studies.

Clinical-based Measures

Both code-based measures described above rely solely on comorbidity information available from the ICD-9-CM codes and sometimes demographic information. As mentioned earlier, there exists a need to complement ICD-9-CM code-based measures with another source of comorbidity information. Medical records represent an invaluable source of such information, containing data on vital signs, patient risk factors, and test results. Clinical data measures tend to capture more completely the acuity and severity of disease of patients than code-based measures.[32,33] However, clinical-based measures suffer from two major drawbacks. First, extracting clinical details for more precise measurements is prohibitively more expensive on the large scale needed to develop and validate a comorbidity index. In addition, this type of measure would not be broadly applicable to administrative data that are in common use today (such as Medicaid and Medicare). Clinical epidemiologists report that a good patient

history can often provide sufficient information and that diagnostic testing may not always generate additional predictive power.[30,34] As Roos suggested several claims measures might "well do better than one or more variables collected in an expensive manner," such as diagnostic tests and/or chart reviews.[30] Clearly, the gain in precision measuring risk based on clinical measures needs to be weighed against its added costs. As Harrell suggested, "when researchers using inexpensive non-intrusive measures (such as claims) must decide whether or not to invest scarce resources in more data collection, evaluating the likely yield of such additional information is critical."[35]

Drug-based Risk Adjustment Measures

As an alternative to clinical-based measures, detailed prescription files can serve as an inexpensive and complementary source of information on patients' comorbidities. To date, one research team, the Group Health Cooperative (GHC) of Pudget Sound, Seattle, WA has developed and evaluated a drug-based index: the chronic disease score (CDS). Von Korff evaluated "the usefulness of a measure of chronic disease status in terms of stability over time and its association with other health status measures after controlling for age, gender, and level of utilization of care."[36] The scores on the CDS were initially assigned by a multidisciplinary group including GHC physicians, pharmacists, epidemiologists, and health services researchers following a number of set principles. Although Johnson[37] independently tested and validated the use of CDS as a readily accessible low cost measure of health status, until recently little published research used the CDS as a health status indicator.[38,39,40] Problems with the original version of the CDS were that scores were not empirically derived and that many new therapeutic classes were not represented in the CDS. In a revised version of the CDS, weights were derived empirically controlling for age and gender.[41] Weights were estimated with regression models that used a split-random one-half sample technique on 250,000 managed care enrollees, aged 18 and older. The revised CDS included drug treatments that reflect chronic conditions that might not be life threatening (e.g., mental

illnesses), but with potential for increase in overall health care costs and primary care visits. The revised CDS revealed to be a better predictor of mortality than the ambulatory care groups, which utilize outpatient diagnoses to form mutually exclusive diagnostic categories.[19]

Risk Adjustment Measures in Indigent Populations

Low economic status has been linked to excess mortality rates.[42] Epstein noted that uninsured or Medicaid patients in Massachusetts were significantly more likely than privately insured patients to be hospitalized for potentially avoidable causes, such as asthma, gangrene, hypokalemia, malignant hypertension, and bleeding ulcers.[43] Another study of 14,577 patients[44] found that Medicaid patients had significantly higher MedisGroups admission scores, therefore poorer health status than other patients.[45] Such patients often have a higher risk of death, increased chance of complications, impaired recuperative abilities; all these factors negatively affect their longevity.[46]

Medicaid is a jointly funded Federal-State health insurance program covering over 36 million individuals (http://www.hcfa.gov/). Although Medicaid databases contain demographic, medical and drug utilization information for the indigent US population necessary to perform longitudinal studies, little research has developed and validated risk adjustment indices specific to this population. In the literature several classification systems have been proposed for ambulatory populations.[9] Kronick developed the only risk adjustment model specific to a subset of the Medicaid population (DPS). The DPS is a system of diagnostic categories that Medicaid programs can adapt to adjust capitation payments to health plans that enroll people with disability.[21] Another system, the Diagnostic Cost Groups (DCGs), has been re-weighted and tested on a Medicaid patient population.[11] DCGs use age, sex, and diagnoses generated from patient encounters to infer which medical problems are present for each individual and their likely effect on health care costs for a population. DCGs were initially developed in the late 1980's for inpatient admission type of encounters in Medicare populations.[15,16,20]

The nature of the Medicaid databases is one of the major reasons why risk adjustment methods for such a large segment of the US population have not been studied. Their sheer-size and complexity and lower visibility than Medicare files "may have caused some analysts to despair and decide that Medicaid data are hopeless."[47] Furthermore, the lack of consistency of data across states has impaired researchers' ability to formulate research models from one state and to validate these models in other states. A major issue in the development of risk-adjustment models is that of independent sample validation. Indeed, a risk adjustment system is only appropriate when it has been demonstrated to predict the outcome of interest in a population similar but independent to that in question.[24]

However, risk adjustment indices not specific to indigent populations have been used in studies that examined outcomes for Medicaid recipients.[48,49,50,51,52] Weiner found that risk adjustment as measured by the Ambulatory Care Group index plays an essential role in Medicaid populations when explaining variations in patterns of ambulatory care practice.[52] Conversely, Macario found that the Charlson comorbidity score was not a consistent predictor of hospital costs and length of stay for three types of elective surgery (laparoscopic cholecystectomy, colectomy, and knee replacement) across several types of insurance schemes.[48] Another study developed and tested a risk adjustment index to predict 2-year all cause mortality for Georgia Medicaid stroke patients.[53] The study group (n = 4,888 stroke patients) was randomly split two-ways into an exploratory and validation sample. Separate models were derived from the ICD-9-CM-based Deyo's adaptation of the Charlson index and Von Korff's Chronic Disease drug-based score and the combined Charlson and CDS categories. Researchers found that the CDS-based index predicted mortality just as well as the Charlson-derived index. The best model was obtained when demographic information was included and all Charlson and CDS derived comorbidities were allowed to enter the model through a stepwise procedure. Table 1 presents the empirical odds-ratio from the final model, combining ICD-9-CM- and CDS-based comorbidities.

Table 1: Two-year All Cause Mortality for First Time Stroke Medicaid Patients: Empirical Odds-Ratio (OR)

| Covariates | OR < 1 | 1 < OR ≤ 2 | 2 < OR ≤ 10 | OR > 10 |
|---|---|---|---|---|
| Age | | 1.6 (10 years) | | |
| Gender | | 1.5 (male) | | |
| Ischemic | | 2.1 * | | |
| Hemorrhagic | | | 5.8 * | |
| NDC Drug Based | Antilipid therapies (0.46) | Rheumatologic / Parkinson / Insulin | 3 cardiac drugs 4 cardiac drugs | Antiviral drugs or AIDS diagnosis |
| ICD-9-CM Based | | PVD** / Renal / Malignancy | Solid tumor / Mild-liver | |

* Base case was Transient Ischemic Attacks; ** PVD: Peripheric Vascular Diseases

Classes defined from the Charlson and CDS complemented each other. The combined index showed a stepwise linear relationship with mortality when tested on the validation sample (as measured by the log-rank test). Therefore, the potential for drugs to be used as the basis for the development of a new class of comorbidity indices needs to be further explored in disease-specific and ambulatory populations.

A second study examined the economic burden of dementia / Alzheimer's disease (D/AD) to Georgia Medicaid.[49] This analysis used a cross sectional matched control group design where cases were defined as persons aged 50 or over with an ICD9-CM code indicative of dementia. For every case, three non-demented controls were selected, matched on age and gender. A total number of 8,671 D/AD cases and 26,013 controls were obtained in 1994. A comorbidity score based upon the Deyo's adaptation of the Charlson Comorbidity Index was used to identify and weight comorbidities. During the course of this investigation, it was discovered that nursing homes customarily code a single ICD-9-CM code per recipient claim and only bill Georgia Medicaid once a month. Therefore, the combination of the low number of nursing home claims per year and a single ICD-9-CM code for each claim yielded a very limited array of ICD-9-CM codes for nursing home residents. Such a limitation resulted in lower than expected Charlson Comorbidity Index score for the D/AD subjects, suggesting that the Charlson index did

not adequately quantify comorbidities in the demented Georgia Medicaid population and that a measure incorporating drug exposure might be beneficial.

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# CHAPTER TWO

# OBJECTIVES AND HYPOTHESES

The objective of this research was to develop a new risk adjustment method improving upon existing risk adjustment techniques. More specifically, the researchers developed and tested the external validity of generic and disease-specific risk adjustment indices based on the combined information from prescription drugs and diagnosis codes. Administrative data containing prescriptions dispensed and diagnoses coded at provider visits were used. Researchers believed that a combined (a diagnosis- and drug-based) risk adjustment method could bridge some of the shortcomings of the use of either method alone. This type of combined (drug- and diagnosis-based) risk adjustment indices represented a new venue in the field of risk adjustment.

## Objectives

This research utilized two distinct and independent large Medicaid administrative claims databases to develop and validate risk adjustment measures. More specifically, the objectives were to:

1) Combine ICD-9-CM risk adjustment measures developed by Elixhauser and Deyo (Charlson index).

2) Refine and update the revised version of the drug-based Chronic Disease Score developed by Von Korff and revised by Clark and develop a crossover algorithm from drugs, to therapeutic classes, and ultimately to comorbidities.

3) Use drug exposure and ICD-9-CM code-based information to develop combined indices on the Georgia Medicaid population.

4) Assess the performance of the drug-based and diagnosis-based indices separately, and compare them to that of the combined drug and diagnosis index in the Georgia Medicaid population.

5) Test the performance of the new indices on the North Carolina Medicaid population.

## Research Hypotheses

The dissertation project tested the following two hypotheses:

1) Risk adjustment models based on drug exposure information can perform as well as the traditional models based on ICD-9-CM disease information.
2) Risk adjustment models based on combined information (ICD-9-CM diagnosis and drug exposure) can outperform models based on the use of either source of information alone and bridge some of their shortcomings.

## Solutions to Shortcomings of Prior Risk Adjustment Indices

Substantial research has already been published on the role of comorbidity conditions and the use of administrative data. This study addressed the shortcomings of the previous comorbidity studies in the following manner:

1) A major shortcoming preventing a large-scale use of administrative data has been the inability to identify whether a condition became apparent before the inclusion of a patient in the study period. This is a major concern for many studies, since most examined short-term inpatient utilization and mortality[1] We collected data from entire claims databases that included inpatient, long-term stay, and ambulatory care claims as well as pharmaceutical claims. Dated claims allowed identifying the timing of diagnoses and prescriptions, thus, offering a way to distinguish between comorbidities and complications of a disease or event.

2) The development and testing of the comorbidity on the same data and the use limited sets of patients tend to overestimate the gains in explained variance. Indeed, most

studies have developed comorbidities on limited sets of patients.[2,3,4,5,6,7,8,9] The overestimation is amplified when comorbidity indices are tested on limited sets of patients, as shrinkage increases with small sample sizes and with the number of covariates tested. We developed and tested comorbidity indices on two entirely distinct patient populations, namely Georgia and North Carolina Medicaid recipients over an 8-year period. In addition, when feasible, bootstrapping techniques with built-in shrinkage control were used to obtain nearly unbiased internal assessment of the predictive accuracy of a reduced model.

3) With the exception of one generic instrument, the health services scientific community had ignored the potential of drug claims in the development of comorbidity measures. One of the reasons why drugs were seldom used in the development of comorbidity indices, or more generally risk adjustment methods, is that not all databases provide a reliable and complete history of prescription drugs. For instance, the largest claims database in the U.S., Medicare, provides no information on prescription drugs. Medicaid's computerized pharmacy data files contain information on all prescriptions dispensed by pharmacies in ambulatory, home care, and long term care settings, including the beneficiaries identification number, prescription date, specific drug (oftentimes the National Drug Code), quantity, and reimbursement information for covered drugs. Such a detailed information, the sheer number of recipients, and the fact that claims represent prescriptions actually filled instead of prescriptions written make Medicaid pharmacy data a valuable tool in the development of risk adjustment indices based on drug exposure.

4) No matter how sophisticated, diagnosis codes do not completely describe patients' comorbidity profiles and are sometimes biased toward diagnoses that yield a higher reimbursement rate. Drug-based codes rely on prescriptions, which in some instances may be used for the treatment of various comorbidities for which claim data may not yield corresponding ICD-9-CM codes. We hypothesized that a dual approach methodology combining drug- and diagnosis-based information together would help

address some of the shortcomings of the use of either alone. Researchers believed that combined the combined approach could alleviate some of the administrative left censoring effects that can occur when a chronic condition is diagnosed in a time period prior to a study time frame but is actively being treated with prescription drugs. Combined indices can also provide some information on disease severity where prescription drugs can be used as markers of morbidity within a disease.

## Medicaid Patient Cohorts

The predictors and weights for particular comorbidities should be estimated separately for different populations and different outcomes because their predictive values differ by patient groups.[10] Therefore, the scope of this research limited the development and validation of comorbidity indices to three patient populations with distinct characteristics:

1) A population that experienced a finite acute event, i.e., a cerebrovascular event.

2) A population diagnosed with a lasting chronic condition, i.e., Alzheimer's Dementia and Related Dementias (AD/D).

3) A population of ambulatory patients.

The two disease-specific conditions were chosen because of their high prevalence and increasing clinical importance in an aging America.

## Intents for Use of Developed Models

The major goal of this study was to provide a tool to Medicaid programs and health service researchers to initially stratify or otherwise control for varying levels of disease severity and comorbid illnesses for ambulatory Medicaid recipients and Medicaid patients that will exact an increasing toll on Medicaid resources. Future longitudinal health service research investigations will be able to use models developed in this study when assessing mortality and cost outcomes.

A secondary goal of this study was to develop resources specific to Medicaid patient populations to eventually help to prospective profiling of patients within medical practices or within a geographic area.

A long-term goal for cost risk adjustment indices developed in this study is to help predict future Medicaid costs of certain Medicaid recipients. However, further refinements and independent testing of our cost models will most likely be needed before they can reliably and accurately predict future levels of resource needs.

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# CHAPTER THREE

# RESEARCH DESIGN, SUBJECTS, DATA SOURCES, AND METHODS

## Research Design

This study utilized a retrospective longitudinal review of Medicaid administrative claims data to develop three types of risk adjustment indices: one based on drug exposure, one on ICD-9-CM codes, and one the combined information from drug exposure and ICD-9-CM diagnoses codes. Risk adjustment indices were developed and tested for three patient cohorts: patients with a new/first cerebrovascular event; patients with a first diagnosis of Alzheimer's dementia and related dementias (AD/D); and patients living in the ambulatory setting. The Deyo's adaptation of the Charlson index and the Elixhauser index served as the basis of the diagnosis ICD-9-CM-based measures; Von Korff's Chronic Disease Score provided the foundation of the drug exposure measures. Models were developed on the Georgia Medicaid population and tested on the North Carolina Medicaid population.

Outcomes of interest were one-year total direct medical and pharmaceutical expenditures to Medicaid, 30-day all-cause mortality for the cerebrovascular cohort, six-month all-cause mortality for the AD/D cohort, one- and two-year all-cause mortality for the cerebrovascular and AD/D cohorts and seven-year survival for ambulatory patients. The entire study period used data spanning from January 1990 to December 1997.

## Research Subjects

The inclusion and exclusion criteria specific to the three patient cohorts (cerebrovascular, AD/D, and ambulatory patients) are described in detail in the chapters

devoted to each of the three cohorts. For each cohort, these criteria were uniformly applied to the Georgia and North Carolina Medicaid recipients.

Data Collection

The Georgia and North Carolina Medicaid databases (years 1990 to 1997) were used respectively to develop and test risk adjustment indices for each of the three patient populations. Administrative data of this type were chosen because they allow a detailed description of prescription claims and ambulatory physician, inpatient hospital, outpatient hospital, nursing homes, and other outpatient services utilization. Additionally, these data have been found valid for economic, epidemiologic, and pharmacoepidemiologic investigations.[1,2,3,4,5,6,7] The Georgia Department of Medical Assistance (GDMA) is the state agency responsible for operating the Medicaid program in Georgia and the North Carolina Department of Medical Assistance for North Carolina (NCDMA). Electronic Data Systems, Inc. (EDS) is the fiscal agent for both Medicaid programs. The two Medicaid programs have similar eligibility criteria, demographic composition (Southern U.S.), and drug coverage policies, which brings a certain level of uniformity in the two Medicaid databases and populations.

1) The Georgia Medicaid data are housed at the University of Georgia where they have been converted to SAS data sets stored on 3490E 76K BPI cartridges (SAS Institute, Cary, NC, USA). The data were output in character and numeric format and visually inspected and found to be consistent with supplied documentation. The data consist of adjudicated claims for over a million Georgia Medicaid recipients with over 120 million medical and pharmaceutical claims in the 8-year study period (1990-1997). The data are organized in four broad types of files:

a) Monthly medical history files that contained information for all reimbursed, non-drug, medical claims;

b) Monthly pharmaceutical history files that supplied all prescription transactions reimbursed by the DMA Drug Program;

c) Annual recipient eligibility files that contained demographic profile and eligibility history for each Medicaid enrollee month by month;

d) Annual provider files that contained providers' identification number, specialty, and practice setting.

2) The North Carolina Medicaid data were housed at the North Carolina DMA facility in Raleigh, NC. The data consisted of non-adjudicated claims for over a million recipients with over 200 million claims in the 8-year study period (1990-1997). In December 1997, Mrs. Daphne O. Lyon, Deputy Director of the North Carolina Division of Medical Assistance[1], approved a synopsis of the proposal and the transfer of all North Carolina Medicaid data from January 1, 1990 to December 31, 1997 from the NC State Information Processing Center to the University of Georgia (Appendix A). All North Carolina claims along with the information on providers and recipients' demographics and eligibility status were copied onto compressed 3490E 76K BPI cartridges. Tapes were cataloged and copied for back up. Ineligible system claims that represented financial and banking transactions within the NC DMA were discarded. Finally, North Carolina SAS data sets were built by transferring data from a COBOL non-adjudicated claim format to SAS monthly claims data sets that mirror the layout and organization of the Georgia Medicaid data files.

3) Structural Attributes of Medicaid Data

Each Georgia and North Carolina Medicaid recipient is identified by a unique patient identification number (called "base id") that remains constant despite changes in eligibility status. Therefore, information about service and drug use can be linked at the individual patient level, across settings of care, month after month, year after year. Georgia and North Carolina medical history files collect the principal diagnosis,

[1] Mrs. Daphne O. Lyon, Deputy Director, North Carolina Division of Medical Assistance, P.O. Box 29529, Raleigh, NC 27626-0529.

procedure, and up to eight secondary diagnoses and four secondary procedures for certain types of medical claims. In both states, each prescription claim includes a National Drug Code field. Lastly, in order to protect patient confidentiality, Georgia and North Carolina EDS scramble identifiers of all recipients and providers, and remove personal information that could potentially help a researcher determine the identity of a given patient. The principal investigator obtained Institutional Review Board approval for the project (project number H980679 - CFR category 46.101 (4) - Institution Assurance number M1047 - Appendix B).

## Risk Adjustment Algorithms

Risk adjustment indices were based on medical and pharmaceutical encounters that occurred during the 12-month observation period prior to the index dates of the cerebrovascular, dementia, and ambulatory groups. Index dates were defined as the first date of a cerebrovascular diagnosis (stroke) for the cerebrovascular cohort and the first date of a Alzheimer's dementia or related dementias diagnosis for the AD/D cohort. Index dates for the ambulatory cohort were arbitrarily defined as the first day of the calendar years 1991 through 1996.

### 1) Comorbidity ICD-9-CM Code-based Measures

Researchers combined elements of the Deyo's adaptation of the Charlson Index,[8] and the updated set of comorbidity measures published by Elixhauser.[9] The latter was specifically developed for use with large administrative data sets and tested on homogeneous as well as on heterogeneous patient populations. Our research team, however, made minor changes to the Elixhauser's proposed classification since the set of 30 comorbidities geared toward inpatient data and not toward retrospective longitudinal studies. First, we added back from the Deyo's adaptation of the Charlson index the definition of three comorbidities: myocardial infarct (MI), cerebrovascular accidents, and dementia. These comorbidities have been shown to impact mortality and/or utilization in ambulatory populations. MI is a known risk factor for stroke survival.[10,11] Further, we

merged blood loss and deficiency anemias into a single comorbidity class (anemias). In addition, a preliminary study on Medicaid stroke patients indicated that it would be beneficial to merge complicated and uncomplicated hypertension into a single comorbidity class: hypertension.[12] We also combined the complementary definitions of paralysis (hemiplegia and paraplegia) from Elixhauser and Deyo. Lastly, we used the Deyo's broader definition of ulcer since it applies to longitudinal studies with an observation period prior an index date. The final set of 31 comorbidities along with their ICD-9-CM codes is displayed in Table 1.

2) National Drug Codes and Drug Exposure Measures

Drug code-based measures were built from drug exposure and not ICD-9-CM codes information. The Chronic Disease Score developed by Von Korff[13] and revised by Clark,[14] and the rationale supporting it, served as the foundation of our drug code measures. National Drug Code (NDC) serves as a universal product identifier for human drugs. The 11-digit NDC format used by HCFA has become the universal standard and is the coding scheme used in the Georgia and North Carolina Medicaid databases, where one and only one NDC is assigned to a drug claim.

Study investigators used Multum Information Services Therapeutic classification and database as the backbone of the crosswalk from NDC to therapeutic classes (http://www.multum.com). The Multum data base is updated weekly with the latest published NDC's. Multum obtains its information on NDC's from the pharmaceutical industry, wholesalers, the Federal government, drug catalogs, etc. As of October 1998, there were 181 active therapeutic classes. Classes that were too heterogeneous were partitioned further by the investigators. For instance, the class 129 (miscellaneous respiratory agents) was split four ways between leukotrien asthma agents (class 930), cystic fibrosis alpha agents (class 931), sodium chloride (class 932), and surfactant agents (class 933).

Table 1: Definitions of ICD-9-CM based Comorbidities and their Operational Definitions

| Comorbidities | ICD-9-CM Codes |
|---|---|
| 1. Congestive heart failure | 389.91, 402.11, 402.91,404.11, 404.13, 404.91, 404.93, 428.0-428.9 |
| 2. Myocardial infarction | 410-410.9, 412, 429.71, 429.79 |
| 3. Cardiac arrhythmias | 426.10, 426.11, 426.13, 426.2-426.53, 426.6-426.89, 427.0, 427.2, 427.31, 427.60, 427.9, 785.0, V45.0, V53.3 |
| 4. Valvular disease | 093.20-093.24, 394.0-397.1, 424.0-424.91, 746.3-746.6, V42.2, V43.3 |
| 5. Pulmonary circulation disorders | 416.0-416.19, 417.9 |
| 6. Peripheral vascular disorders | 440.0-440.9, 441.2, 441.4, 441.7, 441.9, 443.1-443.9, 447.1, 557.1, 557.9, 785.4, V43.4 |
| 7. Hypertension (complicated and uncomplicated) | 401.1, 401.9, 402.10, 402.90, 404.10, 404.90, 405.11, 405.19, 405.91, 405.99 |
| 8. Hemiplegia / paraplegia | 342.0-344.9 |
| 9. Other neurological disorders | 331.9, 332.0, 333.4, 333.5, 334.0-335.9, 340, 341.1-341.9, 345.00-345.11, 345.40-345.51, 345.80-345.91, 348.1, 348.3, 780.3, 784.3 |
| 10. Chronic pulmonary disease | 490-492.8, 493.00-493.91, 494, 495.0-505, 506.4 |
| 11. Diabetes, uncomplicated | 250.00 - 250.33 |
| 12. Diabetes, complicated | 250.40 - 250.73, 250.90-250.93 |
| 13. Hypothyroidism | 243-244.2, 244.8, 244.9 |
| 14. Renal failure and chronic disorders | 403.11, 403.91, 404.12, 404.92, 582-582.9, 583-583.7, 585, 586, 588-588.9, V42.0, V45.1, V56.0, V56.8 |
| 15. Liver disease | 070.32, 070.33, 070.54, 456.0, 456.1, 456.20, 456.21, 571.0, 571.2, 571.3, 571.40-571.49, 571.5, 571.6, 571.8, 571.9, 572.3, 572.8, V42.7 |
| 16. Peptic ulcer disease | 531-534.9, V12.71 |
| 17. AIDS | 042-044.9 |
| 18. Any malignancy, including leukemia and lymphoma | 140.0-172.9, 174.0-175.9, 179-195.8, 200.00-202.38, 202.50-203.01, 203.8-203.81, 238.6, 273.3, V10.00-V10.9 |
| 19. Metastatic solid tumor | 196.0-199.1 |
| 20. Rheumatoid arthritis / collagen vascular disease | 701.0, 710.0-710.9, 714.0-714.9, 720.0-720.9, 725 |
| 21. Coagulopathy | 286.0-286.9, 287.1, 287.3-287.5 |
| 22. Obesity | 278.0 |
| 23. Weight loss / malnutrition | 260-263.9 |
| 24. Fluid and electrolyte disorders | 276.0-276.9 |
| 25. Anemia | 280.0-281.9, 285.9 |
| 26. Alcohol abuse | 291.1, 291.2, 291.5, 291.8, 291.9, 303.90-303.93, 305.00-305.03, V11.3 |
| 27. Drug abuse | 292.0, 292.82-292.89, 292.9, 304.00-304.93, 305.20-305.93 |
| 28. Psychoses | 295.00-298.9, 299.10-299.11 |
| 29. Depression | 300.4, 301.12, 309.0, 309.1, 311 |
| 30. Cerebrovascular disease | 430-438 |
| 31. Dementia / Alzheimer | 290-290.9, 331-331.9, 797, 294.9 |

ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification

Note on Operational Definitions: A hierarchy was developed between the following pairs of comorbidities.[9] If both uncomplicated diabetes and complicated diabetes are present, count only complicated diabetes. If both solid tumor without metastasis and metastatic solid tumor are present, count only metastatic cancer. This hierarchy helped reduce multicollinearity as many patients were expected to present uncomplicated and complicated diabetes or tumor without metastasis and metastatic solid tumor simultaneously.

Other classes were simply added to the existing classification, such as medical, diagnostic supplies, and nutritional supplement class (class 999). As of November 1998, the classification counted 200 therapeutic classes (Appendix C).

There were over 41,000 distinct NDC's in the Georgia and 38,000 in North Carolina Medicaid databases from 1990 to 1997. The North Carolina and Georgia Medicaid NDC's were merged into a single data set where duplicate NDC's were discarded. This data set was then merged with the Multum NDC database. The Multum - Medicaid combined data set included almost 78,000 NDC's, 52,000 of them directly originated from the Multum database and 26,000 from the Medicaid databases. Medicaid-based NDC's were assigned to a Multum class based on the information gathered from the following sources:

i) The National Drug Code Directory Support Files, ninth edition, which are created by the FDA. The NDC System contains information for the most frequently prescribed drugs only and can be downloaded from the Internet (http://www.fda.gov/cder/ndc/index.htm).

ii) Drug Product Data files which contain the entire formulary of drugs that are available under the Medicaid Drug rebate program (56,000 NDC's). These files are prepared by the Health Care Financing Administration and can be downloaded from the HCFA website (http://www.hcfa.gov). State drug utilization information, however, is only available for outpatient drugs purchased on or after January 1, 1994, by State Medicaid agencies.

iii) The computerized version of the International Pharmaceutical Abstracts compiled by the American Society of Health-System Pharmacists.

iv) The search engine of Thrive on Health, a large consumer health site that catalogs information on medicine (http://www.thriveonline.com/health).

v) The American Hospital Formulary Service Drug Information, [15] a comprehensive source of evaluative drug information written by the American Society of Hospital Pharmacists.[2]

vi) American Drug Index references books.[16,17]

After searching all the above sources, only 1,045 Georgia and North Carolina Medicaid NDC's could not be assigned to a Multum therapeutic class, representing less than 0.2% of the total number of prescriptions paid for by the two Medicaid programs between 1990 to 1997. The final data set holds the following information for all Multum native NDC's and almost every Medicaid native NDC that was successfully matched: trade name, drug name, strength, dosage, and a Multum therapeutic class. Based on the NDC therapeutic classes developed as part of this study and the prior work from Von Korff and Clark,[14,13] we defined 27 distinct drug classes, presented in the Table 2.

Statistical Models

Once patient cohorts were identified in the Georgia Medicaid population, models that estimated mortality, survival, and total Medicaid expenditures were developed. Statistical models for the dependent variables fell into one of three categories:

- A logistic model for a binary discrete outcome: mortality at 30-day, six-month, one-year, and two-year all cause mortality;

- A Cox proportional hazards regression models for continuous censored outcome: survival time for ambulatory patients as mortality was lower in the ambulatory cohort, with a 2.8% mortality rate over up to seven-year follow-up.

- A weighted-variance OLS model with Huber-White heteroskedasticty-consistent covariance matrix estimator for continuous uncensored outcome: one-year total Medicaid expenditures.[18,19]

[2] The 1993 edition of AHFS and the 1991 and 1992 editions of the American Drug Index were used because in the Goeriga and North Carolina Medicaid databases most remaining unmatched NDC's dated from claims submitted in the early 1990's.

Table 2: Definitions of Therapeutic Classes (from National Drug Codes) based Comorbidities and their Operational Definitions

| Comorbidity | Therapeutic Classes |
|---|---|
| 1. Cardiac agents | (1) Antiarrythmic, inotropic, cardiac vasopressor agents (2) ACE inhibitors or angiotensin II antagonists - (3) Antianginal agents - (4) Loop diuretics |
| 2. Antiparkinson agents | Antiparkisonian agents (anticholinergic, dopamine agonists, and miscellaneous) |
| 3. Coagulation modifiers | Coagulation modifiers (anticoagulants, antiplatelet agents, heparin antagonists, thrombolytics, miscellaneous coagulation modifiers) |
| 4. Antihypertensives | (1) First-line antihypertensive drugs (β-adrenergic blocking agents; potassium-sparing, thiazide, and miscellaneous diuretics) (2) Second-line antihypertensive drugs (peripherally and centrally antiadrenergic agents; calcium channel blocking agents; antihypertensive combinations; vasodilators agents) |
| 5. Respiratory agents | (1) Adrenergic bronchodilatators, asthma vasopressors, and bronchodilatator combinations - (2) Methylxanthines (3) respiratory inhalant, leukotrien asthma agents, antiasthmatic combinations |
| 6. Drugs for NID diabetes | Oral hypoglycemiant agents |
| 7. Insulins | Insulins |
| 8. Antineoplastics (cancer) | Antineoplastics (alkylating, antibiotics/antineoplastics, antimetabolites, hormones/antineoplastics, miscellaneous antineoplastics, mitotic inhibitors, colony stimulating factors) and 5HT3 antagonists |
| 9. Antiepileptics / anticonvulsants | Anticonvulsants (hydantoin, succinimide, barbiturate, oxazolidinedione, certain benzodiazepine, and miscellaneous anticonvulsants) |
| 10. Acid peptic disease agents | H2 antagonists, proton pomp inhibitors, sucralfate, and antibiotherapy cocktails |
| 11. Glaucoma | Ophthalmic glaucoma agents |
| 12. Antigout agents | Allopurinol, colchicine, probenecid, and miscellaneous |
| 13. Anti-hyperlipidemia, hypercholesterolemia | HMG-CoA reductase inhibitors, fibrates, sequestrants, probucol, and miscellaneous |
| 14. Antiretrovirals (aids) | Protease, nucleoside, and non-nucleoside reverse transcriptase inhibitors |
| 15. Thyroid agents | Levothyroxine and thyroid replacement agents |
| 16. Narcotic analgesics | Narcotic analgesics |
| 17. Antidepressants | SSRI, tricyclic, MAO, and miscellaneous antidepressants |
| 18. Neuroleptics | Phenothiazine, trazodone, and miscellaneous antipsychotics |
| 19. Dementia agents | Donepezil and tacrine |
| 20. Antituberculosis agents | Ethambutol, isoniazid, rifampin, pyrazinamide, and miscellaneous |
| 21. Drug for rheumatologic conditions | Gold salts and hydroxychloroquin |
| 22. Systemic steroids | Systemic adrenal cortical steroids |
| 23. Drug for Irritable bowel disease | Mesalamine, olsalazine, infliximab |
| 24. End stage renal disease | Hematopoietic agents (marrow stimulants, erythropoietin) |
| 25. Immunosuppressive agents | Azathioprine, basiliximab, cyclosporine, daclizumab, muromonab-CD3, mycophenolate mofetil, and tacrolimus |
| 26. Antimigraine agents | Triptans, ergotamines, and miscellaneous combinations |
| 27. Drugs for bone diseases (Padget's disease, osteoporosis) | Alendronate, etidronate, pamidronate, risedronate, tiludronate, raloxifene, cacitonin, and calcium carbonate products (with or without added vitamin D) |

ACE inhibitors, angiotensin converting enzyme inhibitors; CHF, congestive heart failure; ESRD, end stage renal disease; HIV, Human Immunodeficiency Virus; IBD: irritable bowel disease; MAO, monoamine oxydase inhibitors; NDC, National Drug Codes; NID Diabetes, non insulin-dependent diabetes; SSRI, selective serotonin reuptake inhibitors.

Note that angiotensin II antagonist and non-nucleoside reverse transcriptase inhibitors were not yet commercialized at the time of the study period.
Note on Operational Definitions: A hierarchy was developed between certain therapeutic classes.[13,14] If both non insulin-dependent and insulin-dependent diabetes drugs were present, we counted only insulin-dependent diabetes drugs. If both first- and second-line antihypertensive drugs were present, we counted only second-line antihypertensive drugs.[20]
If drugs from only one therapeutic respiratory illnesses were found for a given patient, then the dummy RESPIRATORY-1 variable was set to 1, 0 elsewhere; if two classes were found then RESPIRATORY-2 was set 1, 0 elsewhere; likewise for the RESPIRATORY-3 variable. A similar coding system was used for the therapeutic classes from the cardiac conditions with the definition of the CARDIAC-1 to CARDIAC-4 variables. The clinical panel felt that systemic adrenal cortical steroids should be assigned to their own class since they have multiple indications.

Logistic, Cox proportional hazards regression, and weighted least square models were estimated with:

- Intercept;

- Age and possibly a quadratic age term to flexibly fit the smooth relationship between age and its dependent variables;

- One dummy variable for race (black vs. other);

- A set of dummy variables coded 1 for the presence and 0 for the absence of a given comorbidity. The 31 comorbidities along with their ICD-9-CM codes are presented in Table 1 along with their operational definitions;

- A set of dummy variables coded 1 for the presence and 0 for the absence of a drug (NDC) in a given therapeutic class. The 27 drug exposure definitions along with their therapeutic classes are presented in Table 2 along with their operational definitions;

- One dummy variable for the type of stroke in the cerebrovascular cohort;

- Two dummy variables for the place of treatment/residence within two weeks prior to the index AD/D diagnosis or at the time of the stroke event.

- Medicaid eligibility (blind-disabled) and Medicare eligibility for the ambulatory cohort.

- Interaction terms between age and gender, between race and gender.

Expenditure data were adjusted for medical and drug inflation through the use of the consumer price index (CPI) for medical commodities and services (http://stats.bls.gov/cpihome.htm). The year 1995 served as the baseline year for the

cerebrovascular and AD/D cohorts and the year 1996 for the ambulatory cohort as 1995 and 1996 were, respectively, the last year of inclusion in the study for each cohort.

One-year total expenditures are a function of the survival time during a year. In order to prospectively account for follow-up time in a cost model, we used the method described by Ash.[21] During the follow-up year, Georgia Medicaid expenditures were prorated to 12 months for patients who died during the one-year follow-up, e.g., total expenditures of a patient who expired at end of month six were doubled. Additionally, the variance of all observations was weighted by the fraction of the year during which the person remained alive for Medicaid reimbursement, e.g., variance of a patient who expired at end of month six was doubled.[21,22]

## Model Derivation

Researchers estimated and externally tested 30 models: six for the ambulatory cohorts and twelve for the cerebrovascular and AD/D cohorts. Models derived risk adjustment indices based on ICD-9-CM codes alone, drug exposure alone, and ICD-9-CM and drug exposure simultaneously. Once all data on all three cohorts were assembled, they were imported from a MVS to a PC environment.

### 1) Data (variable) reduction

When many predictor variables are analyzed, variable screening based on statistical significance and stepwise variable selection involve multiple comparisons that lead to unreliable models.[23] However, if the total number of events (e.g., patients expired in the case of a mortality outcome study) is at least 10 times greater than the number of potential predictors then the final model should achieve good predictive discrimination.[24] In that case, researchers may omit the use of true variable reduction techniques such as principal components and variable clustering.[25,26]

2) Analytic methods

Models examining total Medicaid expenditures, a continuous outcome, suffered from heteroskedasticity. They were therefore estimated with the sandwich estimator of variance that provides a heteroskedasticty-consistent covariance matrix estimator.[18,19] STATA Version 6.0 was used to derive expenditure models (STATA Corporation, College Station, TX, USA).

Logistic regression was used to model the binary mortality outcome in the cerebrovascular and demented cohorts (PROC LOGISTIC under SAS 6.12). It is the most widely used approach for modeling dichotomous dependent variables. It performs favorably even compared with other, more complex modeling approaches.[27,28]

Cox proportional hazards regression was used to model survival with a maximum censoring at 7 years in the ambulatory cohort. SAS PROC PHREG (SAS 6.12) was used to derive parameter estimates, and model calibration and discriminations indices.

3) Step 1: Initial comorbidity variable screening

Comorbidity and drug exposure burden was assessed in each of the three patient cohorts for the year prior to the index date. When the prevalence was low, i.e., total number of cases less than 20 for cerebrovascular and AD/D cohorts and 100 for ambulatory cohort, then two approaches were considered. First, we attempted to merge the low-prevalence comorbidity variable with another one, so that the resulting variable was clinically meaningful. Second, if the comorbidity was such that it could not be meaningfully merged with another one or if its prevalence was zero, then the comorbidity variable was dropped altogether from further analysis. For instance, the variable coding for the irritable bowel disease was dropped in all three cohorts. Lastly, because of the possible overlap in certain drug- and ICD-9-CM-defined classes, information from the two sources could be aggregated in the combined models, such as antiretroviral therapy and a diagnosis claim for aids.

4) Step 2: Initial stepwise procedure

All potential covariates were included in a stepwise selection procedure with a significance level for entry of 0.20 and for staying in the model of 0.10.[29] As noted earlier, an inherent problem with stepwise variable selection is that the variables selected, especially in the later steps, may represent noise and cause prediction ability actually to worsen in a new sample. The 10% significance level required for a variable to stay in the model limited the inclusion of noise variables in our comorbidity indices.[30,31]

5) Step 3: Internal validation with bootstrapping

The principal methods for internal validation are data splitting, cross-validation, and bootstrapping.[32,33,34] This research used a bootstrap technique, the most rigorous of the three methods of internal validation, to increase the internal validity of the cerebrovascular and AD/D models developed on the Georgia Medicaid cohorts. It involved taking a large number of samples with replacement from the original sample.[35] It provides a nearly unbiased estimate of predictive accuracy and requires fewer model estimations than cross-validation. Bootstrapping also has the advantage of using the entire data set for model development and minimizes influences of potential outliers.

Mortality models derived for stroke and AD/D cohorts were submitted to the bias-corrected bootstrap internal validation procedure that was described in detail by Harrell.[36] In this procedure, a measure of "apparent accuracy" was first computed on the model that made most clinical sense using all n subjects. Then a sample of size n with replacement was generated from the original sample (200 times) and the measure of accuracy on the bootstrap sample was computed. The bootstrapped model was then frozen and its performance evaluated on the original data set. The optimism in the fit from the bootstrap sample is defined as the difference between the bootstrapped measure of accuracy and the one obtained on the original data set with the frozen model. The final bootstrap corrected performance estimate of the model was the difference between the "apparent accuracy" and the average optimism over the 200 bootstrapped samples. It

represents is a nearly unbiased estimate of the expected value of the external predictive discrimination. In other words, it is the honest estimate of the internal validity, penalizing for overfitting.

Expenditure models derived for cerebrovascular and dementia cohorts were submitted to a bootstrap internal validation procedure in conjunction with a robust estimator of the variance comatrix for each bootstrapped sample. Note that the large sample size in the GA ambulatory cohort (n > 270,000 patients) rendered the application of bootstrap technique unfeasible (even on a MVS platform).

6) Step 4: Clinical expert judgment

Univariate statistical analyses, detailed results from the initial stepwise procedures, and summaries from the bootstrap simulations were presented to panels of stroke, AD/D, and general medicine clinical experts comprised of physicians and clinical pharmacists. Clinical experts reviewed the findings and helped determine which of the variables should stay in the models and be submitted to the external validation procedure. Like Keeler,[37] during the development phase of the APACHE III, researchers were allowed to drop factors empirically identified on sole statistical evidence but that might be unlikely predictor of the outcome studied based on clinical expertise.

Measures of Model Accuracy and Performance

Predictive accuracy carries a dual meaning in this research. It quantifies the utility of the models for prediction to identify subjects at increased risk of death or higher health care utilization. It also checks whether a given model suffers from overfitting (fitting noise resulting in unstable regression coefficients) or lack of fit (improper model specification or underfitting).[36] There are two components to predictive accuracy: calibration and discrimination. Calibration refers to the extent of the bias for the outcome measure. Discrimination measures a predictor's ability to separate patients with different responses. Discrimination was assessed on the Georgia and North Carolina cohorts.

However, calibration could only be meaningfully assessed on the validation population, i.e., North Carolina data.

1) Linear regression: one-year total Medicaid expenditures outcome

In the case of a continuous uncensored outcome, discrimination is related to the expected square error and to the correlation between predicted and observed responses. In the case of ordinary multiple linear regression (OLS), discrimination can be measured by the squared multiple correlation coefficient $R^2$. $R^2$ was adjusted for shrinkage.[38] It was corrected for the number of candidate predictors that were initially tested and not limited to the number of covariates that entered the final model. The formula of the shrunk $R_A^2$ is as follows: $R_A^2 = 1 - (1- R^2) (N -1) / (N - p - 1)$
where N is the number of patients, p is the total number of candidate predictor variables.

2) Logistic regression: one-month, six-month, one-year, and two-year all-cause mortality outcomes

When modeling binary outcome, the usual mean-square error type measure does not apply to assess discrimination. In that case, the c index (concordance) index is the most widely used measure. This index of predictive discrimination is related to the rank correlation between predicted and observed outcomes, derived from the Kendall-Goodman-Kruskal-Somers type rank correlation.[25] The c index reflects the proportion of all usable pairs of patients in which the predictions and outcomes are concordant. The c statistic is easy to interpret since it estimates the probability that for a randomly chosen pair of patients, the one having the higher predicted survival is the one who survives longer. A value of c of 0.5 indicates no predictive discrimination whereas a value of 1.0 indicates perfect separation of patients with different outcomes. A shrunk estimate of c with its 95% non-parametric bootstrap confidence interval was computed.

Logistic model explained variation was assessed by calculating $R_{SS}^2$ adjusted for shrinkage.[39] $R_{SS}^2$ adjusted permits an analogous calculation to the $R_{adj}^2$ in linear

regression models by controlling for the inflation tendency in situations where there are a large number of candidate covariates relative to the sample size.

3) Cox proportional hazards regression: survival outcome for ambulatory cohort

When dealing with a censored continuous dependent outcome, such as survival, the Somer's $D_{yx}$ rank correlation is a widely used measure of discrimination. It is the correlation between predicted log hazard and observed survival time. It penalizes for ties, and is defined as follows:[40]

$$D_{yx} = [P(\text{concordance}) - P(\text{discordance})]/[1 - P(\text{tied on Y})]$$

The Somer's $D_{yx}$ rank correlation was computed with STATA for the survival outcome and transformed back to a c-statistic measure, as c-statistic = $(D_{yx} + 1) / 2$.

4) Measure of Models Performance

In the case of a continuous dependent variable, $R^2$, coefficient of determination, is the standard summary measure of model performance. For a binary outcome such as death, the Hosmer-Lemeshow statistic for the logistic regression was used to evaluate the fit of each logistic model, with a p value less than 0.05 indicating a poor model fit.[41]

Models External Validation

The most stringent test of a model is external validation: the application of a 'frozen' model to a new population.[36] The value of a set of predictors depends upon reproducibility in an independent sample. Without an external validation, investigators may remain unaware that some factors represent spurious associations with the outcome because of 'noise' in the data or multiple comparisons.[25,42] The bootstrap process defined above tested the internal validity of 24 models for three Georgia Medicaid patient cohorts. After clinical expert review, the models were then 'frozen' and externally tested on North Carolina Medicaid cohorts. A description of discrimination, explained variation, and model performance statistics that were computed for each model are presented in the Table 3.[43,44] Programs used to obtained discriminative and calibration

performance of the GA. Models on the NC cohorts are presented in the Appendix D (logistic models with c-statistic and Hosmer-Lemeshow test), Appendix E (least square models with R2), and Appendix F (Cox proportional hazard models with c-statistic).

Table 3: Measures of discrimination, model performance, and explained variation for each model on North Carolina Cohorts

| Model | Outcome | Discrimination | Explained Variation | Model Performance |
|---|---|---|---|---|
| OLS | Expenditures | $R^2$ | $R^2$ | $R^2$ |
| Logistic | Mortality | c statistic | $R_{SS}^2$ | Hosmer-Lemeshow (1980) |
| Proportional Cox Hazards | Survival | Somer's $D_{yx}$ (c statistic) | $R^2$ | - |

The performance of each model was compared with that of other models (drug only, ICD-9-CM only, and combined models) and at the different follow-up times when feasible (e.g., at one month, one and two years for the mortality outcome in the stroke cohort). In the cost models, we tested the relative performance ($R^2$) of the drug only and ICD-9-CM only models with respect to that of the combined model with a J-Test.[45] Whenever possible, we also compared the performance of our models with that of similar published models for the same patient population (e.g., stroke or ambulatory) and to that of accepted benchmarks. For instance, "20% is generally considered the current upper bond of explainable variation; the rest simply may be random or unforeseeable (such as expenditures related to accidents."[46,47]

The inclusion and exclusion criteria used to define the three North Carolina cohorts were the same as those used for the Georgia recipients. Final cohort sample sizes were larger in NC than in GA. Each of the three NC samples was randomly divided into two subsets. The first one, the test sample with 60% of the observations, was used for testing the external validity of the GA models. The second one, the holdout sample with the remaining 40% of the observations, was saved for future validation, in case models would have to be re-estimated.

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# CHAPTER FOUR

# PROSPECTIVE MORTALITY RISK ADJUSTMENT INDICES FOR STROKE USING ADMINISTRTIVE DATA[1]

[1]Ricci, JF., S. C. Fagan, and B. C. Martin. To be submitted to Stroke, 2001.

ABSTRACT

***Background and Purpose*** – Several clinical and/or diagnostic-based models have been developed to predict short-term post-stroke mortality. These models are to guide clinicians in their decision making process for the management of a stroke patient. No model has yet been developed to predict short- or long-term mortality outcomes of stroke patients at a population level. This research describes the development and independent validation of prospective mortality risk-adjustment indices for incident cases of ischemic and hemorrhagic stroke based on automated pharmacy and medical claims data.

***Methods*** – A retrospective review of Georgia (training sample) and North Carolina (validation sample) claims Medicaid data for eight years (1990 to 1997) was used to detect persons with a first stroke event (primary ICD-9-CM codes 430.XX; 431.XX; 434.XX; 436.XX) in a 12-month period. ICD-9-CM-based comorbidities and drug exposure the year prior to the index stroke were collected along with demographic information to predict one-month, one- and two-year post-stroke all cause mortality. Three types of models were developed: models with drug exposure data, models with ICD-9-CM codes, and models with combined drug exposure and ICD-9-CM information. Multivariate logistic regression techniques were used to develop the models, bootstrapping to assess internal validity on GA training sample, and c-statistic to assess predictive discriminative ability. Risk factors, identified on statistical empirical evidence in the GA sample, were subsequently submitted to a clinical panel of stroke experts for validation. Clinically validated GA models were then re-estimated, 'frozen', and prospectively validated on the external NC stroke sample.

***Results*** – We identified samples of 4,632 and 4,500 GA and NC Medicaid stroke patients, with mean ages of 66 and 76 years, respectively. At two-year follow-up from stroke onset, 32% of GA and 40% of NC recipients expired. In all GA models, c-statistic adjusted for shrinkage ranged from 0.673 to 0.734 and adjusted $R_{SS}^2$ ranged from 0.03 to 0.14, with larger model performance observed in the combined models. A large number of classes of cardiac drugs, systemic steroids, opiates, antiretroviral therapy, aids, tumors/cancers, cardiac and organ diseases (renal failure, liver diseases) were factors each associated with increased odds of death of at least 30%. Conversely, the use of coagulation modifiers reduced the odds of 1-month post-stroke death by 38%, the use of lipid-lowering agents reduced the odds of 2-year post-stroke death by 33%, and the use of antidepressants reduced the odds of 1- and 2-year post-stroke death by 30%. When GA 'frozen' models were prospectively tested on the external NC sample, c-statistic ranged from 0.63 to 0.67 and $R^2$ from 0.03 to 0.08. Drug exposure and ICD-9-CM comorbidity provided complementary information.

***Conclusions*** – Drug exposure information has similar predictive ability as ICD-9-CM code-based information at one-month, one- and two-year post-stroke onset. Combined drug and ICD-9-CM variables, however, better predict mortality outcomes than either source alone. Stroke mortality models developed should perform reasonably well in other Medicaid states as they were developed and tested in independent populations.

Key Words: Medicaid; Risk Adjustment; Cerebrovascular Diseases; Comorbidity Index; Mortality; Administrative Data.

INTRODUCTION

Cerebrovascular accidents (CVA) represent a major public health problem in the United States. Stroke alone is the third major cause of death, surpassed only by ischemic heart disease and all forms of cancer, and the leading cause of disability in the United States and other industrialized countries.[1,2] Although with 700,000 new cases a year, the incidence of stroke has been decreasing over the past three decades, the decreasing trend in stroke mortality has slowed down since 1990 and its prevalence. The U.S. prevalence, however, has held steady at 3 million.[3,4] Consequently, the large number of stroke patients has an increasing impact on health care costs as 30% of stroke survivors require assistance in their activities of daily living and 15% are institutionalized.[5] Once stroke patients become disabled, most will become Medicaid eligible , exacting a large toll on Medicaid programs and resources. Medicaid programs, however, operate with limited resources. Models that provide a tool to Medicaid programs and health service researchers to initially stratify or otherwise control for varying levels of disease severity and comorbid illnesses could help better forecast future resource needs and medical planning at of a stroke patient cohort.

Some disease-specific risk adjustment methods for stroke patient populations already exist,[6] however, they have focused on the short-term mortality (1 to 3 months) and/or are based on clinical and/or imaging information.[7,8,9,10,11] Most studies also use information obtained after the stroke onset, such 48-hour CT scan, to predict patient recovery, neurological improvement, survival, or to guide the early management of the patient. This type of information is not readily available from large insurer groups (such as Medicaid) that do not have direct access to clinical and diagnostic information but to large secondary medical and pharmacy claims databases. Generic comorbidity risk-adjustment models have been used to control for comorbidity and severity in stroke population studies to mostly predict health hospital performance, hospital mortality, and hospital length of stay.[12,13,14] No disease risk-adjustment model that predicts stroke

mortality at the population level and/or for long follow-up periods has been developed and externally validated.

To date, the development of risk adjustment indices with administrative databases has mostly relied on diagnosis codes such as the International Classification of Disease, Ninth Revision, Clinical Modifications (ICD-9-CM) codes. Charlson developed one of the first published indices that was later adapted for use with administrative databases.[15,16,17,18,20,21] More recently, a team from the Agency for Health Care Policy and Research (AHCPR) center examined a large sample of hospital discharge data and developed a more comprehensive set of 30 comorbidities based on ICD-9-CM definitions for use with administrative data. ICD-9-CM code-based measures, however, present with a potential for omission bias in coding comorbidities in the context of longitudinal studies.[23] Doctors who treat patients for a given condition at a given time may not always code for that condition at every medical encounter. Also, the comorbidity profile of ambulatory patients with no or few medical encounters might not be accurately represented when all comorbidity information is abstracted from administrative medical data.

Given the limitations of ICD-9-CM code-based risk adjustment models, there exist opportunities to complement these measures with another source of comorbidity information. Medical records represent an invaluable source of such information, containing data on vital signs, patient risk factors, and test results. Clinical data measures tend to capture more completely the acuity and severity of disease of patients than code-based measures.[24,25] Unfortunately, the information needed to code for clinical indicators is not yet recorded in administrative databases such as Medicaid, making their use in population studies almost impossible and prohibitively expensive on the scale needed to develop and validate a comorbidity index. As Roos suggested several claims measures might "well do better than one or more variables collected in an expensive manner," such as diagnostic tests and/or chart reviews.[26] As a research team from the Group Health Cooperative (GHC) of Pudget Sound, Seattle, WA demonstrated, detailed prescription

files can serve as an inexpensive and complementary source of information on patients' comorbidities derived from ICD-9-CM code-based information.[27] Von Korff developed the first published drug-based index, the chronic disease score (CDS). He evaluated its "usefulness of a measure of chronic disease status in terms of stability over time and its association with other health status measures after controlling for age, gender, and level of utilization of care." Early on, Johnson independently tested and validated the use of the CDS as a readily accessible low cost measure of health status.[28] Until recently, however, few published studies have incorporated the CDS as a generic health status indicator.[29,30,31]

Medicaid programs cover most of the long-term care needs of stroke patients needing post-stroke institutional care and Medicaid databases contain demographic, medical, and drug utilization information for the indigent US population necessary to perform longitudinal studies. Low economic status has been linked to excess mortality rates.[32] Epstein (1989) noted that uninsured or Medicaid patients in Massachusetts were significantly more likely than privately insured patients to be hospitalized for potentially avoidable causes, such as asthma, gangrene, hypokalemia, malignant hypertension, and bleeding ulcers.[33,34] Such patients often have a higher risk of death, increased chance of complications, impaired recuperative abilities; all these factors negatively affect their longevity.[35] Using U.S. census data, Casper (1997) found that the highest rates of premature stroke mortality were observed among the lowest social classes.[36] Still, little published research has developed and validated mortality risk adjustment indices specific to Medicaid populations. The nature of the Medicaid databases is one of the major reasons why risk adjustment methods for such a large segment of the US population have not been studied. Their sheer-size, complexity, and lower visibility than Medicare files "may have caused some analysts to despair and decide that Medicaid data are hopeless".[37] Furthermore, the lack of consistency of data across states has impaired researchers' ability to formulate research models from one state and to validate these models in other states. Therefore, the objectives of this study were twofold:

1) To develop population-based mortality risk-adjustment indices for Medicaid stroke patients based on ICD-9-CM codes and drug exposure separately and combined ICD-9-CM codes and drug exposure data. One-month, one- and two-year prospective mortality indices were developed to test whether risk factors for patients who survive the acute post-stroke mortality window differ from those who do not.

2) To test the validity of new indices on an independent external Medicaid patient population from another state.

## SUBJECTS AND METHODS

### Data Sources

A retrospective review of the Georgia and North Carolina Medicaid claims data was used to detect patients with a primary diagnosis of stroke. The Georgia and North Carolina Department of Medical Assistance are the state agencies responsible for operating the state Medicaid programs. The Georgia and North Carolina Medicaid data are housed at the University of Georgia Computer Center where they have been converted to SAS data sets stored on 3490E 76K BPI cartridges. The data consist of adjudicated claims for over a million Medicaid recipients in each state with all pharmaceutical and medical claims examined in the 8-year study period (1990-1997). The training sample was obtained from the Georgia Medicaid population and the out-of-sample validation set from the North Carolina Medicaid population. Demographic and eligibility characteristics, associated comorbidities, drug exposure, and mortality outcome were recorded for each patient.

### Cohort Definitions

Due to differences in genesis of cerebrovascular diseases, the etiology of stroke in older patients differs from that in younger subjects. In fact, as low as 3% of cerebral infarction occur in patients under the age of 40.[38] As a consequence, our study limited the patient population to recipients 40 years of age older the day of their recorded stroke

claim. Hemorrhagic and ischemic strokes have different pathophysiologies and prognoses and often require different treatments.[39] Therefore, patients with a CVA were divided into two categories based on the primary ICD-9-CM coded on the initial cerebrovascular claims:[40]

- Ischemic stroke: 434.XX and 436.XX;
- Hemorrhagic stroke: 430.XX and 431.XX.

Patients with a primary CVA diagnosis code of 432.XX, 433.XX, or 437.XX were excluded from the study because these ICD-9-CM series were found unreliable markers of stroke when ascertained against medical records reviews.[41,42,43] In addition, patients with a primary diagnosis code of 438.xx were not included because the 438.xx series identifies patients suffering from complications of a prior CVA and not from a new CVA event. The date of a recipient's first stroke claim during the inclusion period (January 1, 1991 to December 31, 1995) was termed their index date. Patients remained in the study cohort if they met the following inclusion criteria. Patients had to be continuously eligible the year prior to their index stroke claim and free of any stroke event (primary and all secondary ICD-9-CM codes 430.XX to 438.XX) during these 12 months. Patients also had to be eligible for two years after the initial stroke event or die any time after their index stroke event while continuously eligible. We collected all outpatient pharmacy and medical claims for the 12 month-period prior to and up to 24 months after the index stroke event.

Comorbidity Definitions

To develop the list of potential ICD-9-CM code-based comorbidity markers, we combined elements of the Deyo's adaptation of the Charlson Index[(44)] and the updated set of comorbidity measures published by Elixhauser.[23] Based on Deyo's method, we adapted the classification proposed by Elixhauser for use in retrospective longitudinal studies since the set of 30 comorbidities by Elixhauser was geared toward the use of inpatient data. First, we added back from the Deyo's adaptation of the Charlson index the

definition of two comorbidities: myocardial infarct (MI) and dementia as these comorbidities have been shown to be associated with stroke incidence.[45,46,47] Further, we merged blood loss and deficiency anemias into a single comorbidity class. In addition, based on the results of an earlier study of Medicaid stroke patients, complicated and uncomplicated hypertension were combined into a single comorbidity class.[48] We also combined the complementary definitions of paralysis (hemiplegia and paraplegia) from Elixhauser and Deyo. Lastly, we used the Deyo's broader definition of ulcer since it applies to longitudinal studies with an observation period prior an index date. The final set of 31 comorbidities (ICD-9-CM codes) is displayed in Table 1. By study design, patients with a diagnosis code for cerebrovascular events during the one-year observation prior to their index date were excluded from the study.

The Chronic Disease Score developed by Von Korff,[27] and revised by Clark,[49] and the rationale supporting it, served as the foundation of our drug exposure measure that includes 27 drug-based categories (Table 2). All drug claims during the one-year pre-index date observation period were sorted by National Drug Code number and assigned to a therapeutic class using a classification algorithm (http://www.multum.com). As the CDS was published in 1992, we updated different drug classes to reflect the availability of newer pharmacological classes and agents.

In addition to comorbidity and drug definitions described above, covariates coding for demographic, eligibility, stroke-specific information (ischemic vs. hemorrhagic stroke), a quadratic term for age, and interaction terms were allowed to enter each of the drug-based, ICD-9-CM-based, and combined (i.e., drug- and ICD-9-CM-based) models. Place of treatment of the initial stroke event was categorized between inpatient (hospital), nursing home residence, and ambulatory setting.

## Mortality Models

The prevalence of code-based comorbidities and drug exposure, as defined in Tables 1 and 2, was obtained in the Georgia Medicaid patient cohort. When the one-year

observation period prevalence was low, i.e., total number of cases less than 20, two approaches were considered. First, if possible, a variable with a low-prevalence was combined with another one to create a clinically meaningful covariate. Second, if the comorbidity was such that it could not be combined with another one or if its prevalence was zero, then the variable was dropped altogether from further analysis. Lastly, because of the possible overlap in certain drug- and ICD-9-CM-defined classes, information from the two sources could be aggregated in the combined models. For instance, as 93% of the patients using antiretrovirals also had a diagnosis claim for aids, the two dummy variables coding for the presence of a diagnosis of aids and use of antiretrovirals were combined.

Multivariate logistic regression was used to model the binary mortality outcome at one month and one and two years to screen candidate variables in the GA training sample. Logistic regression is the most widely used approach for modeling dichotomous dependent variables and performs favorably even compared with other, more complex modeling approaches.[50,51] The significance of all potential covariates was first tested in a stepwise logistic regression procedure predicting mortality for each of the nine models at a significance level for entry of 0.20 and for staying in the models of 0.10.[52] The 10% significance level required for a variable to remain in a model limited the inclusion of noise variables in our comorbidity indices.[53,54] As stepwise variable selection processes can lead to model overfitting, we used a bias-corrected bootstrap validation to assess the internal validity of each of the nine models developed on the Georgia Medicaid sample. Resampling occurred 200 times for each bootstrap validation as bootstrapping requires fewer model estimations than cross-validation.[55,56] In logistic regression models, the c index is a widely accepted measure of predictive discrimination.[57] Model explained variation was assessed by calculating $R_{SS}^2$ adjusted for shrinkage.[58] $R_{SS}^2$ adjusted permits an analogous calculation to the $R_{adj}^2$ in linear regression models by controlling for the inflation tendency in situations where there are a large number of candidate covariates relative to the sample size. Bias corrected c-statistic and adjusted $R_{SS}^2$ were computed

along with their 95% non-parametric bootstrap confidence intervals. The goodness-of-fit of the multivariate logistic models was assessed with the Hosmer-Lemeshow test.[59] SAS version 6.12 software (SAS Institute, Cary, NC, USA) was used to extract the final analytical samples. Descriptive analyses, model estimations, and external validation were carried out in SAS or STATA Version 6.0 (STATA Corporation, College Station, TX, USA).

## Clinical Expert Review

Univariate statistical analyses, detailed results from the initial stepwise procedures, and summaries from the bootstrap simulations were presented to clinical experts (three neurologists and one stroke clinical pharmacist). Clinical experts reviewed the findings and helped determine which of the variables should stay in the models and submitted to the external validation procedure. Like Keeler during the development phase of the APACHE III, clinicians were allowed to drop factors empirically identified on sole statistical evidence but that might be unlikely predictor of the outcome studied (i.e., mortality) based on clinical expertise.[60] One-month, one- and two-year mortality models were subsequently re-estimated on the GA sample to reflect clinicians' decisions on each of the nine models.

## External Model Validation

Upon clinical expert review and subsequent model re-estimations, the reduced models were 'frozen' and tested on the North Carolina Medicaid sample. Correct probability of prediction of death (external predictive discrimination) in the final reduced models was assessed by the Somer's $D_{yx}$ rank correlation and back transformed to a measure of c-statistic, as c-statistic = (1 + Somer's $D_{yx}$) / 2.[61] Explained variation was assessed by the sum of square $R^2$ and model fit with the Hosmer-Lemeshow test.

Institutional Review Board was obtained from the University of Georgia Research Office (project number H980679 - CFR category 46.101 (4) - Institution Assurance number M1047).

## RESULTS

### Demographics and Eligibility

Table 3 presents demographic, eligibility and stroke-specific information for the Georgia and North Carolina Medicaid samples. There were a total of 4,632 and 4,500 patients in the GA and NC samples, respectively. GA patients were younger (mean ages of 66 vs. 76 years). The GA sample included a smaller proportion of white patients (39% vs. 50%). GA patients were more likely to be institutionalized in a nursing home at the time of treatment of their initial stroke (33% vs. 27%). Gender, Medicare eligibility, and mortality rates at one month (7% vs. 9%) were similar, but crude mortality rates at one (23% vs. 29%) and two years (32% vs. 40%) were lower in the GA than in the older NC sample.

### Comorbidity Burden

The prevalence of the 31 ICD-9-CM code-based comorbidities and 27 drug exposure categories in the GA Medicaid sample the year prior to the index diagnosis of stroke are presented in Table 1 and Table 2, respectively. The most prevalent ICD-9-CM code-based conditions were hypertension (31%), diabetes (18%), chronic pulmonary disorders (12%), miscellaneous neurologic disorders (10% - e.g., epilepsy), CHF (9%), and psychoses (8%). Classes of drugs used by most patients pre-stroke were antihypertensives (58%), acid peptic disease agents (31%), cardiac (48%) and chronic respiratory (22%) agents, antidepressants (20%), antiepileptics (18%), and neuroleptics

(14%). Classification tables 4 and 5 summarize for the GA sample the impact of the number of ICD-9-CM code-based comorbidities and drug exposure burden on one-month, one-year, and two-year mortality. Patients had on average 1.4 ICD-9-CM code-based comorbidities (median 1) and three drug-exposure classes (median 3) during the year prior to their index date. There was no relationship between the number of drug classes and mortality at one month and one and two years (Pearson $\chi^2$ test P value > 0.025 – Table 5). A circuitous J-shaped relationship emerged between ICD-9-CM comorbidity burden and mortality (Pearson $\chi^2$ test P value < 0.025 and Cochran-Armitage linear trend test P value < 0.025 – Table 4). Note, a level of significance at 0.025 was specified *a priori* to control for test multiplicity, as differences at each follow-up period were two ways: once for association with drug exposure and once for association with ICD-9-CM burden. Patients with no ICD-9-CM code-based comorbidities had larger crude mortality rates than patients with up to four comorbidities at one- and two-year follow-up. The latter, however, had lower mortality rates than patients with 5 or 6 comorbidities. These patients in turn had lower crude mortality rates than patients with 6 or more ICD-9-CM code-based comorbidities did.

## Model Building

The variable coding for the presence of anemia was not entered in any stepwise ICD-9-CM-based risk adjustment model because of a low prevalence (<20). For the same reason, six drug-based variables were excluded from the stepwise risk adjustment models (i.e., drugs for Alzheimer's dementia, irritable bowel disease, end stage renal disease, bone diseases, migraine, and immunosuppressive agents). Also, due to the small number of patients using antiretroviral therapy (<20), this drug class was combined with

use of anti-tuberculosis agents in all three drug-based only models. Lastly, because of the overlap in certain drug- and ICD-9-CM-defined classes, information from the two sources was aggregated in the combined models in six cases: 1) antiretrovirals and aids diagnosis; 2) antidepressants and depression diagnosis; 3) insulins and diabetes with complications; 4) antipsychotics and psychoses; 5) antiulcer agents and ulcer; 6) second-line antihypertensives and hypertension.

## Clinical Expert Review

Following recommendations from the clinical panel, patients who presented with an initial cerebrovascular event for a transient ischemic attack (TIA) but otherwise met all inclusion criteria were discarded from the study (index primary diagnosis code of 435.xx; n = 1,049; data not presented). The clinical panel advised that mortality risk factors for TIA are different enough from those for ischemic/hemorrhagic stroke to warrant the exclusion of TIA patients from the study. Additionally, in a couple of models, exposure to glaucoma agents and oral hypoglycemiants had a “protective” effect (post-stepwise regression modeling). The clinical panel found these statistically derived relationships aberrant, with no clinical relevance, and recommended that the two covariates be dropped from the final models.

## Mortality Models

Odds ratios (O.R.) of each covariate in the one-month, one- and two-year drug, ICD-9-CM, and combined models are presented in Table 6 and summary statistics for each of the nine models in Table 7. Of the 35, 38, and 58 potential variables tested for entry in the drug, ICD-9-CM, and combined models, 10 to 18 remained in the drug and

ICD-9-CM only models and 17 to 23 in the combined models (Table 7). There were 333, 1,054, and 1,493 recorded deaths (events) in the GA sample at one month, and one and two years respectively (Table 3). Therefore the largest event-to-variable ratio was observed in the two-year drug model (43:1 ≈ 1,493:35) and the smallest event-to-variable ratio in the six-month combined model (6:1 ≈ 333:58). The use of screening techniques for selection of candidate variables (discarding covariates with low "prevalence" or combining those clinically relevant) limited to one the number of models with an event-to-variable ratio well below 10.[57] Consequently, no other data reduction technique was performed prior to the stepwise regression modeling stage.

In all nine GA models, discrimination, as indicated by c-statistic, ranged from 0.673 to 0.732. At any given follow-up time, c-statistic was higher in the combined models than in the ICD-9-CM-based models, and in the ICD-9-CM-based models than in the drug-based models. $R_{SS}^2$ adjusted for shrinkage ranged from 0.03 to 0.13. In general, a longer follow-up time was associated with a higher discriminative ability and a larger $R_{SS}^2$. Non-parametric bootstrapped confidence intervals for the c-statistic and $R_{SS}^2$ adjusted for shrinkage are presented in Table 7. All logistic models had acceptable goodness-of-fit as the Hosmer-Lemeshow p-value of each model was greater than 0.05.

Risk/Protective Factors

The impact of age was nearly constant across all models. For a one-year increase in age at the time of an initial stroke event, risk of death increased by 1 to 4% or by 10 to 50% for every 10 years of age. Females were in general 20% less likely to die than their counterparts. Place of treatment at the time of stroke in hospital or nursing home (base

case was ambulatory setting) was a strong and consistent predictor of death. Residence/admission to a nursing home had a nearly constant impact at all three time-points ($1.8 < O.R. \leq 2.3$). However, odds ratios for a hospital admission were higher at one-month ($O.R. > 3.0$) and returned to levels similar to that of nursing homes stay for longer follow-up times ($O.R. \approx 2.0$).

Among all drug-based variables, exposure to antiretroviral therapy and/or anti-tuberculosis agents the year prior to the index stroke was the strongest predictor of death, associated with increasing risk of death over longer follow-up periods. The stepwise approach used to operationalize cardiac drug classes allows for two types of comparisons, between and within models. First, pre-stroke exposure to cardiac drugs was associated with larger O.R. over longer follow-up periods. Second, a consistent linear relationship was observed within each of all six models as for a given follow-up time, patients exposed to a larger number of classes experienced higher risk of death than patients who were exposed to fewer classes of cardiac drugs. For instance, in the two-year drug-based model, O.R. were 1.39, 2.22, and 3.85 for patients who were exposed to two, three, and four classes of cardiac drugs, respectively. Conversely, the use of coagulation modifiers (e.g., anticoagulants, heparins, antiplatetlet agents) prior to the stroke event reduced the odds of 1-month post-stroke death by 38%. Similarly, the use of lipid-lowering agents reduced the odds of 2-year post-stroke death by 33%.

Among all ICD-9-CM code-based variables tested, the presence of a diagnosis of aids, metastatic solid tumor, liver diseases, or renal failures the year prior to the index stroke were the strongest risk factors (ICD-9-CM and combined models). O.R. for metastatic solid tumors and malignancies were consistently lower in the combined than in

the ICD-9-CM only models. As in the drug models, presence of cardiac comorbidities (i.e., CHF, arrhythmias, and myocardial infarct) was associated with larger odds of death with longer follow-up periods in both ICD-9-CM and combined models. Hypertension reduced the odds of 1- and 2-year post-stroke death by 20%. This "apparent" protective effect, however, was only observed in two out of six models. The use of antidepressants in the drug models and the use of antidepressant and/or a diagnosis of depression in the combined models reduced the odds of 1- and 2-year post-stroke death by over 30%.

## External Model Validation

Table 7 presents for each of the GA 'frozen' reduced models, estimates of the external predictive discrimination (c-statistic), explained variation (sum of square $R^2$), and model fit (p value of Hosmer-Lemeshow test). C-statistic, derived from the Somer's $D_{yx}$, ranged from 0.63 to 0.67 across all 9 models. C-statistic values on the NC samples were either included in the GA sample 95% confidence intervals adjusted for shrinkage (2 models), or within one (5 models) or two percentage points (2 models) of their respective lower 95% confidence interval bond. Out-of-sample $R^2$ ranged from 0.03 to 0.08, with higher $R^2$ for longer follow-up times. Adequacy of model fit, calibration, was questionable, however, as all Hosmer-Lemeshow tests were rejected with a $p < 0.01$.

## DISCUSSION

Although Medicaid databases contain demographic, medical and drug utilization information for the indigent US population, little research has developed and validated risk adjustment indices specific to this population. Risk adjustment indices not specific to indigent populations have, however, been used in studies that examined cost or utilization but not mortality outcomes for Medicaid recipients.[62,63,64,65] This research represents a first attempt to develop and validate mortality risk-adjustment indices for

Medicaid populations. It focuses on patients who presented with a first stroke event in a 12-month period.

## Study Design

The study was designed to maximize the likelihood to correctly identify, from secondary claims databases, patients with a new/first ischemic or hemorrhagic stroke. Patients had to be free of any diagnosis claim (primary and/or secondary) of stroke (ICD-9-CM 430.XX-438.XX) for at least a year prior to their index diagnosis and patients with complications of stroke were discarded (ICD-9-CM 438.XX). The study design did not require a stroke-free period longer than one year prior to the index date in order to conserve a reasonably large sample, which is necessary to derive and test population-based risk-adjustment indices. We further limited the definition of stroke to patients with a primary diagnosis code of 430.XX, 431.XX, 434.XX, and 436.XX. Other ICD-9-CM diagnosis codes were discarded as they are unreliable markers of stroke when ascertained against medical records reviews (ICD-9-CM 432.XX; 433.XX; 437.XX).[41,42,43]

## Crude Mortality Rates

Patients with a hemorrhagic stroke were 50% more likely to die and twice as likely to be admitted to a hospital than patients with an ischemic stroke (40% vs. 18%). However, no more than 20% of patients were admitted to/resided at the hospital at the time of their initial stroke and only 30% were admitted/resided in a nursing home setting. Therefore, half of the patients, both in GA and NC, were seen and diagnosed in a physician office or an urgent/emergency care facility but were not admitted to an intensive or long-term care setting for the acute treatment phase of their stroke. Short-term prognosis of hemorrhagic stroke patients is worse than that of ischemic stroke patients and hemorrhagic stroke is more likely to require inpatient treatment.[66,67] The direction of our findings (higher crude mortality in hemorrhagic stroke patients) is therefore clinically relevant but the relatively high percentage of patients (around 50% in

each state) that remained in an ambulatory setting to manage their stroke is higher than what we had anticipated. However, ischemic stroke patients constituted 95% of all cases in both samples and early spontaneous improvement is a frequent occurrence in the clinical course of ischemic stroke.[10,68,69] Most pharmacotherapies (e.g., antiplatelet agents, subcutaneous or intravenous heparin, and oral anticoagulants) can also be administered and titrated in an outpatient facility or even at the office.

As much as 42% of the GA patients had none of the 31 comorbid conditions used in the development of the ICD-9-CM code-based measures (Table 4) whereas as low as 11% of patients had not had exposure to any of the 27 drug classes (Table 5). A marked J-shaped curve relationship was observed between mortality rates and the number of ICD-9-CM comorbidities. Patients with no comorbid condition exhibited higher crude one- and two-year mortality rates than patients with one to four comorbidities. This finding is counterintuitive. Indeed, one would expect to observe a proportional linear or exponential relationship between comorbidity burden and mortality. The year prior to the index stroke, patient with no comorbid conditions had on average 50% fewer nursing home claims, 30% fewer non-MD claims, and 40% fewer outpatient hospital claims but the same number of office visits and inpatient stays. Fewer medical encounters translated into lower pre-stroke ICD-9-CM comorbidity burden and a 21% lower pre-stroke total Medicaid costs. This finding contrasts with the higher cost (10%) the year post-stroke and the higher one- and two-year post-stroke mortality. As Iezzoni suggested, it is possible that patients with "more regular contacts with doctors have their acute illnesses identified at earlier stages or at a lower severity," thus potentially improving their relative risk of death after an acute event such as stroke.[6]

Independent Risk Factors

Thirty-day, one- and two-year all cause mortality indices were developed as risk factors for patient who survive the acute post-stroke mortality window may differ considerably from those who do not.[70] Across all nine models, odds of death were

consistently higher (10 to 25%) in men than in women and the difference was more pronounced with longer follow-up times (Table 6). Male sex is a known risk factor for first stroke and stroke mortality in the US is higher in men than in women, though the difference tends to narrow considerably with older ages.[4,71] Race, conversely, was not associated with a higher mortality burden in any of the nine models. The medical literature reports that African American and Hispanic ethnic origins are risk factors for a first stroke[71] All nine population-based models, however, suggest that, in Medicaid populations, after controlling for other demographics, type of stroke, place of stroke treatment, and pre-stroke comorbidity and/or drug exposure burden, black patients are not at a greater risk of post-stroke death than their counterparts. The assumption that ethnicity can be used as an isolated epidemiological factor, defining clinically distinct disease subgroups is controversial.[72] Race may be a surrogate measure for medical process, as differences in processes of care have been observed between different ethnic groups.[73] The findings of this study would tend to support that race does not impact post-stroke mortality within an indigent population.

Several drug exposure covariates had a protective effect on post-stroke mortality but over different time periods. The use of coagulation modifiers (e.g., anticoagulants, antiplatelet agents, heparin antagonists, thrombolytics) prior to the initial stroke reduced the odds of 1-month post-stroke death by 38%, controlling for all other covariates. This observed "protective" effect, however, did not carry over to longer follow-up periods, i.e., one and two years. Antiplatelet and antithrombolytic therapies have become a mainstay of secondary stroke prevention as they act on the thrombus formation.[74,75] Both in the GA and NC samples, twice as many ischemic (15%) as hemorrhagic stroke patients (7%) had received coagulation modifiers prior to their initial stroke. The study design was such that no information was recorded on the patient medical history beyond one year before the initial stroke. It is therefore possible that some of the patients may have suffered a stroke more than a year before their study index date. If these patients received coagulation modifier therapy to prevent a secondary stroke, it could have in

turn, improved their odds of short-term post-stroke survival.[76] Conversely, the use of cholesterol and lipid-lowering agents (e.g., HMG-CoA reductase inhibitors, fibrates, sequestrants) during the 12-month prior to the initial stroke reduced the odds of 2-year post-stroke death by 33% but did not impact shorter survival periods. HMG-CoA reductase inhibitors have been approved for stroke prevention in some patients as they reduce stroke risk by about 30% in patients with elevated cholesterol and/or symptomatic atherosclerosis, and after a MI.[77] HMG-CoA reductase inhibitors have also been found to reduce the incidence of stroke in hyperlipidemic patients who have not had a prior stroke.[78] No published study provides clinical evidence that the protective effect of such therapies could carry over such a long period of time (two years). It may be that patients who started lipid/cholesterol lowering therapies prior to their index stroke were more likely to receive lipid/cholesterol lowering agents post-stroke, which in turn, could have resulted in a reduction in their long-term cardiovascular disease death risk. At the same time, we cannot exclude that long-term treatment impact on patients with elevated LDL cholesterol reduce stroke and "statins" may benefit associated coronary artery disease, so often life-limiting in stroke patients. Similarly, the use of antidepressants reduced one- and two-year post stroke mortality odds by 31 to 34% but had no impact on one-month mortality. This effect was so strong and so consistent throughout all six drug-based models that the clinical panel did not recommend dropping the covariate. Validation of this finding in other similar patient populations is needed. The only ICD-9-CM code-based measure that was associated with lower odds of death is hypertension. The literature is replete with references on the role of hypertension, a key modifiable risk factor for stroke.[79,80,81] In the GA sample, over 80% of patients with a diagnosis of hypertension were taking antihypertensive drugs (not counting cardiac drug classes - Table 1). These patients were therefore taking medications that are known to improve cardiovascular risk and mortality post-MI.[82,83,84] As the protective effect of hypertension was only observed in the ICD-9-CM only models and not in the combined ICD-9-CM and drug models, a diagnosis of hypertension may be a surrogate marker for patients who

were using antihypertensive agents. Additionally, as Iezzoni suggested, patients with "chronic conditions (e.g., diabetes mellitus, hypertension) have more regular contacts with doctors and thus have their acute illnesses identified at earlier stages or at a lower severity."[6]

To the exception of hypertension, all ICD-9-CM code-based covariates were associated with increased odds of death. Patients presenting with "fluid-electrolyte" disorders had increased odds of 1-month post-stroke death by 180%, but were at the same risk of death from all causes at longer follow-up times (one and two years). "Fluid-electrolyte" disorders are a surrogate marker for chemical imbalances (e.g., hypo- or hypernatremia, hyperkalemia, acidosis, alkalosis, volume depletion). Such disorders can be the manifestation of severe conditions, such as heat illness, post-operative complications, and renal failure, which can have deadly consequences in the short-term for older populations. "Fluid-electrolyte" disorders have also recently been identified as risk factors for peripartum and postpartum stroke.[85] Patients with comorbidities associated with chronic alcohol consumption or alcohol abuse, such as alcoholic psychoses and alcohol dependence syndrome, had a 60 to 80% increase in odds of death at all three follow-up times. This finding corroborates with several studies on the impact of heavy alcohol consumption and stroke.[86] For instance, a 20-year long cohort study found that drinking habits were associated with increased odds of death from ischemic stroke, even long after an individual had quit drinking.[87] Other ICD-9-CM code-based covariates with high O.R. were, to name a few, aids, metastatic solid tumors, liver and renal diseases, and cardiovascular conditions (e.g., CHF, MI, cardiac arrhythmia).

Model Performance

In the GA stroke sample, models that included both drug exposure and ICD-9-CM burden information had higher discriminative ability (c-statistic) than models based on either source of information. Bootstrap validation demonstrated the internal validity with narrow confidence intervals in all nine models and good or very god calibration (p value

of Hosmer-Lemeshow test > 0.05). The GA 'frozen' models were independently tested and validated with a NC out-of-sample Medicaid stroke cohort. C-statistic values on the NC sample were either included or within one or two percentage points of their respective predicted lower 95% confidence interval bond. The lowest and highest c-statistic values in the NC sample at one month, one and two years were within two percentage points of each other. Combined models always achieved marginally larger c-statistic and $R^2$ predicted values. Therefore, all three types of models had almost an equivalent overall ability to separate patients who survived and died in the independent sample at one month, one and two years after an index stroke event. Adding drug information to ICD-9-CM code-based models and vice-versa did not dramatically improve model discrimination or performance.

As noted by Harrell, a bias-corrected internal bootstrap validation can yield a nearly unbiased estimate of the expected value of the external predictive discrimination.[61] The ability to discriminate outcomes of a disease with such a large heterogeneity of characteristics and outcomes based on secondary claims data in an independent sample is encouraging. 'Frozen' models, however, failed to exhibit good calibration properties when tested in the independent NC sample. Calibration is the ability to predict probability of the outcome across all ranges of risk. One of the main risk factor for post-stroke mortality is age and the NC stroke sample was 10 years older than the GA sample. In order to contain the number of candidate variables to around 1 for 10 observed events (i.e., death), we were not able to test interactions between age and drug exposure covariates and age and ICD-9-CM code-based covariates. Such interactions terms might have help increase the external predictive ability and calibration of our models. Overall, we still observe a strong relationship between the covariates included in the final models and mortality outcome as c-statistic, ranged from 0.673 to 0.732 on the GA sample and from 0.63 to 0.67 on the NC sample.

The majority of the information in our models was collected prior to the stroke event (pre-existing drug exposure and ICD-9-CM codes), to the exception of the stroke

type and place of treatment that were gathered at the stroke onset (initial Medicaid stroke claim). Prospective models do tend to perform less well as models that use concurrent discharge clinical or claims information. For instance, Johnston used clinical (e.g., National Institutes of Health Stroke Scale) and imaging variables (infarct volume) to predict three-month clinical outcomes in patients hospitalized for an acute ischemic stroke.[7] Model discrimination, that ranged from 0.75 to 0.88 when predicting a "very poor outcome," was based on variables collected up to 7 to 10 days after the stroke onset (e.g., infarct volume measured by noncontrast head CT scan). The latter proved to be the strongest and more consistent predictor of poor outcome in the study. Iezzoni compared 11 severity risk-adjustment measures to assess post-stroke death rates across 94 hospitals.[88] Models containing clinical information (e.g., Medis Groups, Physiology Score 1 and 2) were the best predictors of hospital mortality with c-statistic ranging from 0.80 to 0.87. Models with resource-based information (with discharge data and length of stay information, e.g., Acuity Index Method, All Patients Refined Diagnosis Related Groups) were the second best predictors of inpatient death with c-statistic ranging from 0.66 to 0.74. Lastly, models using discharge abstract data, (e.g., Disease Staging, Deyo's adaptation of the Charlson Index) were the least discriminative of all, with c-statistic ranging from 0.60 to 0.74. Models' $R^2$ followed a similar trend with the higher values observed in models with clinical data-based information (0.15 to 0.24) and the lowest with models using discharge abstract data (0.01 for the Deyo's adaptation of the Charlson Index to 0.11). Again, in that study, models used post-stroke clinical and discharge abstract data to predict patient discharge status. Model performance was not assessed prospectively. It is interesting to note that clinical-based models in Iezzoni and Johnston studies had equivalent discriminative abilities.

A main objective of the study was to explore the discriminative ability of drug exposure with respect to mortality and to test whether or not this source of information could be combined in a clinically meaningful way with ICD-9-CM code-based data. Von Korff discovered the potential of predictive ability of drug exposure in cost models.[27]

However, no published studies have yet explored its potential as a health status indicator in mortality models and compared its discriminative ability to that of ICD-9-CM code-based information. Therapeutic classes, such as antidepressants, opiates, systemic steroids, may have multiple indications across many different disease states. Therefore, unlike ICD-9-CM code-based information, drug exposure data is rarely specific to an organ or a disease. Cardiac arrhythmia, liver diseases, renal diseases, Alzheimer's dementia are straightforward makers of organ dysfunctions.

In the case of stroke patients, exposure to cardiac drug classes adds a unique "severity" dimension, not observable with a simple ICD-9-CM algorithm. Indeed, at all three follow-up times, patients who were using two classes of cardiac drugs had a 30 to 40% increase in likelihood of death compared to patients who received no or only one class of cardiac drugs. Similarly, patients with three cardiac drug classes had a nearly 50% increase in likelihood of death over patients with two classes. Lastly, patients with at least one drug in each of the four cardiac classes had a 30 to 100% increase in likelihood of death over patients with three classes of cardiac drugs (controlling for all other covariates). After combining information from the two sources (drug exposure and ICD-9-CM codes), odds ratios associated with exposure to cardiac drugs were consistently lower in the combined models than in the drug only models. Similarly, odds ratios for CHF were lower in the combined than in the ICD-9-CM only models. The tapering effect was more pronounced for cardiac arrhythmia and MI, as these factors were quasi no longer significant in the combined models. In short, combining the information from the two sources sorted out what proportion of the incremental risk of death was due to mere presence of a diagnosis and to the severity of the condition (as measured by the number of classes of cardiac drugs).

Combining the drug and ICD-9-CM information can also help reduce the coding bias inherent to secondary claims data. For instance, antineoplastic agents did not enter any drug exposure models. The presence of a diagnosis of metastatic solid tumor and/or malignancy, however, was associated with some of the highest O.R. observed across all

nine regression models as a diagnosis for metastatic solid tumor increased the risk of death by 4 to 12 times in the ICD-9-CM code-based models. The counterintuitive absence of antineoplastic agents from the drug-based models can be explained by the fact that Medicaid programs only capture and report ambulatory prescription use. As most anticancer therapies are not administered through outpatient pharmacies, these prescriptions are not captured in Medicaid claims databases.

Limitations

There are several limitations to this study. Variables in the GA models were initially chosen by stepwise techniques, which can make the resulting models more sensitive to the characteristics of the population from which they were derived and more sensitive to overfitting.[61] However, we were careful to screen drug exposure and ICD-9-CM code-based candidate variables from prior studies that had established their relevance as potential markers of health status.[15,23,27] Second, we combined stepwise logistic regression with clinical judgement. Along with data reduction by cluster analysis, our method is one that provides models with the best predictive power.[89] Third, using bootstrap techniques to internally validate the models and penalizing for optimism enables to assess and confirm model stability (narrow 95% confidence intervals). Lastly, we submitted our models to the most rigorous validation procedure: external validation with an entirely independent data set, which "provides the strongest test of predictive validity."[6] We are not aware of any published disease-specific risk-adjustment instrument that has gone through the rigor of an external validation process.

The study identified pre-stroke mortality risk or protective factors for large population based on secondary claims data and not on clinical data themselves. Clinically based indices allow a gain in precision over code-based measures. They can provide information on behavioral factors that can influence stroke outcomes, such as smoking, heavy alcohol use, diet, and physical activity.[75] This gain, however, needs to be weighted against added cost and intended use. Our risk-adjustment models were

developed for use with large populations and not to guide clinical decision making at a patient level. As Harrell suggested,[90] "researchers using inexpensive non-intrusive measures (such as claims) must decide whether or not to invest scarce resources in more data collection, evaluating whether the likely yield of such additional information is critical." It is important to note that the c-statistic does not depend on the prevalence of the condition (e.g., death rate in the population), which limits our ability to compare model performance across different populations and different follow-up times for a same population.

In an effort to assess mortality risk for a cohort of newly diagnosed stroke patients, we discarded patients who had any claim for a cerebrovascular condition during the year prior to their index date. Therefore, an artifact of our study design is that we discarded patients with a prior TIA and/or stroke. TIA and stroke are known risk factors for subsequent stroke, with a recurrence risk of 5 to 25% a year.[75,91] Consequently, this algorithm should not be applied to patients with a known stroke or TIA event in the last year prior to their index date, unless and until the models are re-estimated for a broader stroke population.

We have showed that there exists a strong relationship between pre-stroke comorbidity burden and drug exposure with post-stroke mortality. The relationship is stronger for longer follow-up times. Also, synergies between drug exposure and ICD-9-CM code-based information exist. A simple hierarchical categorization of drug exposure data can provide information on the severity of disease: the larger number of cardiac drug classes, the greater the post-stroke mortality. On the other hand, ICD-9-CM code-base better convey disease/organ specificity information. This study provides “initial” evidence that stroke mortality at a population level can be prospectively evaluated using large administrative claims databases. Validation of these models in other Medicaid populations is desirable and application of the same methods to other disease states is needed.

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TABLE 1: ICD-9-CM-based Comorbidities One Year Prior to Stroke in the GA Sample and their Operational Definitions

| Comorbidities | Patients n (%) | ICD-9-CM Codes |
|---|---|---|
| 1. Congestive heart failure | 409 (8.8%) | 389.91, 402.11, 402.91,404.11, 404.13, 404.91, 404.93, 428.0-428.9 |
| 2. Myocardial infarction | 93 (2.0%) | 410-410.9, 412, 429.71, 429.79 |
| 3. Cardiac arrhythmias | 208 (4.5%) | 426.10, 426.11, 426.13, 426.2-426.53, 426.6-426.89, 427.0, 427.2, 427.31, 427.60, 427.9, 785.0, V45.0, V53.3 |
| 4. Valvular disease | 158 (3.4%) | 093.20-093.24, 394.0-397.1, 424.0-424.91, 746.3-746.6, V42.2, V43.3 |
| 5. Pulmonary circulation disorders | 34 (0.7%) | 416.0-416.19, 417.9 |
| 6. Peripheral vascular disorders | 210 (4.5%) | 440.0-440.9, 441.2, 441.4, 441.7, 441.9, 443.1-443.9, 447.1, 557.1, 557.9, 785.4, V43.4 |
| 7. Hypertension (complicated and uncomplicated) | 1,432 (30.9%) | 401.1, 401.9, 402.10, 402.90, 404.10, 404.90, 405.11, 405.19, 405.91, 405.99 |
| 8. Hemiplegia / paraplegia | 99 (2.1%) | 342.0-344.9 |
| 9. Other neurological disorders | 465 (10.0%) | 331.9, 332.0, 333.4, 333.5, 334.0-335.9, 340, 341.1-341.9, 345.00-345.11, 345.40-345.51, 345.80-345.91, 348.1, 348.3, 780.3, 784.3 |
| 10. Chronic pulmonary disease | 560 (12.1%) | 490-492.8, 493.00-493.91, 494, 495.0-505, 506.4 |
| 11. Diabetes, uncomplicated | 470 (10.1%) | 250.00 - 250.33 |
| 12. Diabetes, complicated | 355 (7.7%) | 250.40 - 250.73, 250.90-250.93 |
| 13. Hypothyroidism | 86 (1.9%) | 243-244.2, 244.8, 244.9 |
| 14. Renal failure and chronic disorders | 146 (3.2%) | 403.11, 403.91, 404.12, 404.92, 582-582.9, 583-583.7, 585, 586, 588-588.9, V42.0, V45.1, V56.0, V56.8 |
| 15. Liver disease | 73 (1.6%) | 070.32, 070.33, 070.54, 456.0, 456.1, 456.20, 456.21, 571.0, 571.2, 571.3, 571.40-571.49, 571.5, 571.6, 571.8, 571.9, 572.3, 572.8, V42.7 |
| 16. Peptic ulcer disease | 128 (2.8%) | 531-534.9, V12.71 |
| 17. Aids | 30 (0.6%) | 042-044.9 |
| 18. Any malignancy, including leukemia and lymphoma | 144 (3.1%) | 140.0-172.9, 174.0-175.9, 179-195.8, 200.00-202.38, 202.50-203.01, 203.8-203.81, 238.6, 273.3, V10.00-V10.9 |
| 19. Metastatic solid tumor | 51 (1.1%) | 196.0-199.1 |
| 20. Rheumatoid arthritis / collagen vascular disease | 88 (1.9%) | 701.0, 710.0-710.9, 714.0-714.9, 720.0-720.9, 725 |
| 21. Coagulopathy | 50 (1.1%) | 286.0-286.9, 287.1, 287.3-287.5 |
| 22. Obesity | 67 (1.4%) | 278.0 |
| 23. Weight loss / malnutrition | 35 (0.8%) | 260-263.9 |
| 24. Fluid and electrolyte disorders | 39 (0.8%) | 276.0-276.9 |
| 25. Anemias | 0 (0.0%) | 280.0-281.9, 285.9 |
| 26. Alcohol abuse | 204 (4.4%) | 291.1, 291.2, 291.5, 291.8, 291.9, 303.90-303.93, 305.00-305.03, V11.3 |
| 27. Drug abuse | 46 (1.0%) | 292.0, 292.82-292.89, 292.9, 304.00-304.93, 305.20-305.93 |
| 28. NOPD | 379 (8.2%) | 295.00-298.9, 299.10-299.11 |
| 29. Depression | 142 (3.1%) | 300.4, 301.12, 309.0, 309.1, 311 |
| 30. Cerebrovascular disease | 0 (0.0%) | 430-438 |
| 31. Dementia / Alzheimer | 164 (3.5%) | 290-290.9, 331-331.9, 797, 294.9 |

ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification.
Aids: Acquired Immune Deficiency Syndrome; NOPD, Non-organic psychotic disorders.
Note on Operational Definitions: In order to account for the fact that additional diagnoses within a category more likely reflect additional diagnosis of the same underlying condition rather than additional severity of illness a hierarchy counting was developed for the following comorbidities.[23] If both uncomplicated diabetes and complicated diabetes are present, count only complicated diabetes. If both solid tumor without metastasis and metastatic solid tumor are present, count only metastatic cancer. This hierarchy

helped reduce multicollinearity as many patients were expected to present uncomplicated and complicated diabetes or tumor without metastasis and metastatic solid tumor simultaneously.

TABLE 2: Drug Exposure One Year Prior to Stroke in the GA sample and their Operational Definitions

| Drug Classes | Patients n (%) | Therapeutic Classes |
|---|---|---|
| 1. Cardiac agents | 915 (19.8%) | (1) Antiarrythmic, inotropic, cardiac vasopressor agents |
| | 995 (21.5%) | (2) ACE inhibitors or angiotensin II antagonists |
| | 815 (17.6%) | (3) Antianginal agents |
| | 1,152 (24.9%) | (4) Loop diuretics |
| 2. Antiparkinson agents | 524 (10.3%) | Antiparkisonian agents (anticholinergic, dopamine agonists, and miscellaneous) |
| 3. Coagulation modifiers | 690 (14.9%) | Coagulation modifiers (anticoagulants, antiplatelet agents, heparin antagonists, thrombolytics, miscellaneous coagulation modifiers) |
| 4. Antihypertensives | 334 (7.2%) | (1) First-line antihypertensive drugs (β-adrenergic blocking agents; potassium-sparing, thiazide, and miscellaneous diuretics) |
| | 2,359(50.2%) | (2) Second-line antihypertensive drugs (peripherally and centrally antiadrenergic agents; calcium channel blocking agents; antihypertensive combinations; vasodilators agents) |
| 5. Respiratory agents | 461 (10.0%) | (1) Adrenergic bronchodilatators, asthma vasopressors, and bronchodilatator combinations |
| | 643 (13.9%) | (2) Methylxanthines |
| | 371 (8.0%) | (3) Respiratory inhalants, leukotrien asthma agents, antiasthmatic combinations |
| 6. Drugs for NID diabetes | 444 (9.6%) | Oral hypoglycemiant agents |
| 7. Insulins | 676 (14.6%) | Insulins |
| 8. Antineoplastics (cancer) | 142 (3.1%) | Antineoplastics (alkylating, antibiotics/antineoplastics, antimetabolites, hormones/antineoplastics, miscellaneous antineoplastics, mitotic inhibitors, colony stimulating factors) and 5HT3 antagonists |
| 9. Antiepileptics / anticonvulsants | 852 (18.4%) | Anticonvulsants (hydantoin, succinimide, barbiturate, oxazolidinedione, certain benzodiazepine, and miscellaneous anticonvulsants) |
| 10. Acid peptic disease agents | 1,443 (31.2%) | H2 antagonists, proton pomp inhibitors, sucralfate, and antibiotherapy cocktails |
| 11. Glaucoma | 236 (5.1%) | Ophthalmic glaucoma agents |
| 12. Antigout agents | 204 (4.4%) | Allopurinol, colchicine, probenecid, and miscellaneous |
| 13. Anti-hyperlipidemia, hypercholesterolemia | 236 (5.1%) | HMG-CoA reductase inhibitors, fibrates, sequestrants, probucol, and miscellaneous |
| 14. Antiretroviral therapy (aids) | 15 (0.3%) | Protease, nucleoside, and non-nucleoside reverse transcriptase inhibitors |
| 15. Thyroid agents | 271 (5.9%) | Levothyroxine and thyroid replacement agents |
| 16. Narcotic analgesics | 108 (2.3%) | Narcotic analgesics |
| 17. Antidepressants | 929 (20.1%) | SSRI, tricyclic, MAO, and miscellaneous antidepressants |
| 18. Neuroleptics | 629 (13.6%) | Phenothiazine, trazodone, and miscellaneous antipsychotics |
| 19. Dementia agents | 7 (0.2%) | Donepezil and tacrine |
| 20. Antituberculosis agents | 17 (0.4%) | Ethambutol, isoniazid, rifampin, pyrazinamide, and miscellaneous |
| 21. Drug for rheumatologic conditions | 25 (0.5%) | Gold salts and hydroxychloroquin |
| 22. Systemic steroids | 459 (9.9%) | Systemic adrenal cortical steroids |
| 23. Drug for Irritable bowel disease | 3 (0.1%) | Mesalamine, olsalazine, infliximab |
| 24. End stage renal disease | 7 (0.2%) | Hematopoietic agents (marrow stimulants, erythropoietin) |
| 25. Immunosuppressive agents | 6 (0.1%) | Azathioprine, basiliximab, cyclosporine, daclizumab, muromonab-CD3, mycophenolate mofetil, and tacrolimus |
| 26. Antimigraine agents | 6 (0.1%) | Triptans, ergotamines, and miscellaneous combinations |
| 27. Drugs for bone diseases (Padget's disease, osteoporosis) | 12 (0.3%) | Alendronate, etidronate, pamidronate, risedronate, tiludronate, raloxifene, cacitonin, and calcium carbonate products (with or without added vitamin D) |

HIV, Human Immunodeficiency Virus; SSRI, selective serotonin reuptake inhibitors; NID Diabetes, non insulin-dependent diabetes; MAO, monoamine oxydase inhibitors; ACE inhibitors, angiotensin converting enzyme inhibitors.

Note on Operational Definitions: Before comorbidity variables were tested for entry in the models, a hierarchy was developed between certain therapeutic classes.[27,49] If both non insulin-dependent and insulin-dependent diabetes drugs were present, we counted only insulin-dependent diabetes drugs. If both first- and second-line antihypertensive drugs were present, we counted only second-line antihypertensive drugs (Joint National Committee VI on prevention, detection, evaluation, and treatment of high blood pressure).[92]

If drugs from only one therapeutic respiratory illnesses were found for a given patient, then the dummy RESPIRATORY-1 variable was set to 1, 0 elsewhere; if two classes were found then RESPIRATORY-2 was set 1, 0 elsewhere; likewise for the RESPIRATORY-3 variable. A similar coding system was used for the therapeutic classes from the cardiac conditions for the definition of the CARDIAC-1 to CARDIAC-4 variables.

Note that angiotensin II antagonist and non-nucleoside reverse transcriptase inhibitors were not yet commercialized at the time of the study.

TABLE 3: Demographics, eligibility, and stroke-related information - Georgia and North Carolina Medicaid recipients aged 40 and over with a cerebrovascular event between 1991 and 1995.

| **Patient Group** | **Georgia Medicaid** | **North Carolina Medicaid** |
|---|---|---|
| Number of patients | 4,632 | 4,500 |
| Demographic Information | | |
| Age in years (mean; std) | 65.6 (14.4) | 75.9 (12.5) |
| Age range in years | 40 – 105 | 40 – 110 |
| Gender: female (%) / male (%) | 3,311 (72%) / 1,321 (28%) | 3,240 (72%) / 1,260 (28%) |
| Race: black (%) / white (%) / other (%) | 2,376 (51%) / 1,793 (39%) / 463 (10%) | 1,728 (38%) / 2,266 (50%) / 890 (12%) |
| Eligibility Information | | |
| Medicare eligible: yes (%) / no (%) | 3,924 (85%) / 708 (15%) | 3,879 (86%) / 621 (14%) |
| Age-blind-disabled / other: yes (%) / no (%) | 4,126 (89%) / 506 (11%) | 3,678 (82%) / 822 (18%) |
| Stroke-specific Information | | |
| Ischemic Stroke (%) / intracranial hemorrhage stroke (%) | 4,349 (94%) / 283 (6%) | 4,256 (95%) / 244 (5%) |
| Place of treatment: hospital (%) / nursing home (%) / ambulatory (%) | 937 (20%) / 1,525 (33%) / 2,170 (47%) | 885 (20%) / 1,212 (27%) / 2,403 (53%) |
| Mortality: one month (%) / one year (%) / two years (%) | 333 (7%) / 1,054 (23%) / 1,493 (32%) | 425 (9%) / 1,284 (29%) / 1,793 (40%) |

Std: standard deviation.

TABLE 4: ICD-9-CM Code-Based Comorbidity Count One Year Prior to Stroke and Mortality Rates (max score 29) in Georgia Medicaid Patients

| Number of | Number (%) | Percent of Patients Expired | | |
|---|---|---|---|---|
| Comorbidities | of Patients | One Month | One Year | Two Years |
| 0 | 1,983 (42.8%) | 3.0% | 25.5% | 37.9% |
| 1 | 978 (21.1%) | 6.4 % | 21.5 % | 28.9 % |
| 2 | 683 (14.7%) | 6.1 % | 17.0% | 23.3% |
| 3-4 | 700 (15.1%) | 8.0% | 20.6% | 26.9% |
| 5-6 | 233 (5.0%) | 11.1% | 25.8% | 35.2% |
| > 6 | 55 (1.2%) | 16.4% | 32.7% | 54.6% |
| **Total** | **4,632** | **7.2%** | **22.8%** | **32.2%** |

P value of Pearson $\chi^2$ test > 0.025* at one month, and one and two years and P value of Cochran-Armitage linear trend test < 0.025* at one month, one and two years
* P value of 0.025 was chosen a priori to control for test multiplicity

TABLE 5: Drug Exposure Count One Year Prior to Stroke and Mortality Rates (max score 26) in Georgia Medicaid Patients

| Number of | Number (%) | Percent of Patients Expired | | |
|---|---|---|---|---|
| Drug Classes | of Patients | One Month | One Year | Two Years |
| 0 | 523 (11.3%) | 8.6% | 23.1% | 32.2% |
| 1 | 579 (12.5%) | 6.9% | 20.7 % | 27.6% |
| 2 | 839 (18.1%) | 7.5% | 22.9% | 32.3% |
| 3-4 | 1,709 (36.9%) | 6.6% | 22.4% | 32.5% |
| 5-6 | 807 (17.4%) | 7.6% | 23.8% | 34.2% |
| > 6 | 175 (3.8%) | 6.3% | 26.3% | 36.0% |
| **Total** | **4,632** | **7.2%** | **22.8%** | **32.2%** |

P value of Pearson $\chi^2$ test > 0.025* at one month, and one and two years
* P value of 0.025 was chosen a priori to control for test multiplicity

Table 6: Odds Ratios by Index Type and Time Period in Georgia Medicaid Patients

| | Drug-based | | | ICD-9-CM-based | | | Drug- and ICD-9-CM-based | | |
|---|---|---|---|---|---|---|---|---|---|
| Candidate Variables | 1-month | 1-year | 2-year | 1-month | 1-year | 2-year | 1-month | 1-year | 2-year |
| Age | 1.01 | 1.02 | 1.03 | 1.02 | 1.03 | 1.04 | 1.02 | 1.02 | 1.04 |
| Female | 0.83 | 0.78 | 0.75 | 0.90 | 0.82 | 0.80 | 0.90 | 0.82 | 0.80 |
| Hospital | 3.13 | 1.94 | 1.86 | 3.16 | 2.01 | 1.92 | 3.17 | 1.95 | 1.88 |
| Nursing Homes | 1.96 | 2.06 | 1.84 | 2.22 | 2.26 | 2.03 | 2.32 | 2.34 | 2.10 |
| Hemorrhagic stroke | 3.08 | 2.03 | 2.02 | 3.16 | 1.97 | 2.00 | 3.15 | 2.06 | 2.11 |
| | | | | | | | | | |
| **Drug-based covariates** | | | | | | | | | |
| Two classes of cardiac drugs | - | 1.35 | 1.39 | | | | - | 1.30 | 1.31 |
| Three classes of cardiac drugs | - | 2.09 | 2.22 | | | | - | 1.91 | 2.02 |
| Four classes of cardiac drugs | 2.07 | 2.97 | 3.85 | | | | - | 2.44 | 3.17 |
| Antidepressants | - | 0.68 | 0.69 | | | | * | * | * |
| Antiretroviral (aids) and antituberculosis agents | 4.42 | 7.07 | 8.10 | | | | * | * | * |
| Insulins | - | - | 1.22 | | | | * | * | * |
| Cholesterol lipid lowering agents | - | - | 0.67 | | | | - | - | 0.66 |
| Coagulation modifiers | 0.61 | - | - | | | | 0.63 | - | - |
| Opiates | - | 1.99 | 2.31 | | | | - | 1.50 | 1.66 |
| Systemic steroids | 1.39 | 1.30 | 1.33 | | | | 1.43 | 1.29 | 1.31 |
| Acid peptic disease drugs | 1.29 | - | - | | | | | | |

Table 6: Odds Ratios by Index Type and Mortality in Georgia Medicaid Patients (cont'd)

| | Drug-based | | | ICD-9-CM-based | | | Drug- and ICD-9-CM-based | | |
|---|---|---|---|---|---|---|---|---|---|
| Candidate Var. | 1-month | 1-year | 2-year | 1-month | 1-year | 2-year | 1-month | 1-year | 2-year |
| **ICD-9-CM based covariates** | | | | | | | | | |
| Aids | | | | 7.23 | 11.43 | 33.24 | * | * | * |
| Alcohol abuse | | | | 1.63 | 1.67 | 1.74 | 1.60 | 1.74 | 1.82 |
| Cardiac arrhythmia | | | | - | 1.34 | 1.38 | | | |
| CHF | | | | 1.48 | 1.80 | 1.94 | 1.52 | 1.39 | 1.47 |
| Dementia Alzheimer | | | | 1.63 | 1.52 | - | 1.62 | 1.69 | 1.46 |
| Diabetes with complications | | | | - | - | 1.37 | * | * | * |
| Fluid electrolyte disorders | | | | 2.80 | - | - | 2.71 | - | - |
| Hypertension | | | | - | 0.83 | 0.78 | | | |
| Liver diseases | | | | 2.37 | - | 2.30 | 2.28 | - | 2.27 |
| Any malignancy | | | | - | 1.80 | 1.60 | 2.38 | 1.83 | 1.66 |
| MI | | | | 2.27 | 1.94 | 1.64 | - | 1.64 | - |
| PVD | | | | - | - | 1.37 | - | - | 1.39 |
| Renal failure and chronic disorders | | | | 1.66 | 2.09 | 2.09 | 1.68 | 1.92 | 2.00 |
| Metastatic solid tumor | | | | 3.78 | 9.00 | 11.86 | 3.68 | 7.93 | 10.72 |
| Sudden weight loss | | | | 2.54 | - | 1.99 | 2.49 | - | 1.97 |
| **Covariates with combined drug and ICD-9-CM information** | | | | | | | | | |
| Antiretroviral therapy - aids | | | | | | | 6.26 | 10.6 | 26.37 |
| Insulin – diabetes w/ complications | | | | | | | - | - | 1.27 |
| Depression - antidepressants | | | | | | | - | 0.67 | 0.66 |

Aids: Acquired Immune Deficiency Syndrome; PVD: Peripheral vascular disorders.

* represents a variable that was included in the ICD-9-CM or drug based model and that was combined with its counterpart in the combined model.

- represents a variable that was included in the ICD-9-CM or drug based model but that failed to enter its respective combined model.

Table 7: Model Statistics for GA and NC Samples by Index Type and Time Period

| **GA Training Sample** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Drug-based | | | ICD-9-CM-based | | | Drug- and ICD-9-CM-based | | |
| | 1-month | 1-year | 2-year | 1-month | 1-year | 2-year | 1-month | 1-year | 2-year |
| Max. number of covariates | 35 | 35 | 35 | 38 | 38 | 38 | 58 | 58 | 58 |
| Included covariates | 10 | 12 | 14 | 15 | 15 | 18 | 17 | 19 | 23 |
| Event-to-variable ratio | ≈10 | ≈30 | ≈43 | ≈9 | ≈28 | ≈39 | ≈6 | ≈18 | ≈26 |
| P value Hosmer-Lemeshow test | 0.89 | 0.99 | 0.68 | 0.06 | 0.64 | 0.17 | 0.34 | 0.48 | 0.09 |
| C-statistic* | 0.673 | 0.682 | 0.705 | 0.707 | 0.691 | 0.718 | 0.712 | 0.706 | 0.732 |
| C-statistic 95% CI* | 0.64 – 0.71 | 0.67 – 0.70 | 0.69 – 0.72 | 0.67 – 0.74 | 0.68 – 0.71 | 0.70 – 0.74 | 0.68 – 0.74 | 0.69 – 0.73 | 0.72 – 0.75 |
| C-statistic 95% CI** | 0.65 – 0.67 | 0.65 – 0.68 | 0.67 – 0.69 | 0.67 – 0.71 | 0.66 – 0.69 | 0.58 – 0.70 | 0.66 – 0.70 | 0.66 – 0.67 | 0.53 – 0.70 |
| $R^2$ *** | 0.04 | 0.07 | 0.11 | 0.04 | 0.08 | 0.13 | 0.05 | 0.09 | 0.13 |
| $R^2$ * | 0.03 | 0.07 | 0.11 | 0.04 | 0.07 | 0.12 | 0.03 | 0.08 | 0.13 |
| $R^2$ 95% CI** | 0.01 – 0.05 | 0.05 – 0.08 | 0.09 – 0.12 | 0.02 – 0.06 | 0.06 – 0.09 | 0.10 – 0.14 | 0.02 – 0.06 | 0.07 – 0.10 | 0.12 – 0.16 |
| **NC Test Sample** | | | | | | | | | |
| | Drug-based | | | ICD-9-CM-based | | | Drug- and ICD-9-CM-based | | |
| | 1-month | 1-year | 2-year | 1-month | 1-year | 2-year | 1-month | 1-year | 2-year |
| C-statistic | 0.64 | 0.63 | 0.65 | 0.66 | 0.65 | 0.67 | 0.65 | 0.65 | 0.67 |
| Hosmer and Lemeshow p value | < 0.01 | < 0.01 | < 0.01 | < 0.01 | < 0.01 | < 0.01 | < 0.01 | < 0.01 | < 0.01 |
| $R_{SS}^2$ | 0.03 | 0.03 | 0.05 | 0.03 | 0.05 | 0.08 | 0.03 | 0.04 | 0.07 |

* adjusted for shrinkage - original sample

** adjusted for shrinkage over bootstrap samples

*** not adjusted for shrinkage - original sample

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# CHAPTER FIVE

# PROSPECTIVE MORTALITY RISK ADJUSTMENT INDICES FOR ALZHEIMER'S DISEASE AND RELATED DEMENTIAS USING ADMINISTRATIVE DATA[1]

[1]Ricci, JF. and B. C. Martin. To be submitted to Annals of Internal Medicine, 2001.

ABSTRACT

***Background and Purpose*** – Alzheimer's dementia and related dementia (AD/D) is one of the most common diseases in the elderly and a major cause of disability and mortality in the US. It has an increasing impact on patients' lives and exacts a large toll on society. Although dementia may interact with other conditions to predispose early death, to date no risk-adjustment model exists to predict short-term or long-term post-Alzheimer's dementia mortality. This research describes the development and independent validation of prospective mortality risk-adjustment indices for incident cases of AD/D based on automated pharmacy and medical claims data.

***Methods*** - A retrospective review of Georgia (training sample) and North Carolina (validation sample) claims Medicaid data for eight years (1990 to 1997) was used to detect persons with a first AD/D diagnosis (primary ICD-9-CM codes 290; 290.0; 290.1; 290.10; 290.11; 290.12; 290.13; 290.2; 290.20; 290.21; 290.3; 290.9; 331; 331.0; 331.2; 331.89; 331.9; 797) in a 12-month period. ICD-9-CM-based comorbidities and drug exposure the year prior to the index AD/D diagnosis were collected along with demographic information to predict six-month, one- and two-year post-AD/D all cause mortality. Three types of models were developed: models with drug exposure data, models with ICD-9-CM codes, and models with combined drug exposure and ICD-9-CM information. Multivariate logistic regression techniques were used to develop the models, bootstrapping to assess the internal validity on the GA training sample, and c-statistic to assess the predictive discriminative ability. Risk factors, identified on statistical empirical evidence in the GA sample, were subsequently submitted to a clinical panel of AD/D experts for validation. Clinically validated GA models were then re-estimated, 'frozen', and prospectively validated on the external NC AD/D sample.

***Results*** - We identified samples of 4,986 and 5,000 GA and NC Medicaid AD/D patients, with mean ages of 75 and 81 years, respectively. At two-year follow-up time from AD/D diagnosis, 34% of GA and 38% of NC recipients expired. In all GA models, c-statistic ranged from 0.686 to 0.710 and adjusted $R_{SS}^2$ from 0.04 to 0.11. Prior exposure to opiates, cardiac and respiratory drugs, a prior diagnosis code for tumors/cancers, cardiac and organ diseases (renal failure, liver diseases), and sudden weight loss were factors each associated with increased odds of death of at least 25% at all follow-up times. Conversely, the presence of comorbid non-organic psychotic disorders and alcohol abuse reduced the odds of six-month, one- and two-year post-AD/D death by 30 to 50%. When GA 'frozen' models were prospectively tested on the external NC sample, c-statistic ranged from 0.65 to 0.67 and $R^2$ from 0.01 to 0.09. At times, drug exposure and ICD-9-CM comorbidity provided complementary information. Combined models had higher $R^2$ than ICD-9-CM code-based models and than drug exposure models, but there was no marked differences in terms of discriminative ability.

***Conclusions*** – Drug exposure information has similar predictive ability on mortality as ICD-9-CM code-based information at six-month, one- and two-year post-AD/D onset. Combined drug and ICD-9-CM variables predicted mortality only slightly better than drug or ICD-9-CM code-based information alone. Therefore either source of information could be used independently to predict post-AD/D mortality at a population level. AD/D mortality models developed should perform reasonably well in other Medicaid states as they were developed and tested in independent populations.

Key Words: Medicaid; Risk Adjustment; Alzheimer's Dementia and Related Dementia; Comorbidity Index; Mortality; Administrative Data.

INTRODUCTION

Alzheimer's disease and related dementias (AD/D) is a fatal and dehabilitating condition with an incidence that progressively increases with age. It is estimated that there are 360,000 newly diagnosed cases each year.[1] Over four million people in the US have AD/D, with a prevalence estimated to increase to 14 million by the middle of the century.[2] Two-third of AD/D patients are women and 43% being between the ages of 75 and 85.[1] With a total annual cost already approaching $70 billion,[3] an average lifetime cost per person of $140,000,[2] and a graying population, AD/D has become a significant public health problem. AD/D is one of the most common diseases in the elderly and a major cause of disability and mortality in the US.[4,5,6] In 1995, more than 7% of all deaths were attributable to Alzheimer's, placing AD/D at par with cerebrovascular diseases as the third leading cause of death in the US.[7] The economic burden of this illness is of particular relevance to Medicare, Medicaid, and other programs that will be providing services to an increasing number of persons afflicted with AD/D in an aging America.

Knowledge regarding prospective prognostic factors for AD/D patients can help clinicians in caring for their patients. At a population level, prognosis of AD/D is an important part of medical planning for a program such as Medicaid that covers most of the long-term care benefits of AD/D patients. Disease-specific risk adjustment methods have been developed in other conditions such as stroke, pneumonia, myocardial infarct, and congestive heart failure.[8] No such methods have yet been published for AD/D patient populations, although dementia may interact with other conditions to predispose early death.[9] One study assessed the prevalence of comorbid conditions and key pharmacological treatments to identify possible differences in patterns and severity of comorbidities by gender in nursing home AD/D residents.[10] However, this study did not describe an inception cohort, lacking documentation about a patient's earlier medical history. Most of the research around mortality in dementia has focussed on patients in geriatric or dementia clinics, assessing comorbid conditions in prevalent rather than incident cases.[11,12] The few studies that addressed incident cases of dementia may have

lacked the sample size to detect true difference in comorbid variables that were uncommon in their populations.[13,14,15] Therefore, we are still unable to identify prospective risk profile for patients from the time of their initial AD/D diagnosis and reliably estimate the length of time to death based on AD/D specific models. In fact, generic comorbidity risk-adjustment models have just recently been used to control for comorbidity conditions in AD/D population studies.[16,17,18,19,20] However, as Warshaw pointed out "these existing measures of comorbid medical illness focus on system diseases and may not be applicable to the types of comorbid problems important to the AD patient." Most of the physical health problems encountered in AD/D patients are not unique to these patients, but they may have more functional impact in adults with AD. Further understanding of the impact of coexistent illnesses in AD/D requires the development of new measures of the cumulative occurrence of comorbid illnesses in this population.[21]

The development of risk adjustment indices with administrative databases has been described previously (refer to Chapter 4: "Prospective Mortality Risk Adjustment Indices for Stroke Using Administrative Data"). In summary, it mostly relied on diagnosis codes such as the International Classification of Disease, Ninth Revision, Clinical Modifications (ICD-9-CM) codes.[22,23,24] ICD-9-CM code-based measures, however, present with a potential for omission bias in coding comorbidities in the context of longitudinal studies. Therefore, there exists a need to complement ICD-9-CM code-based measures with another source of comorbidity information. Medical records represent an invaluable source of such information, containing data on vital signs, patient risk factors, and diagnostic and test results.[25,26] Unfortunately, the information needed to code for clinical indicators is usually not recorded in administrative databases such as Medicaid, making their use in large-scale studies almost impossible and prohibitively expensive on the scale needed to develop and validate a comorbidity index. As Roos suggested several claims measures might "well do better than one or more variables collected in an expensive manner," such as diagnostic tests and/or chart reviews.[27] As a

research team from the Group Health Cooperative of Pudget Sound, Seattle, WA showed with the Chronic Disease Score (CDS), detailed prescription files can serve as an inexpensive and complementary source of information on patients' comorbidities derived from ICD-9-CM codes.[28,29] Until recently, however, few published studies have incorporated the CDS as a health status indicator.[30, 31,32]

Although Medicaid program cover most of the long-term care needs of AD/D patients and Medicaid databases contain demographic, medical, and drug utilization information for the indigent US population necessary to perform longitudinal studies, little published research has developed and validated risk adjustment indices specific to this population. The nature of the Medicaid databases is one of the major reasons why risk adjustment methods for such a large segment of the US population have not been studied. Their sheer-size, complexity, and lower visibility than Medicare files "may have caused some analysts to despair and decide that Medicaid data are hopeless."[33] Furthermore, the lack of consistency of data across states has impaired researchers' ability to formulate research models from one state and to validate these models in other states. Therefore, the objectives of this study were twofold:

1) To develop population-based mortality risk-adjustment indices for Medicaid AD/D patients based on ICD-9-CM codes and drug exposure separately and combined ICD-9-CM codes and drug exposure information. Six-month, one- and two-year prospective mortality indices were developed to test whether risk factors for patients who survive the initial AD/D diagnosis phase differ from those who do not.

2) To test the validity of new indices on an independent AD/D Medicaid patient population of another state.

## METHODS

### Data Sources

A retrospective review of the Georgia and North Carolina Medicaid claims data was used to detect patients with a diagnosis of AD/D. The Georgia and North Carolina

Department of Medical Assistance are the state agencies responsible for operating the state Medicaid programs. The Georgia and North Carolina Medicaid data are housed at the University of Georgia Computer Center where they have been converted to SAS data sets stored on 3490E 76K BPI cartridges. The data consist of adjudicated claims for over a million Medicaid recipients in each state with all pharmaceutical and medical claims examined in the 8-year study period (1990-1997). The training sample was obtained from the Georgia Medicaid population and the out-of-sample validation set from the North Carolina Medicaid population. The demographic and eligibility characteristics, associated comorbidities, drug utilization, and mortality outcome were recorded for each patient.

Cohort Definitions

Claims data from all medical claims from Georgia and North Carolina Medicaid from January 1, 1990 to December 31, 1997 were reviewed. Patients were identified by screening for claims with a primary diagnosis ICD-9-CM code for Alzheimer's disease and/or related dementia. Support for the decision to include selected related dementias comes from the literature as other investigators have estimated that 60-70% of persons with certain organic brain syndromes suffer from Alzheimer's disease.[34] Three series of ICD-9-CM codes were searched:

- The 290 series (senile and presenile dementia) with the codes 290; 290.0; 290.1; 290.10; 290.11; 290.12; 290.13; 290.2; 290.20; 290.21; 290.3; or 290.9.
- The 331 series with the 331; 331.0 (Alzheimer's disease); 331.2; 331.89; or 331.9 codes.
- And, the 797 series (senility).

Truncated ICD-9-CM codes (290; 290.2; and 331) are not valid ICD-9-CM codes per se, as there exist lower hierarchical ICD-9-CM codes. However, patients presenting one of these codes were included because previous research on dementia within the

Georgia Medicaid population has shown that Medicaid providers coded 75% of the AD/D patients with the 290 and 331 codes alone.[19] Recipients presenting ICD-9-CM diagnosis codes (primary and/or secondary) of vascular dementia (VaD) or unspecified senile dementia (codes 290.8; 294; 294.0; 294.1; 290,41; 290.42; 290.43; 294.8; 331.1; 331.3; 331.4; 331.7; 331.8; and 331.81) were excluded from the study population.[5] VaD and AD/D have a distinct etiology, and patients with VaD have different comorbidity burden and mortality relative to patients with AD/D.[35]

The date of a recipient's first AD/D claim during the inclusion period (January 1, 1991 to December 31, 1995) was termed their index date. Patients remained in the study cohort if they met the following criteria. AD/D mostly affect older patients, therefore subjects younger than 50 years of age at their index date were discarded. Patients had to be continuously eligible the year prior to their index AD/D claim (observation period) and be free of any dementia-related diagnosis code (all inclusion and exclusion ICD-9-CM codes for dementia) and/or prescriptions for donepezil® and/or tacrine® during that period. Patients also had to be continuously eligible for 24 months after the initial AD/D event or die any time after their index AD/D event while continuously eligible. We collected all outpatient pharmacy and medical claims for the 12 month-period prior to and up to 24 months after the index diagnosis for all incident cases of AD/D.

Comorbidity Definitions

To develop the list of potential ICD-9-CM code-based comorbidity markers, we combined elements of the Deyo's adaptation of the Charlson Index[23] and the updated set of comorbidity measures published by Elixhauser.[24] Details on the adaptation of the Charlson and Elixhauser methods have been described elsewhere (refer to Chapter 4, "Prospective Mortality Risk Adjustment Indices for Stroke Using Administrative Data"). The final set of 31 comorbidities along with their ICD-9-CM codes is displayed in Table 1. By study design, patients with a diagnosis code for dementia or a dementia-related drug during the observation prior to their index date were excluded from the study.

The Chronic Disease Score developed by Von Korff[28] and revised by Clark,[36] and the rationale supporting it, served as the foundation of our drug exposure measure that includes 27 drug expsoure categories (Table 2). All drug claims during the one-year pre-index date observation period were sorted by National Drug Code number and assigned to a therapeutic class using a classification algorithm (http://www.multum.com). As the CDS was developed in 1992, we updated different drug classes to reflect the availability of newer pharmacological classes and agents.

In addition to comorbidity definitions described above, a set of covariates coding for demographic, eligibility, a quadratic term for age, interaction terms (e.g., age and gender, age and race), and place of residence during the two weeks prior to the AD/D diagnosis was tested for entry in all nine prospective models. Place of residence was categorized between inpatient (hospital), nursing home residence, and ambulatory setting.

Mortality Models

The prevalence of code-based comorbidities and drug exposure, as defined in Tables 1 and 2, was checked in the Georgia Medicaid patient sample. The three-step initial variable selection performed prior to the modeling stage has been described elsewhere (See Chapter 4: "Prospective Mortality Risk Adjustment Indices for Stroke Using Administrative Data").

Multivariate logistic regression was used to model the binary mortality outcome at six months and one and two years to screen candidate variables in the GA training sample. Logistic regression is the most widely used approach for modeling dichotomous dependent variables and performs favorably even compared with other, more complex modeling approaches.[37,38] The significance of all potential covariates was first tested in a stepwise logistic regression procedure predicting mortality for each of the nine models at a significance level for entry of 0.20 and for staying in the models of 0.10.[39] The 10% significance level required for a variable to remain in a model limited the inclusion of noise variables in our comorbidity indices.[40,41] As stepwise variable selection processes

can lead to model overfitting, we used a bias-corrected bootstrap validation to assess the internal validity of each of the nine models developed on the Georgia Medicaid sample. Resampling occurred 200 times for each bootstrap validation, as bootstrapping requires fewer model estimations than cross-validation.[42,43] In logistic regression models, the c index is a widely accepted measure of predictive discrimination.[44] Model explained variation was assessed by calculating $R_{SS}^2$ adjusted for shrinkage.[45] $R_{SS}^2$ adjusted permits an analogous calculation to the $R_{adj}^2$ in linear regression models by controlling for the inflation tendency in situations where there are a large number of candidate covariates relative to the sample size. Bias corrected c-statistic and adjusted $R_{SS}^2$ were computed along with their 95% non-parametric bootstrap confidence intervals. The goodness-of-fit of the multivariate logistic models was assessed with the Hosmer-Lemeshow test.[46] SAS version 6.12 software (SAS Institute, Cary, NC, USA) was used to extract the final analytical samples. Descriptive analyses, model estimations, and external validation were carried out in SAS or STATA Version 6.0 (STATA Corporation, College Station, TX, USA).

Clinical Expert Review

Univariate statistical analyses, detailed results from the initial stepwise procedures, and summaries from the bootstrap simulations were presented to clinical experts (one internist, one clinical pharmacologist, one psychiatrist). Clinical experts reviewed the findings and helped determine which of the variables should stay in the models and be submitted to the external validation procedure. Like Keeler during the development phase of the APACHE III,[47] clinicians were allowed to drop factors empirically identified on sole statistical evidence but that might be unlikely predictor of the outcome studied (i.e., mortality) based on clinical expertise. Six-month, one- and two-year GA mortality models were subsequently re-estimated to incorporate clinicians' decisions on each of the nine models.

External Model Validation

Upon clinical expert review and subsequent model re-estimations, the reduced models were 'frozen' and tested on the North Carolina Medicaid sample. Correct probability of prediction of death (external predictive discrimination) in the final reduced models was assessed by the Somer's $D_{yx}$ rank correlation and back transformed to a measure of c-statistic, as c-statistic = (1 + Somer's $D_{yx}$) / 2.[48] Explained variation was assessed by the sum of square $R^2$ and model fit with the Hosmer-Lemeshow test.

Institutional Review Board was obtained from the University of Georgia Research Office (project number H980679 - CFR category 46.101 (4) - Institution Assurance number M1047).

RESULTS

Demographics and Eligibility

Table 3 presents demographic, eligibility, and AD/D-specific information for the Georgia and North Carolina Medicaid samples. There were a total of 4,986 and 5,000 patients in the GA and NC samples, respectively. GA patients were younger (mean ages of 75 vs. 81 years). The GA sample included a smaller proportion of white patients (51% vs. 60%). GA patients were more likely to be institutionalized in a nursing home at the time of diagnosis (58% vs. 42%). Gender, Medicare eligibility, and mortality rates at six months (14% vs. 15%) and one (21% vs. 24%) and two years (34% vs. 38%) were similar between the two AD/D patient samples.

Comorbidity Burden

The prevalence of the 31 ICD-9-CM code-based comorbidities and 27 drug exposure categories in the GA Medicaid sample the year prior to the index diagnosis of AD/D are presented in Table 1 and Table 2, respectively. The most prevalent ICD-9-CM code-based conditions were hypertension (17%), non-organic psychotic disorders (NOPD) (13%), cerebrovascular (9%), chronic pulmonary (8%) diseases, and other

neurological disorders (7% - e.g., epilepsy, Parkinson disease). Classes of drugs most frequently prescribed were antihypertensives (46%), cardiac drugs (43%), neuroleptics (36%), acid peptic disease agents (28%), antidepressants (21%), chronic respiratory agents (20%), anti-Parkinson agents (19%), and antiepileptics (16%). Classification Tables 4 and 5 summarize the impact of the number of ICD-9-CM- and drug-based comorbidities in the GA sample on six-month, one-year, and two-year mortality. GA AD/D patients had on average one ICD-9-CM-based comorbidity (median 0) and were exposed to three drug classes (median 3) during the year prior to their index date. No relationship was observed between six-month mortality and ICD-9-CM code-based burden or drug exposure (Pearson $\chi^2$ test P value > 0.025 – Tables 4 and 5). A circuitous J-shaped relationship emerged between drug exposure and one- and two-year mortality (Pearson $\chi^2$ test P value < 0.025 and Cochran-Armitage linear trend test P value < 0.025 – Table 5). Note, a level of significance at 0.025 was specified *a priori* to control for test multiplicity, as differences at each follow-up period were tested two ways: once for association with drug exposure and once for association with ICD-9-CM burden. Patients with exposure to no drug classes had larger crude mortality rates than patients with up to four drug classes at one- and two-year follow-up. The latter, however, had lower mortality rates than patients with exposure to 5 or 6 drug classes. These patients in turn had lower crude mortality rates than patients with exposure to 6 or more drug classes. A similar J-shaped curve was observed with ICD-9-CM code-based comorbidities and one- and two-year mortality (Table 4).

Model Building

The variable coding for the presence of anemias was not entered in any stepwise ICD-9-CM-based risk adjustment regression models because fewer than 20 patients presented with this comorbidity. For the same reason, five drug variables were excluded from the stepwise drug-based risk adjustment regression models (i.e., drugs for rheumatologic conditions, irritable bowel disease, end stage renal disease, migraine, and

immunosuppressive agents). Lastly, because of the overlap in certain drug classes and ICD-9-CM codes, information from the two sources was aggregated in the combined models in five cases: 1) antidepressants and depression diagnosis; 2) insulins and diabetes with complications; 3) antipsychotics and NOPD; 4) antiulcer agents and ulcer; 5) second-line antihypertensives and hypertension.

## Clinical Expert Review

Following recommendations from the clinical panel, patients who presented with any claim with a diagnosis for aids (ICD-9-CM 042.X-044.9X) and/or any aids-specific drugs (i.e., protease, nucleoside, and non-nucleoside reverse transcriptase inhibitors) the year prior to the AD/D index diagnosis date were discarded from the study (53 patients – data not presented). Aids dementia complex (ADC) is believed to be directly related to HIV infection of the brain and therefore patients with ADC have a distinct dementia etiology from that of dementia patients without aids.[49,50] Also, in a couple of models, exposure to lipid/cholesterol lowering agents and oral hypoglycemiants had a "protective" effect on survival (post-stepwise regression modeling). The clinical panel found these statistically derived relationships aberrant, with no clinical relevance, and recommended that the two covariates be dropped from the final models. Lastly, the clinical panel recommended testing the predictive ability of place of residence within two weeks prior to the index AD/D diagnosis.

## Mortality Models

Odds ratios (O.R.) of each covariate in the six-month, one- and two-year drug, ICD-9-CM, and combined models are presented in Table 6 and summary statistics for each of the nine models in Table 7. Of the 34, 37, and 56 potential variables tested for entry in the drug, ICD-9-CM, and combined models, 14 to 19 remained in the drug and ICD-9-CM only models and 17 to 26 in the combined models (Table 7). There were 677, 1,063, and 1,675 recorded deaths (events) in the GA sample at six months, and one and

two years respectively (Table 3). Therefore the largest event-to-variable ratio was observed in the two-year drug model (49:1 ≈ 1,673:34) and the smallest event-to-variable ratio in the six-month combined model (12:1 ≈ 677:56). The use of screening techniques for selection of candidate variables (discarding covariates with low "prevalence" or combining those clinically relevant) limited the number of covariates to no more than 1 for each 10 observations of the least frequent outcome, i.e., death.[44] Consequently, no other data reduction technique was employed prior to the stepwise regression modeling stage.

In all nine GA models, discrimination, as indicated by c-statistic, ranged from 0.686 to 0.710. $R_{SS}^2$ adjusted for shrinkage ranged from 0.04 to 0.11. In general, a longer follow-up time was associated with a larger $R_{SS}^2$ but not a higher discriminative ability. Non-parametric bootstrapped confidence intervals for the c-statistic and $R_{SS}^2$ adjusted for shrinkage are presented in Table 7. All logistic models had acceptable goodness-of-fit as the Hosmer-Lemeshow p-value of each model was greater than 0.15.

Risk/Protective Factors

To the exception of the two-year drug model, the impact of age was almost constant. For a one-year increase in age at time of AD/D diagnosis, risk of death increased by 4 to 6%, or by 50% to 80% for every 10 years of age. In general, males were twice as likely to die than their counterparts. Place of residence in hospital or nursing home (base case was ambulatory setting) was a strong predictor of death. However, whereas residence in a nursing home had almost a constant effect at all three time-points ($1.46 \leq$ O.R. $\leq 1.60$), the impact of establishing the diagnosis upon a hospital stay decreased with longer follow-up periods: O.R. $> 2.0$, $\approx 2.0$, and $< 2.0$ at six months, and one and two years respectively. Black race had an ambivalent impact, not being significant in all models, with increasing odds of death in some models, and decreasing odds in others.

Among all drug-based variables tested, the use of narcotic analgesics was the stronger predictor of death (drug and combined models), with increasing risk of death observed over longer follow-up periods. The stepwise approach used to operationalize cardiac and respiratory drug classes allows for two types of comparisons, between and within models. First, pre-AD/D exposure to cardiac and respiratory drugs was associated with larger O.R. over longer follow-up periods. Second, a consistent linear relationship was observed within each of all six drug models as for a given follow-up time, patients exposed to a larger number of classes of cardiac drugs experienced higher risk of death than patients who were exposed to fewer classes of cardiac drugs. For instance, in the two-year drug-based model, O.R. were 1.28, 1.48, 2.04, and 3.19 for patients who were exposed to one, two, three, and four classes of cardiac drugs, respectively. A similar trend was observed with exposure to chronic pulmonary disease drugs. Conversely, the use of neuroleptics the year prior to the AD/D diagnosis reduced the odds of two-year post-AD/D death by 18%.

Among all ICD-9-CM code-based variables tested, the presence of a diagnosis of metastatic solid tumor, malignancies, liver diseases, and sudden weight loss the observation year prior to the AD/D index diagnosis were the stronger predictors of death (ICD-9-CM and combined models). The effect of sudden weight loss waned over time (O.R. > 3.8 at 6 months and O.R. < 2.5 at two years) in the ICD-9-CM and combined models. Cardiac comorbidities (i.e., CHF, arrhythmia) were predictors of death in both the ICD-9-CM and combined models whereas chronic pulmonary diseases (e.g., chronic bronchitis, emphysema, asthma, and pneumoconiosis) were only significant predictors in the ICD-9-CM models at 6 months and one year. Conversely, patients with comorbidities associated with chronic alcohol consumption or alcohol abuse, such as alcoholic psychoses and alcohol dependence syndrome, had a consistent 30 to 45% decreased odds of death at all three follow-up times. A diagnosis of obesity had the strongest protective effect (O.R = 0.13 and 0.33 respectively). This ‘apparent’ protective effect, however, was only observed in two out of six models. Finally, the presence of a

diagnosis of NOPD in the ICD-9-CM only models was associated with lower odds of death (-30%) at six-month, one- and two-year follow-up. Likewise, the use of neuroleptics and/or the presence of a diagnosis for NOPD the observation year prior to the AD/D index date were associated with lower odds of death (-16%) in the two-year combined post-AD/D model.

External Model Validation

Table 7 presents for each of the GA 'frozen' reduced models, estimates of the external predictive discrimination (c-statistic), explained variation (sum of square $R^2$), and model fit (p value of Hosmer-Lemeshow test). C-statistic, derived from the Somer's $D_{yx}$, ranged from 0.65 to 0.67 across all 9 models. C-statistic values on the NC samples were either included in the GA sample 95% confidence intervals adjusted for shrinkage (7 models) or within one percentage point (2 models) of their respective lower 95% confidence interval bond. Out-of-sample $R^2$ ranged from 0.01 to 0.09, with higher $R^2$ observed for longer follow-up times. Adequacy of model fit, or calibration, was questionable, however, as Hosmer-Lemeshow tests were rejected in 6 models with a $p < 0.01$.

DISCUSSION

Although Medicaid databases contain demographic, medical and drug utilization information for the indigent US population, little research has developed and validated risk adjustment indices specific to this population. Risk adjustment indices not specific to indigent populations have, however, been used in studies that examined cost or utilization but not mortality outcomes for Medicaid recipients.[51,52,53] As one additional study showed, the absence of Medicaid specific models can have direct consequences on the ability to characterize comorbidity burden with an AD/D population.[19] This study used a cross sectional matched control group design where cases were defined as GA Medicaid recipients aged 50 or over with an ICD9-CM code indicative of dementia. A

comorbidity score based upon the Deyo's adaptation of the Charlson Comorbidity Index was used to identify and weight comorbidities.[23] During the course of this investigation, it was discovered that nursing homes customarily coded a single ICD-9-CM code per recipient claim and only billed Georgia Medicaid once a month. Therefore, the combination of the low number of nursing home claims per year and a single three-digit ICD-9-CM code for each claim yielded a very limited array of ICD-9-CM codes for nursing home residents, resulting in lower than expected Charlson Comorbidity Index score for the AD/D subjects. The study suggests that the Deyo's adaptation of the Charlson index did not adequately quantify comorbidities in the demented Georgia Medicaid population and that a measure specific to AD/D patients, possibly by supplementing or replacing ICD-9-CM code-based information with drug exposure, would be beneficial. The lack of published risk-adjustment models specific to AD/D population is detrimental to Medicaid programs, as Medicaid program cover a large portion of the patient population with AD/D and are the primary payer for long-term institutionalized services.[2] Additionally, a major issue in the development of risk adjustment models is that of independent sample validation as a risk adjustment system is only appropriate when it has been demonstrated to predict the outcome of interest in a population similar but independent to that in question.[54] This is the first study that developed mortality risk-adjustment indices specific to AD/D population and further, attempted to obtain an unbiased estimate of the true predictive ability of the indices on an independent Medicaid population.

Dementias can have different etiology, risk factors, and mortality patterns.[5,55] Therefore, in an effort to develop models for a homogeneous group of dementia patients, the study included only those patients with AD/D and excluded patients with any diagnosis for VaD or unspecified senile dementia. Also, patients had to be free of any diagnosis claim (primary and/or secondary) of AD/D or VaD for at least a year prior to their index diagnosis. The observation period was not extended beyond one year prior to

the index date in order to conserve a reasonably large sample, necessary to derive and test population-based risk-adjustment indices.

Crude Morbidity/Mortality and Nursing Home Residence

As much as 56% of the GA patients had none of the 31 comorbid conditions (mean 0) used in the development of the ICD-9-CM code-based measures (Table 4) whereas as low as 13% of patients had not had exposure to any of the 27 drug classes (Table 5). Underrepresentation of comorbid condition among AD/D patients has been reported elsewhere.[56,57] The underreporting of ICD-9-CM codes may have been compounded by the fact that a least 58% of the GA Medicaid patients had at some point resided in a nursing home during the year prior to their index AD/D diagnosis. A disproportionate proportion of the GA patients (70%) that resided in a nursing home during the two-week period prior to their index diagnosis date presented with none of the 31 comorbid conditions. In comparison, only 36% of the patients not residing in a nursing home during these two weeks did not present with any of the 31 comorbid conditions. Additionally, GA Medicaid patients residing in a nursing home the two weeks prior to their index diagnosis were more likely to die after a 6-month (16%), one- (25%) and two-year (40%) follow-up than ambulatory or hospitalized patients. Indeed, a J-shaped curve relationship was observed between one- and two-year post-AD/D all-cause mortality and the number of ICD-9-CM comorbidities or the exposure to drug classes. It is possible that in reality patients presented with a larger number of comorbidities than the ones that were coded on their Medicaid claims. However, because of an underreporting practice by nursing homes for GA Medicaid recipients, these comorbidities may not have been not reported on their monthly claims.[19] In one study of elderly living in long-term care, patients with cognitive impairments had lower survival rates, although they appeared “to have fewer comorbidities and were less likely to receive medications” than other patients.[56] Similarly, in our population we found that patients with exposure to no drug class experienced larger one- and two-year crude mortality rates

than patients with up to four drug classes. As Landi expressed it, "additional studies are needed to understand whether demented patients may paradoxically be considered healthier or, instead, are only neglected."[56]

Independent Risk Factors

Shorter survival in dementia has been associated with dependence in daily living, rate of cognitive deterioration, behavioral, language, and sensory impairments.[13,35,58] Therefore, research has linked AD/D survival to cognitive and communication impairment, surrogate measures for disease severity. No research, however, has prospectively examined the influence of drug exposure and comorbid conditions on AD/D patients' survival. Six-month, one- and two-year all cause mortality indices were developed to assess the effect of comorbidity on the time frame of observation. Across all nine models, odds of death were 80 to 100% higher in men than in women but the difference was less pronounced with longer follow-up times (Table 6). Female sex has been associated, although not consistently, with longer survival time in AD/D patients.[9,13,15,59,60,61] It has been hypothesized that "the survival advantage of women with AD/D relative to men may occur as a result of fewer comorbid clinical conditions."[10] However, even after controlling for up to 30 comorbidities and exposure to 27 drug classes, our models show that males have higher odds of death than females. The role of gender on pathogenesis and prognosis of AD/D remains unclear. It may be due to differences in risk factors such as genetic susceptibility,[62] biochemical measurements,[63] or neurodegeneration.[64]

Younger age at time of diagnosis was associated with decreased odds of death,[13] as for a ten-year increase in age at time of AD/D diagnosis, risk of death increased by 50% to 80%. Race, conversely, was either not associated with mortality (all combined models), or exhibited an ambivalent relationship in the drug and ICD-9-CM models. Previous research on the impact of ethnicity on survival of AD/D patients is inconclusive. Some studies found increased risk of death in white,[9,60] whereas other studies did not

find any racial differences.[59,65] Lastly, another study found opposite race effects within the same cohort, where race interacted with the presence/absence of senile condition.[9] As our study shows, the assumption that ethnicity can be used as an isolated epidemiological factor, defining clinically distinct disease subgroups remains controversial.[66]

The presence of several comorbid conditions the year prior to the index diagnosis had a protective effect on post-AD/D mortality. The comorbidity with the strongest and most persistent protective effect was linked to chronic alcohol consumption or alcohol abuse (e.g., alcoholic psychoses and alcohol dependence syndrome) with a consistent 30 to 45% decreased odds of death at all three follow-up times in both ICD-9-CM only and combined models. Alcohol-related dementia (ARD) is one of the main causes, along with drug toxicity and depression, for '*reversible*' dementia or 'potentially *reversible* cognitive impairment'. A potentially *reversible* dementia is one in which a patient's baseline intellectual function can be restored. One of the few papers to address follow-up of demented patients after treatment analyzed 32 studies including 2889 patients. The study found that 13 percent of patients had potentially *reversible* dementias, 11 percent improved with treatment, and 3 percent experienced complete reversal with treatment.[67] As in another study,[68] GA Medicaid patients with a history of alcohol abuse were about 10 years younger (mean age of 65 years) than the rest of the GA AD/D patient cohort (76 years). One study noted that up to 63% of alcoholics aged 60 years or older suffered from some form of dementia, their dementia being irreversible in only 33% of the cases.[69] Therefore, GA recipients with a known history of alcohol abuse may have suffered a temporary loss of their cognitive functions. They were assigned a diagnosis code for dementia, as there are no guidelines to assist clinicians distinguishing ARD from dementia from other causes, such as AD/D.[70] However, once their acute *reversible* episode was over, a larger proportion of these patients returned to a normal cognitive state, with a more favorable prognosis and a longer survival expectancy than true AD/D patients.

The presence of a diagnosis of non-organic psychotic disorders (NOPD) prior to that of dementia was associated with lower odds of death (by 30%) in the three ICD-9-CM only models. Conversely, in the drug only model, exposure with neuroleptics was only associated with decreased odds of death after a two-year follow-up. A similar two-year only relationship was observed in the combined model, where the impact of a diagnosis of NOPD may have been diluted by the larger pool of patients who had been exposed to neuroleptic drugs but had not received a diagnosis code for NOPD. Cognitive impairment is a well-recognized element of schizophrenia.[71] It is a prominent feature of schizophrenia after the onset of NOPD, which increases in severity and prevalence with aging.[72,73] Cognitive impairment is not associated with neuroleptic treatment or other possible previous somatic treatments.[72,73] In sort, this study corroborates with the hypothesis that schizophrenia itself, not neuroleptics, can cause cognitive impairment similar to those of AD/D. Patients with a diagnosis of NOPD prior to their AD/D index date are not typical demented patients: they must be for the most part patients with psychosis features exhibiting Alzheimer-like senile degenerative abnormalities, as cognitive impairment does occur in chronic schizophrenia.[74] It is rather tempting to speculate that patients with NOPD have a different organic etiology of dementia than AD/D only patients, with distinct neurobiologic mechanisms responsible for cognitive impairment.[75] Therefore, their survival follows that of schizophrenia and other NOPD patients, with lower likelihood of death than age- and gender matched AD/D patients. Hence, in our ICD-9-CM only models, NOPD patients had a 30% lowered odds of death at six months, and one and two years post-AD/D index diagnosis code.

Patients who had experienced sudden weight loss the year prior to their index diagnosis of dementia were two to four times more likely to expire at six months, and one and two years post-AD/D index diagnosis. Evans (1991) found that over a median follow-up time of five years, persons with Alzheimer's disease and clear cachexia had more than 5 times the risk of death as person without AD/D.[76] Persons with Alzheimer's disease and probable cachexia had 2.5 times the risk of death as person without AD/D.

Low body weight and unintentional weight loss are highly predictive of mortality and morbidity in the elderly patients.[77] Additionally, weight loss has already been associated with shorter survival times in AD/D patients.[78] Although, "sudden weight loss" does not explicitly include the diagnosis code for cachexia, it does encompass some of its consequences, such as nutritional marasmus, severe protein-calorie malnutrition, and dystrophy due to malnutrition.[76] For instance, protein-calorie malnutrition has been reported in as many as 50% of institutionalized AD/D patients.[79] In our models, the impact of sudden weight loss on all-cause post-AD/D mortality was consistently associated with larger odds of death for shorter follow-up times. This is somewhat consistent with empirical clinical evidence that suggests that rapid involuntary weight loss at an advanced age is a sign of disease and deteriorating physical condition.[77] We would speculate that patients who had a history of sudden weight loss prior to receiving a diagnosis for AD/D were at a higher risk of experiencing post-AD/D severe protein-calorie malnutrition, which in turn increased their odds of death.[78] This increased odds of death for GA Medicaid recipients with a history of sudden weight loss contrasts with reduced odds of death at one- and two-year post-AD/D observed in obese patients. The reduction in odds of death was as high as 70 to 90%. Validation of this apparent 'protective' effect of obesity on post-AD/D mortality requires further exploration from independent studies in other AD/D patient populations.

Other ICD-9-CM code-based covariates associated with increased odds of death were, to name a few, metastatic solid tumors, liver diseases, and cardiovascular conditions (e.g., CHF, cardiac arrhythmia), chronic pulmonary diseases, and cerebrovascular accidents. Their effect on mortality was concordant with their anticipated direction, as these comorbidities have been associated with higher odds of death in prevalent AD/D patient studies.[5,9,12,15,60,80,81]

Model Performance

The initial covariate reduction technique, the stepwise logistic regression modeling, the clinical validation, and bootstrapping testing generated models with good internal validity. The stepwise logistic regression algorithm searched for the best models that combine statistical accuracy with parsimony.[82] The clinical evaluation step added validity to the derived mortality models, ensuring that the pathophysiologic insights obtained from each model was in agreement with accepted clinical interpretation of predictors of the outcome. Bootstrap validation demonstrated the internal validity with narrow confidence intervals in all nine models and good or very god calibration (P value of Hosmer-Lemeshow test > 0.15). As noted by Harrell, a bias-corrected internal bootstrap validation can yield a nearly unbiased estimate of the expected value of the external predictive discrimination.[48] Indeed, when the GA 'frozen' models were independently tested and validated with the NC out-of-sample Medicaid AD/D cohort, most of the c-statistic values on the NC samples were included in their respective predicted lower 95% confidence interval bond. Therefore, the true predictive power of the models was barely overestimated in the training GA sample compared to the independent NC validation sample. C-statistic ranged from 0.686 to 0.710 in the GA sample and from 0.65 to 0.67 in the NC sample. The very close discriminative ability of the models in the GA and NC cohorts closely mirrors the similarity in adjusted death rates for Alzheimer's disease between 1990 and 1996 in GA (3.2 per 100,000) and in NC (3.0).[6]

A main objective of the study was to explore the discriminative ability of drug exposure with respect to mortality and to test whether or not this source of information could be combined in a clinically meaningful way with ICD-9-CM code-based data. Von Korff first suggested the potential predictive ability of drug exposure in cost models.(Von Korff 1994) However, no published studies have yet explored its potential as a health status indicator in mortality models and compared its discriminative ability to that of ICD-9-CM code-based information. Therapeutic classes such as antidepressants, opiates,

systemic steroids, present a challenge as they may have multiple indications across many different disease states. Therefore, unlike ICD-9-CM code-based information, drug exposure data is rarely specific to an organ or a disease. Cardiac arrhythmia, liver diseases, renal diseases, cerebrovascular diseases are, however, straightforward makers of organ/tissue dysfunctions.

In our study, overall, models that included both drug exposure and ICD-9-CM burden information did not exhibit higher discriminative ability (c-statistic) than models based on either source of information. However, if the data necessary to build these models is available, they might still be preferable to drug only or ICD-9-CM models only as the combining of both sources of information can have a complementary effect. For instance, exposure to cardiac and respiratory drug classes adds a unique "severity" dimension, not observable with a simple ICD-9-CM algorithm. Indeed, a 20% increase in likelihood of death was observed at all three follow-up times between patients who were using one class vs. no cardiac drugs, two vs. one class of cardiac drugs, three vs. two classes of cardiac drugs, and four vs. three classes of cardiac drugs. This "dose" effect was even more pronounced with chronic respiratory drugs (controlling for all other covariates). After combining information from the two sources (drug exposure and ICD-9-CM codes), odds ratios associated with exposure to cardiac drugs were systematically lower in the combined models than in the drug only models. Similarly, odds ratios for cardiac arrhythmia and CHF were lower in the combined than in the ICD-9-CM only models. In sort, combining the information from the two sources sorted out what proportion of the incremental risk of death was due to mere presence of a cardiac comorbidity and to the severity of the condition (as measured by the number of classes of cardiac drugs). This effect was even more noticeable in the case of respiratory comorbidities and drug classes as chronic pulmonary diseases were no longer significant in the combined models.

Combining the drug and ICD-9-CM information can also help reduce the coding bias inherent to secondary claims data. For instance, antineoplastic agents entered drug

exposure models but only with marginal odds ratios compared to those for malignancy and solid tumor disease states. The much lower odds of death associated with antineoplastic agents in the drug-based models can be explained by the fact that Medicaid programs only capture and report ambulatory prescription use. As most anticancer therapies are not administered through outpatient pharmacies, these prescriptions are rarely captured in Medicaid claims databases. If antineoplastic prescriptions are captured, they must depict ambulatory patients with lower severity of malignancy than those who receive treatment in an inpatient setting. A similar analogy holds true for patients with end stage renal diseases and acute renal failure, where patients are more reliably captured through ICD-9-CM code-based information than drug exposure data.

Limitations

There are several limitations to this study. Patients were selected on the presence of a primary diagnosis ICD-9-CM code reflecting AD/D. Because of the lack of biological markers for dementias, the perception on the differential diagnosis between AD/D and VaD has become blurred.[55] Thus, although it is currently possible to identify two groups of subjects affected by dementias, mixed or unclear cases of AD/D and VaD may be more common than expected. Therefore, although we excluded all patients with any diagnosis for non-AD/D, it is possible that our ICD-9-CM-defined AD/D population also included patients with mixed AD/D - VaD and/or patients with VaD only.

We modeled six-month, one- and two-year mortality from the initial coded disease diagnosis and not from the disease onset. Therefore, our mortality estimates suffer from a left-censoring effect, a phenomenon intrinsic to all diseases whose symptoms gradually appear over time. However, the calculation of mortality rates and the impact of associated risk factors from the date of disease diagnosis rather than the date of disease onset is more relevant to public health planning. A cohort prospective approach with the application of one-year dementia-free period ensured that individuals with rapidly progressing AD/D and short survival were included in our study. In terms of

model performance, it is important to note that the c-statistic does not depend on the prevalence of the condition (e.g., death rate in the population), which limits our ability to compare model performance across different populations and different follow-up times for a same population.

'Frozen' models had good external predictive ability, but failed to exhibit good calibration properties when tested in the independent NC sample. Calibration is the ability to predict probability of the outcome across all ranges of risk. One of the main risk factor for post-AD/D mortality is age and the NC stroke sample was significantly older than the GA sample. Age differences are important in AD/D patients because age is highly correlated with the number and complexity of comorbidities.[83] It would have therefore been beneficial to test for interactions between age at dementia onset and the presence of prior commodity and drug exposure in order to improve model calibration. However, our study was limited by its sample size and more importantly the total number of events. In order to contain the number of candidate variables to around 1 for 10 observed events (i.e., death), we were not able to test age-interacted condition categories with drug exposure and ICD-9-CM code-based covariates.

This is the only study that examines drug exposure and comorbidity impact in incident cases of dementia. It therefore allows for the survival to be evaluated in the early stage of the disease, thus, avoiding to some extent, the influence on mortality of those with advanced dementia. We have showed that there exists a strong relationship between pre-AD/D comorbidity burden and drug exposure with post-AD/D mortality. Although some synergies between drug exposure and ICD-9-CM code-based information exist, models using either source of information alone have equivalent external predictive abilities than combined models. A simple hierarchical categorization of drug exposure data can provide information on the severity of disease: the larger number of cardiac or respiratory drug classes, the greater the post-AD/D mortality. On the other hand, ICD-9-CM code-based data better convey disease/organ specificity information. This study provides "initial" evidence that AD/D mortality at a population level can be prospectively

evaluated using large administrative claims databases, providing clues to comorbid conditions that may predispose to increased or decreased mortality. It is the first study that prospectively validates mortality risk-adjustment models specific to AD/D patients. Validation of these models in other Medicaid populations is desirable, application of the same methodology to non-Medicaid recipients AD/D population and to other disease states is needed.

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TABLE 1: ICD-9-CM-based Comorbidities One Year Prior to Alzheimer's Dementia or Related Dementia Diagnosis in the GA sample and their Operational Definitions

| Comorbidities | Patients n (%) | ICD-9-CM Codes |
|---|---|---|
| 1. Congestive heart failure | 267 (5.4%) | 389.91, 402.11, 402.91,404.11, 404.13, 404.91, 404.93, 428.0-428.9 |
| 2. Myocardial infarction | 53 (1.1%) | 410-410.9, 412, 429.71, 429.79 |
| 3. Cardiac arrhythmia | 131 (2.6%) | 426.10, 426.11, 426.13, 426.2-426.53, 426.6-426.89, 427.0, 427.2, 427.31, 427.60, 427.9, 785.0, V45.0, V53.3 |
| 4. Valvular disease | 120 (2.4%) | 093.20-093.24, 394.0-397.1, 424.0-424.91, 746.3-746.6, V42.2, V43.3 |
| 5. Pulmonary circulation disorders | 24 (0.5%) | 416.0-416.19, 417.9 |
| 6. Peripheral vascular disorders | 198 (4.0%) | 440.0-440.9, 441.2, 441.4, 441.7, 441.9, 443.1-443.9, 447.1, 557.1, 557.9, 785.4, V43.4 |
| 7. Hypertension (complicated and uncomplicated) | 871 (17.5%) | 401.1, 401.9, 402.10, 402.90, 404.10, 404.90, 405.11, 405.19, 405.91, 405.99 |
| 8. Hemiplegia / paraplegia | 108 (2.2%) | 342.0-344.9 |
| 9. Other neurological disorders | 337 (6.8%) | 331.9, 332.0, 333.4, 333.5, 334.0-335.9, 340, 341.1-341.9, 345.00-345.11, 345.40-345.51, 345.80-345.91, 348.1, 348.3, 780.3, 784.3 |
| 10. Chronic pulmonary disease | 381 (7.6%) | 490-492.8, 493.00-493.91, 494, 495.0-505, 506.4 |
| 11. Diabetes, uncomplicated | 244 (4.9%) | 250.00 - 250.33 |
| 12. Diabetes, complicated | 186 (3.7%) | 250.40 - 250.73, 250.90-250.93 |
| 13. Hypothyroidism | 61 (1.2%) | 243-244.2, 244.8, 244.9 |
| 14. Renal failure and chronic disorders | 97 (1.9%) | 403.11, 403.91, 404.12, 404.92, 582-582.9, 583-583.7, 585, 586, 588-588.9, V42.0, V45.1, V56.0, V56.8 |
| 15. Liver disease | 36 (0.7%) | 070.32, 070.33, 070.54, 456.0, 456.1, 456.20, 456.21, 571.0, 571.2, 571.3, 571.40-571.49, 571.5, 571.6, 571.8, 571.9, 572.3, 572.8, V42.7 |
| 16. Peptic ulcer disease | 81 (1.6%) | 531-534.9, V12.71 |
| 17. Aids | 0 (0.0%) | 042-044.9 |
| 18. Any malignancy, including leukemia and lymphoma | 83 (1.7%) | 140.0-172.9, 174.0-175.9, 179-195.8, 200.00-202.38, 202.50-203.01, 203.8-203.81, 238.6, 273.3, V10.00-V10.9 |
| 19. Metastatic solid tumor | 46 (0.9%) | 196.0-199.1 |
| 20. Rheumatoid arthritis / collagen vascular disease | 51 (1.0%) | 701.0, 710.0-710.9, 714.0-714.9, 720.0-720.9, 725 |
| 21. Coagulopathy | 36 (0.7%) | 286.0-286.9, 287.1, 287.3-287.5 |
| 22. Obesity | 33 (0.7%) | 278.0 |
| 23. Weight loss / malnutrition | 37 (0.7%) | 260-263.9 |
| 24. Fluid and electrolyte disorders | 49 (1.0%) | 276.0-276.9 |
| 25. Anemias | 0 (0.0%) | 280.0-281.9, 285.9 |
| 26. Alcohol abuse | 168 (3.4%) | 291.1, 291.2, 291.5, 291.8, 291.9, 303.90-303.93, 305.00-305.03, V11.3 |
| 27. Drug abuse | 28 (0.6%) | 292.0, 292.82-292.89, 292.9, 304.00-304.93, 305.20-305.93 |
| 28. Non-organic psychoses | 662 (13.3%) | 295.00-298.9, 299.10-299.11 |
| 29. Depression | 118 (2.4%) | 300.4, 301.12, 309.0, 309.1, 311 |
| 30. Cerebrovascular disease | 466 (9.3%) | 430-438 |
| 31. Dementia / Alzheimer | 0 (0.0%) | 290-290.9, 331-331.9, 797 |

ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification;

Note on Operational Definitions: In order to account for the fact that additional diagnoses within a category more likely reflect additional diagnosis of the same underlying condition rather than additional severity of illness a hierarchy counting was developed for the following comorbidities.[24] If both uncomplicated diabetes and complicated diabetes are present, count only complicated diabetes. If both solid tumor without metastasis and metastatic solid tumor are present, count only metastatic cancer. This hierarchy helped reduce multicollinearity as many patients were expected to present uncomplicated and complicated diabetes or tumor without metastasis and metastatic solid tumor simultaneously.

TABLE 2: Drug Exposure One Year Prior to Alzheimer's Dementia or Related Dementia Diagnosis in the GA sample and their Operational Definitions

| Drug Classes | Patients n (%) | Therapeutic Classes |
|---|---|---|
| 1. Cardiac agents | 887 (17.8%) | (1) Antiarrythmic, inotropic, cardiac vasopressor agents |
| | 762 (15.3%) | (2) ACE inhibitors or angiotensin II antagonists |
| | 786 (15.8%) | (3) Antianginal agents |
| | 1,035 (20.8%) | (4) Loop diuretics |
| 2. Antiparkinson agents | 967 (19.4%) | Anticholinergic, dopamine agonists, and miscellaneous |
| 3. Coagulation modifiers | 534 (10.7%) | Anticoagulants, antiplatelet agents, heparin antagonists, thrombolytics, miscellaneous coagulation modifiers |
| 4. Antihypertensives | 815 (16.2%) | (1) First-line antihypertensive drugs (β-adrenergic blocking agents; potassium-sparing, thiazide, and miscellaneous diuretics) |
| | 1,901 (38.1%) | (2) Second-line antihypertensive drugs (peripherally and centrally antiadrenergic agents; calcium channel blocking agents; antihypertensive combinations; vasodilators agents) |
| 5. Respiratory agents | 404 (8.1%) | (1) Adrenergic bronchodilatators, asthma vasopressors, and bronchodilatator combinations |
| | 649 (13.0%) | (2) Methylxanthines |
| | 299 (6.0%) | (3) Respiratory inhalants, leukotrien asthma agents, antiasthmatic combinations |
| 6. Drugs for NID diabetes | 453 (9.1%) | Oral hypoglycemiant agents |
| 7. Insulins | 386 (7.7%) | Insulins |
| 8. Antineoplastics (cancer) | 172 (3.4%) | Alkylating, antibiotics/antineoplastics, antimetabolites, hormones/antineoplastics, miscellaneous antineoplastics, mitotic inhibitors, colony stimulating factors and 5HT3 antagonists |
| 9. Antiepileptics / anticonvulsants | 808 (16.2%) | Hhydantoin, succinimide, barbiturate, oxazolidinedione, certain benzodiazepine, and miscellaneous anticonvulsants |
| 10. Acid peptic disease agents | 1,372 (27.5%) | H2 antagonists, proton pomp inhibitors, sucralfate, and antibiotherapy cocktails |
| 11. Glaucoma | 259 (5.2%) | Ophthalmic glaucoma agents |
| 12. Antigout agents | 145 (2.9%) | Allopurinol, colchicine, probenecid, and miscellaneous |
| 13. Anti-hyperlipidemia, hypercholesterolemia | 165 (3.3%) | HMG-CoA reductase inhibitors, fibrates, sequestrants, probucol, and miscellaneous |
| 14. Antiretrovirals (aids) | 0 (0.0%) | Protease, nucleoside, and non-nucleoside reverse transcriptase inhibitors |
| 15. Thyroid agents | 330 (6.6%) | Levothyroxine and thyroid replacement agents |
| 16. Narcotic analgesics | 86 (1.7%) | Narcotic analgesics |
| 17. Antidepressants | 1,070 (21.5%) | SSRI, tricyclic, MAO, and miscellaneous antidepressants |
| 18. Neuroleptics | 1,799 (36.1%) | Phenothiazine, trazodone, and miscellaneous antipsychotics |
| 19. Dementia agents | 0 (0.0%) | Donepezil and tacrine |
| 20. Antituberculosis agents | 33 (0.7%) | Ethambutol, isoniazid, rifampin, pyrazinamide, and miscellaneous |
| 21. Drug for rheumatologic conditions | 15 (0.3%) | Gold salts and hydroxychloroquin |
| 22. Systemic steroids | 361 (7.2%) | Systemic adrenal cortical steroids |
| 23. Drug for Irritable bowel disease | 3 (0.1%) | Mesalamine, olsalazine, infliximab |
| 24. End stage renal disease | 3 (0.1%) | Hematopoietic agents (marrow stimulants, erythropoietin) |
| 25. Immunosuppressive agents | 2 (0.0%) | Azathioprine, basiliximab, cyclosporine, daclizumab, muromonab-CD3, mycophenolate mofetil, and tacrolimus |
| 26. Antimigraine agents | 2 (0.0%) | Triptans, ergotamines, and miscellaneous combinations |
| 27. Drugs for bone diseases (Padget's disease, osteoporosis) | 25 (0.5%) | Alendronate, etidronate, pamidronate, risedronate, tiludronate, raloxifene, cacitonin, and calcium carbonate products (with or without added vitamin D) |

ACE inhibitors, angiotensin converting enzyme inhibitors; HIV, Human Immunodeficiency Virus; MAO, monoamine oxydase inhibitors; NID Diabetes, non insulin-dependent diabetes; NOPD, Non-organic psychotic disorders; SSRI, selective serotonin reuptake inhibitors.

Note on Operational Definitions: Before comorbidity variables were tested for entry in the models, a hierarchy was developed between certain therapeutic classes.[28,36] If both non insulin-dependent and insulin-dependent diabetes drugs were present, we counted only insulin-dependent diabetes drugs. If both first- and second-line antihypertensive drugs were present, we counted only second-line antihypertensive drugs.[84] If drugs from only one therapeutic respiratory illnesses were found for a given patient, then the dummy RESPIRATORY-1 variable was set to 1, 0 elsewhere; if two classes were found then RESPIRATORY-2 was set 1, 0 elsewhere; likewise for the RESPIRATORY-3 variable. A similar coding system was used for the therapeutic classes from the cardiac conditions for the definition of the CARDIAC-1 to CARDIAC-4 variables.
Note that angiotensin II antagonist and non-nucleoside reverse transcriptase inhibitors were not yet commercialized at the time of the study.

TABLE 3: Demographics, eligibility, and dementia-related information - Georgia and North Carolina Medicaid recipients aged 50 and over with a dementia diagnosis claim between 1991 and 1995.

| **Patient Group** | **Georgia Medicaid** | **North Carolina Medicaid** |
|---|---|---|
| Number of patients | 4,986 | 5,000 |
| <u>Demographic Information</u> | | |
| Age in years (mean; std) | 75.2 (12.3) | 81.2 (10.0) |
| Age range in years | 50 – 105 | 50 – 108 |
| Gender: female (%) / male (%) | 3,729 (75%) / 1,257 (25%) | 3,862 (77%) / 1,138 (23%) |
| Race: black (%) / white (%) / other (%) | 2,036 (41%) / 2,543 (51%) / 397 (8%) | 1,470 (29%) / 2,990 (60%) / 540 (11%) |
| <u>Eligibility Information</u> | | |
| Medicare eligible: yes (%) / no (%) | 4,645 (93%) / 341 (7%) | 4,670 (93%) / 330 (7%) |
| Age-blind-disabled / Other: yes (%) / no (%) | 3,337 (67%) / 1,649 (33%) | 4,591 (92%) / 409 (8%) |
| <u>Dementia-specific Information</u> | | |
| Residence within 2 weeks prior to index diagnosis (%): inpatient hospital / nursing home / ambulatory setting | 447 (9%) / 2,885 (58%) / 1,654 (33%) | 608 (12%) / 2,077 (42%) / 2,315 (46%) |
| Mortality: six months (%) / one year (%) / two years (%) | 677 (14%) / 1,063 (21%) / 1,675 (34%) | 745 (15%) / 1,190 (24%) / 1,906 (38%) |

Std: standard deviation.

TABLE 4: ICD-9-CM-based Comorbidity Count One Year Prior to Dementia and Mortality Rates (max score 29) in Georgia Medicaid Patients

| Number of | Number (%) | Percent of Patients Expired | | |
|---|---|---|---|---|
| Comorbidities | of Patients | Six Months | One Year | Two Years |
| 0 | 2,788 (56%) | 13.8% | 22.5% | 36.3% |
| 1 | 1,096 (22%) | 14.2% | 21.5% | 32.3% |
| 2 | 393 (8%) | 8.9% | 12.2% | 22.1% |
| 3-4 | 455 (9.1%) | 13.0% | 18.0% | 27.9% |
| 5-6 | 184 (3.7%) | 17.4% | 28.8% | 39.7% |
| > 6 | 70 (1.4%) | 14.3% | 25.7% | 32.9% |
| **Total** | **4,986** | **13.6%** | **21.3%** | **33.6%** |

P value of Pearson $\chi^2$ test > 0.025* at month and < 0.025 at one and two years. P value of Cochran-Armitage linear trend test < 0.025* at two years only.
* P value of 0.025 was chosen *a priori* to control for test multiplicity

TABLE 5: Number of Drug Exposure Categories One Year Prior to Dementia and Mortality Rates (max score 26) in Georgia Medicaid Patients

| Number of | Number (%) | Percent of Patients Expired | | |
|---|---|---|---|---|
| Drug Classes | of Patients | Six Months | One Year | Two Years |
| 0 | 653 (13.1%) | 13.0% | 21.3% | 33.4% |
| 1 | 662 (13.3%) | 12.8% | 19.0% | 31.4% |
| 2 | 935 (18.8%) | 12.6% | 19.7% | 32.5% |
| 3-4 | 1,751 (35.1%) | 13.1% | 20.4% | 32.3% |
| 5-6 | 786 (15.8%) | 16.4% | 24.7% | 36.8% |
| > 6 | 199 (4.0%) | 15.6% | 31.7% | 45.7% |
| **Total** | **4,986** | **13.6%** | **21.3%** | **33.6%** |

P value of Pearson $\chi^2$ test > 0.025* at month and < 0.025 at one and two years. P value of Cochran-Armitage linear trend test < 0.025* at one and two years.
* P value of 0.025 was chosen *a priori* to control for test multiplicity

Table 6: Odds-ratio by Index Type and Time Period in the GA Sample

| | Drug-based | | | ICD-9-CM-based | | | Drug- and ICD-9-CM-based | | |
|---|---|---|---|---|---|---|---|---|---|
| Candidate Var. | 6-month | 1-year | 2-year | 6-month | 1-year | 2-year | 6-month | 1-year | 2-year |
| Age | 1.04 | 1.05 | 0.98 | 1.05 | 1.06 | 1.05 | 1.05 | 1.06 | 1.05 |
| Male | 2.03 | 1.94 | 1.85 | 2.04 | 1.91 | 1.82 | 2.06 | 1.94 | 1.88 |
| Black | 0.94 | 2.81 | 2.06 | 0.88 | 2.32 | 0.85 | - | - | 0.88 |
| Age square | - | - | 1.00 | - | - | - | - | - | - |
| Age * Black | - | 0.99 | 0.99 | - | 0.99 | - | - | - | - |
| Hospital Resident | 2.66 | 2.31 | 1.86 | 2.19 | 1.87 | 1.63 | 2.25 | 1.98 | 1.70 |
| Nursing Homes | 1.48 | 1.46 | 1.50 | 1.60 | 1.56 | 1.50 | 1.57 | 1.52 | 1.49 |
| | | | | | | | | | |
| **Drug-based covariates** | | | | | | | | | |
| Cancer drugs | 1.53 | 1.97 | 1.59 | | | | - | 1.71 | 1.41 |
| One class of cardiac drugs | - | 1.18 | 1.28 | | | | - | - | 1.25 |
| Two classes of cardiac drugs | 1.38 | 1.43 | 1.48 | | | | 1.28 | 1.25 | 1.40 |
| Three classes of cardiac drugs | 1.89 | 2.07 | 2.04 | | | | 1.64 | 1.75 | 1.89 |
| Four classes of cardiac drugs | 1.80 | 2.28 | 3.19 | | | | - | 1.87 | 3.07 |
| Insulins | - | 1.36 | 1.45 | | | | * | * | * |
| Narcotic Analgesics | 2.70 | 3.69 | 4.01 | | | | 1.94 | 2.78 | 3.05 |
| One class of respiratory drugs | 1.34 | 1.22 | - | | | | 1.30 | 1.23 | - |
| Two classes of respiratory drugs | 1.41 | 1.63 | 1.33 | | | | - | 1.62 | - |
| Three classes of respiratory drugs | 2.27 | 2.43 | 1.78 | | | | 2.27 | 2.51 | 1.71 |
| Neuroleptics | | | 0.82 | | | | * | * | * |
| Acid peptic disease drugs | 1.20 | - | - | | | | * | * | * |
| Systemic steroids | - | 1.26 | 1.31 | | | | - | - | 1.32 |
| Tuberculosis agents | - | - | 2.10 | | | | - | - | 2.24 |

Table 6: Odds-ratio by Index Type and Time Period in the GA Sample

| Candidate Var. | Drug-based | | | ICD-9-CM-based | | | Drug- and ICD-9-CM-based | | |
|---|---|---|---|---|---|---|---|---|---|
| | 6-month | 1-year | 2-year | 6-month | 1-year | 2-year | 6-month | 1-year | 2-year |
| **ICD-9-CM code-based covariates** | | | | | | | | | |
| Alcohol abuse | | | | 0.46 | 0.49 | 0.62 | 0.46 | 0.56 | 0.67 |
| Cardiac arrhythmia | | | | 2.18 | 1.92 | 1.66 | 2.05 | 1.67 | - |
| CVA | | | | 1.34 | 1.33 | 1.28 | 1.29 | 1.26 | - |
| CHF | | | | 2.02 | 2.10 | 1.88 | 1.71 | 1.64 | 1.47 |
| CPD | | | | 1.36 | 1.38 | - | - | - | - |
| Diabetes with complications | | | | - | - | 1.38 | * | * | * |
| Fluid electrolyte disorders | | | | - | 2.41 | 2.09 | - | 2.41 | 2.14 |
| Liver diseases | | | | - | 2.70 | 2.85 | 2.46 | 3.01 | 2.95 |
| Any malignancy | | | | 3.47 | 2.81 | 2.09 | 3.32 | 2.43 | 1.79 |
| Obesity | | | | - | - | - | - | 0.13 | 0.33 |
| Other neurologic disorders | | | | | 1.36 | 1.53 | - | 1.48 | 1.65 |
| Non-organic psychoses | | | | 0.70 | 0.66 | 0.69 | * | * | * |
| Renal failure and chronic disorders | | | | - | - | 1.94 | - | - | 1.97 |
| Rheumatologic disorders | | | | - | 1.80 | - | - | - | - |
| Metastatic solid tumor | | | | 9.63 | 11.00 | 9.10 | 7.70 | 7.77 | 6.10 |
| Sudden weight loss | | | | 3.82 | 3.16 | 2.28 | 4.15 | 3.43 | 2.42 |
| **Covariates based on drug class and ICD-9-CM information** | | | | | | | | | |
| Insulin – diabetes w/ complications | | | | | | | - | 1.33 | 1.49 |
| Neuroleptics - schizophrenia | | | | | | | - | - | 0.84 |

* represents a variable that was included in the ICD-9-CM- or drug-based model and that was combined with its counterpart in the combined model.
- represents a variable that was included in the ICD-9-CM- or drug-based model but that failed to enter its respective combined model.

Table 7: Model Statistics by Index Type and Time Period

| GA Training Sample | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Drug-based | | | ICD-9-CM-based | | | Drug- and ICD-9-CM-based | | |
| | 6-month | 1-year | 2-year | 6-month | 1-year | 2-year | 6-month | 1-year | 2-year |
| Max. number of covariates | 34 | 34 | 34 | 37 | 37 | 37 | 56 | 56 | 56 |
| Included covariates | 14 | 17 | 19 | 14 | 19 | 18 | 17 | 24 | 26 |
| Event-to-variable ratio | 20:1 | 31:1 | 49:1 | 18:1 | 29:1 | 45:1 | 12:1 | 19:1 | 30:1 |
| P value Hosmer-Lemeshow test | 0.16 | 0.66 | 0.65 | 0.30 | 0.96 | 0.37 | 0.44 | 0.87 | 0.48 |
| C-statistic* | 0.686 | 0.694 | 0.689 | 0.700 | 0.698 | 0.688 | 0.709 | 0.710 | 0.702 |
| C-statistic 95% CI* | 0.67 – 0.71 | 0.68 – 0.71 | 0.68 – 0.70 | 0.68 – 0.72 | 0.680.72 | 0.67 – 0.71 | 0.69 – 0.73 | 0.69 – 0.73 | 0.69 – 0.72 |
| C-statistic 95% CI** | 0.66 – 0.68 | 0.66 – 0.67 | 0.66 – 0.68 | 0.66 – 0.70 | 0.56 – 0.67 | 0.55 – 0.67 | 0.57 – 0.69 | 0.55 – 0.69 | 0.56 – 0.68 |
| $R^2$ *** | 0.05 | 0.08 | 0.10 | 0.07 | 0.09 | 0.10 | 0.07 | 0.10 | 0.12 |
| $R_{SS}^2$ * | 0.04 | 0.07 | 0.10 | 0.06 | 0.08 | 0.09 | 0.06 | 0.09 | 0.11 |
| $R_{SS}^2$ 95% CI ** | 0.03 – 0.06 | 0.06 – 0.09 | 0.08 – 0.11 | 0.04 – 0.08 | 0.06 – 0.10 | 0.08 – 0.11 | 0.05 – 0.08 | 0.07 – 0.11 | 0.09 – 0.13 |
| **NC Test Sample** | | | | | | | | | |
| | Drug-based | | | ICD-9-CM-based | | | Drug- and ICD-9-CM-based | | |
| | 6-month | 1-year | 2-year | 6-month | 1-year | 2-year | 6-month | 1-year | 2-year |
| C-statistic | 0.65 | 0.65 | 0.67 | 0.66 | 0.66 | 0.67 | 0.67 | 0.67 | 0.67 |
| Hosmer and Lemeshow p value | > 0.05 | 0.03 | > 0.05 | < 0.01 | < 0.01 | < 0.01 | < 0.01 | < 0.01 | < 0.01 |
| $R_{SS}^2$ | 0.03 | 0.05 | 0.08 | 0.01 | 0.03 | 0.08 | 0.03 | 0.05 | 0.09 |

* adjusted for shrinkage - original sample

** adjusted for shrinkage over bootstrap samples

*** not adjusted for shrinkage - original sample

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# CHAPTER SIX

# PROSPECTIVE COST RISK ADJUSTMENT INDICES FOR STROKE AND ALZHEIMER'S DEMENTIA USING ADMINISTRATIVE DATA[1]

[1] Ricci, JF., J. A. Dorfman, and B. C. Martin. To be submitted to Medical Care, 2001.

ABSTRACT

***Background and Purpose*** – Alzheimer's dementia and related dementias (AD/D) and stroke represent two of the most devastating diseases in the elderly and a major cause of disability and mortality in the US. Although stroke and AD/D patients exact a large toll on Medicaid programs throughout the country, to date, there is no cost risk adjustment model to help predict Medicaid payments for any of these patient populations. This research describes the development and independent validation of prospective cost risk adjustment indices for incident cases of AD/D and stroke based on automated pharmacy and medical claims data.

***Methods*** – A retrospective review of Georgia (training sample) and North Carolina (test and holdout samples) claims Medicaid data for eight years (1990 to 1997) was used to detect persons with a first AD/D diagnosis and a first stroke event. ICD-9-CM code-based comorbidities and drug exposure the year prior to the index diagnosis date were collected along with demographic information to predict one-year cost to Medicaid. Three types of models were developed: models with drug exposure data, models with ICD-9-CM code information, and models with combined drug exposure and ICD-9-CM information. Weighted multivariate linear regression with Huber-White variance estimator were used to develop the models, bootstrapping to assess the internal validity on the GA training sample, and shrunk $R^2$ to assess the explanatory power of the models. Individual factors were identified on statistical empirical evidence in the GA sample. They were subsequently submitted to clinical panels of AD/D and stroke experts for validation. Clinically validated GA models were then re-estimated, 'frozen', and prospectively validated on the external NC AD/D and stroke samples.

***Results*** – We identified cohorts of 4,986 GA and 5,000 NC Medicaid AD/D patients, with mean ages of 75 and 81 years, one-year mortality rates of 21% and 24%, and one-year cost to Medicaid post-AD/D diagnosis of $17,234 and $17,274 respectively. We also identified cohorts of 4,632 GA and 4,500 NC Medicaid stroke patients, with

mean ages of 66 and 76 years, one-year mortality rates of 23% and 29%, and one-year cost to Medicaid post-stroke event of $16,798 and $16,125 respectively. In all GA AD/D and stroke models, shrunk $R^2$ ranged from 0.18 to 0.22 and 0.12 to 0.17, respectively. In the North Carolina AD/D test sample $R^2$ ranged from 0.09 to 0.12 and was 0.08 in all three NC stroke models. AD/D and stroke models underpredicted future annualized Medicaid costs by 8 to 14% and 7 to 10%, respectively. The GA AD/D model based drug exposure information was superior to the other two models, whereas no differences were observed between the drug exposure, ICD-9-CM, and combined models in the stroke cohort. However, superiority of the drug exposure AD/D model did not carry over when models were tested on the NC holdout sample.

***Conclusions*** – A goal of this study was to provide a tool to Medicaid programs and health service researchers to initially stratify or otherwise control for varying levels of disease severity and comorbid illnesses for inception cohorts of patients with stroke or Alzheimer's dementia and related dementias. The study showed that a model based on drug exposure data can perform as well or better than models based on ICD-9-CM information. Combining information from the two sources does not increase model performance, although it may provide some complementary information, in terms of disease specificity and severity. We advocate that drug information can be as useful a predictor as ICD-9-CM codes in the development of cost risk adjustment models and present a series of recommendations to limit 'gaming' opportunities with drug exposure information. The long-term goal for cost risk adjustment indices is to help predict future Medicaid costs for two patient populations that will impose an ever-increasing burden on Medicaid resources. However, further refinements and independent testing of our models with larger cohorts are needed before they can reliably and accurately predict future levels of resource needs.

Key Words: Medicaid; Risk Adjustment; Cost; Alzheimer's Dementia and Related Dementias; Stroke; Comorbidity Index; Mortality; Administrative Data.

INTRODUCTION

Patient groups with comorbidities are usually of great importance to health care payers as they tend to consume a large portion of health care resources. Medicaid programs throughout the country provide insurance coverage to persons with low revenues and/or high level of disability. The most expensive 10 percent Medicaid recipients with disabilities can account for 63 percent of expenditures whereas the least expensive 50 percent account for less than three percent.[1] Focus on the economic burden of illnesses of particular relevance to Medicaid programs should include patient groups that are likely to become high health care utilizers because of a marked condition. Such groups include patients who have experienced a cerebrovascular event or received a diagnosis for dementia.

Alzheimer's disease and related dementias (AD/D) is a fatal and dehabilitating condition with an incidence that progressively increases with age. It is estimated that there are 360,000 newly diagnosed cases each year.[2] Over four million people in the US have AD/D, with a prevalence estimated to increase to 14 million by the middle of the century.[3] With a total annual cost already approaching $70 billion,[4] an average lifetime cost per person of $140,000,[3] and a graying population, AD/D has become a significant public health problem. AD/D is one of the most common diseases in the elderly and a major cause of disability and mortality in the US.[5,6,7] The major economic burden of Alzheimer's disease is the cost of long-term and institutional care, with a total cost to Medicaid that probably already exceeded that of aids in the early 1990's.[8] AD/D comprise the most important diagnoses in nursing home populations, affecting more than 50% of residents in community facilities,[9] half of the cost being borne by Medicaid programs.[10]

Cerebrovascular accidents (CVA) represent another major public health problem in the United States. Stroke, along with AD/D, is the third major cause of death, surpassed only by ischemic heart disease and all forms of cancer, and the leading cause of disability in the United States.[11,12] With 700,000 new cases a year, the incidence of

stroke has been decreasing over the past three decades. The decreasing trend in stroke mortality has been slowing down after 1990 and its prevalence, over 3 million, does not seem to decrease.[13,14] Consequently, a larger number of stroke patients has an increasing impact on health care costs as 30% of stroke survivors require assistance in their activities of daily living and 15% are institutionalized.[15] Once stroke patients become disabled, most will become Medicaid eligible so that Medicaid programs throughout the country will bear some or most of their direct medical costs. Medicaid programs, however, operate with limited resources. These programs would benefit from population-based models that can provide a tool to initially stratify or otherwise control for varying levels of disease severity and comorbid illnesses in stroke and AD/D cohorts, and later prospectively predict future health care costs of their AD/D and stroke recipients.

Some disease-specific risk adjustment methods for stroke patient populations already exist,[16] however, they have focused on the short-term mortality (1 to 3 months) and/or are based on clinical and/or imaging information.[17,18,19,20,21] No such disease-specific risk adjustment methods have yet been published for AD/D patient populations. Most models are based on concurrent information, obtained after the disease onset, such as 48-hour CT scan. Concurrent indices are well suited for patient profiling, to predict patient recovery, neurological improvement, survival, or to guide the early management of the patient. Clinical-based information is not readily available for large insurer groups (such as Medicaid) that do not have direct access to clinical and diagnostic information but to large secondary medical and pharmacy claims databases. On the other hand, generic comorbidity risk adjustment models have been used to control for comorbidity and severity in studies that predicted hospital performance, hospital mortality, and hospital length of stay in stoke patient populations,[22,23,24] and cost/resource use in AD/D populations.[25,26,27,28,29] However, as Warshaw pointed out “these existing measures of comorbid medical illness focus on system diseases and may not be applicable to the types of comorbid problems important to the AD patient.”[30] Further understanding of the

impact of coexistent illnesses in AD/D and stroke requires the development of new measures of the cumulative occurrence of comorbid illnesses in these populations.

The development of risk adjustment indices with administrative databases has been described previously. (Refer to Chapter 4: “Prospective Mortality Risk Adjustment Indices for Stroke Using Administrative Data”) In summary, it mostly relied on diagnosis codes, most often ICD-9-CM codes. ICD-9-CM code-based measures, however, present with a potential for omission bias in coding comorbidities in the context of longitudinal studies. Therefore, there exists a need to complement ICD-9-CM code-based measures with another source of comorbidity information. Medical records represent a valuable source of such information, containing data on vital signs, patient risk factors, and diagnostic and test results.[31,32] Unfortunately, the information needed to code for clinical indicators is usually not recorded in administrative databases such as Medicaid, making their use in large-scale studies almost impossible and prohibitively expensive on the scale needed to develop and validate a comorbidity index.[33] As a research team from the Group Health Cooperative of Pudget Sound, Seattle, WA showed with the Chronic Disease Score (CDS), detailed prescription files can serve as an inexpensive source of information on patients' health status.[34,35] Until recently, however, few published studies have incorporated the CDS as a health status indicator.[36,37,38]

Although Medicaid program cover most of the long-term care needs of AD/D and stoke patients and Medicaid databases contain demographic, medical, and drug utilization information for the indigent US population necessary to perform longitudinal studies, little published research has developed and validated risk adjustment indices specific to the Medicaid population.[1,39] The nature of the Medicaid databases is one of the major reasons why risk adjustment methods for such a large segment of the US population have not been studied. Their sheer-size, complexity, and lower visibility than Medicare files "may have caused some analysts to despair and decide that Medicaid data are hopeless."[40] Furthermore, the lack of consistency of data across states has impaired researchers' ability to formulate research models from one state and to validate these models in other states.

Therefore, the objectives of the study were twofold:

1) To develop population-based risk adjustment indices for inception cohorts of AD/D and stroke patients based on ICD-9-CM codes and drug exposure separately and combined ICD-9-CM codes and drug exposure data to predict one-year post-stroke and post-AD/D cost to Medicaid.

2) To test the predictive ability of the indices on independent external Medicaid AD/D and stroke populations from another state.

## METHODS

Data sources have already been described elsewhere. (Refer to Chapter 4, Methods, Data Sources: "Prospective Mortality Risk Adjustment Indices for Stroke Using Administrative Data")

### Definition of Stroke and AD/D Cohorts

All medical claims from Georgia and North Carolina Medicaid from January 1, 1990 to December 31, 1997 were reviewed. Patients were identified by screening for claims with a primary diagnosis ICD-9-CM code for AD/D or stroke. The date of a recipient's first AD/D or stroke claim during the inclusion period (January 1, 1991 to December 31, 1995) was termed their index date. Patients remained in the study cohort if they met the following inclusion criteria. Patients had to be continuously eligible the year prior to their index date. Stroke patients had to be free of any stroke event (primary and secondary ICD-9-CM codes 430.XX to 438.XX) during the 12 months prior to their index stroke claim. AD/D patients had to be free of any dementia-related diagnosis code (all inclusion and exclusion ICD-9-CM codes for dementia – see next paragraph) and/or prescriptions for donepezil® and/or tacrine® during the 12 months prior to their index AD/D claim. Patients also had to be eligible for 12 months after the initial AD/D or stroke event or die any time after their index AD/D or stroke event while continuously

eligible. We collected all outpatient pharmacy and medical claims for the 12 month-period prior to and up to 12 months after the index AD/D or stroke event.

Three series of ICD-9-CM codes were searched to identify patients with a primary AD/D diagnosis claim:

- 290 series (senile and presenile dementia) with the codes 290; 290.0; 290.1; 290.10; 290.11; 290.12; 290.13; 290.2; 290.20; 290.21; 290.3; or 290.9;
- 331 series with the 331; 331.0 (Alzheimer's disease); 331.2; 331.89; or 331.9 codes;
- 797 series (senility).

Support for the decision to include selected related dementias comes from the literature as other investigators have estimated that 60-70% of persons with certain organic brain syndromes suffer from Alzheimer's disease.[8] Truncated ICD-9-CM codes (290; 290.2; and 331) are not valid ICD-9-CM codes per se, as there exist lower hierarchical ICD-9-CM codes. However, patients presenting one of these codes were considered for inclusion because previous research on dementia within the Georgia Medicaid population has shown that Medicaid providers coded 75% of the AD/D claims with the 290 and 331 codes alone.[26] Recipients presenting ICD-9-CM diagnosis codes (primary and/or secondary) of vascular dementia (VaD) or unspecified senile dementia (codes 290.8; 294; 294.0; 294.1; 290,41; 290.42; 290.43; 294.8; 331.1; 331.3; 331.4; 331.7; 331.8; and 331.81) were excluded from the study population.[6,41] Lastly, as AD/D mostly affect older patients, subjects younger than 50 years of age at their index date were discarded.

Hemorrhagic and ischemic strokes have different pathophysiologies and prognoses and often require different treatments.[42] Therefore, patients with a CVA were divided into two categories based on the primary ICD-9-CM codes found on the index cerebrovascular claims:[43]

- Ischemic stroke: 434.XX and 436.XX;
- Hemorrhagic stroke: 430.XX and 431.XX.

Patients with primary CVA diagnoses of 432.XX, 433.XX, or 437.XX were excluded from the study because these ICD-9-CM series were found unreliable markers of stroke when ascertained against medical record reviews.[44,45,46] In addition, patients with a primary diagnosis of 438.xx were not included because the 438.xx series identifies patients suffering from complications of a prior CVA and not from a new CVA event. Due to differences in genesis of cerebrovascular diseases, the etiology of stroke in older patients differs from that in younger subjects. In fact, as low as 3% of cerebral infarction occur in patients under the age of 40.[42] As a consequence, our study limited the patient population to recipients 40 years of age older on the day of their recorded index stroke claim (index date).

Definitions of Comorbidities and Drug Exposure

To develop the list of potential ICD-9-CM code-based comorbidity markers, we combined elements of the Deyo's adaptation of the Charlson Index[47] and the updated set of comorbidity measures published by Elixhauser.[48] Details on the adaptation of the Charlson and Elixhauser methods have been described elsewhere. (Refer to Chapter 4, "Prospective Mortality Risk Adjustment Indices for Stroke Using Administrative Data") The final set of 31 comorbidities along with their ICD-9-CM codes is displayed in Table 1. The Chronic Disease Score developed by Von Korff[34] and revised by Clark,[49] and the rationale supporting it, served as the foundation of our drug exposure measure that includes 27 drug exposure categories (Table 2). All drug claims during the one-year pre-index date observation period were sorted by National Drug Code number and assigned to a therapeutic class using a classification algorithm (http://www.multum.com). As the CDS was developed in 1992, we updated different drug classes to reflect the availability of newer pharmacological classes and agents. By study design, patients with a diagnosis code for dementia or a dementia-related drug in the dementia cohort and patient with a CVA in the stroke cohort the year prior to their index date were excluded from the study.

In addition to comorbidity and drug class definitions described above, a set of covariates was tested for entry in all six prospective models. Covariates included information on demographic and eligibility, a quadratic term for age, interaction terms (e.g., age and gender, age and race), type of stroke (hemorrhagic vs. ischemic in stroke models), and place of residence during the two weeks prior to the AD/D diagnosis and at the time of the stroke event. Place of residence was categorized between inpatient (hospital), nursing home residence, and ambulatory setting.

## Cost Models

The prevalence of code-based comorbidities and drug exposure, as defined in Tables 1 and 2, was checked in the Georgia Medicaid patient sample. The three-step initial variable selection performed prior to the modeling stage has been described elsewhere (See Chapter 4: "Prospective Mortality Risk Adjustment Indices for Stroke Using Administrative Data"). Costs to GA and NC Medicaid were annualized based on the number of months of survival in the one-year follow-up period. Weighted least squares regression was used to model the continuous one-year total cost outcome to Medicaid and to estimate the amount of additional expenditures in a given year associated with a person having a given diagnosis claim or exposure to a drug in the previous year. Weights for individual standard error estimates for each observation were set equal to the ratio of 12 over the number of months each patient was eligible in the one-year follow-up, so that patients with the fewer number of months eligible were assigned a larger variance weight in the GA training sample.[50] The significance of all potential covariates was first tested in a stepwise weighted backward regression procedure at a significance level for staying in the models of 0.10.[51] The 10% significance level required for a variable to remain in a model helped limit the inclusion of noise variables in our indices.[52,53] In order to better correct model estimates for the presence of heteroskedasticity, we used Huber-White corrected standard errors.[54] As stepwise variable selection processes can lead to model overfitting, we performed a bias-

corrected bootstrap validation to assess the internal validity of each of the six models developed on the Georgia Medicaid sample.[55,56] Models explained variation and goodness-of-fit were assessed by calculating $R^2$ with its 95% non-parametric bootstrap confidence interval over 1,000 bootstraps. $R^2$ for models only including demographic information and demographic information with place of residence were also computed. $R^2$ was adjusted for shrinkage, correcting for the number of candidate predictors that were initially tested following the method developed by Van Houwelingen and Le Cessie.[57] The presence of outliers and/or influential observations was checked in the stroke and AD/D samples. One outlier, which was very influential in the regression fit (Cook's D standardized residuals of 5.8), was identified in the Georgia AD/D cohort. This patient was dropped and was not used to derive AD/D model's coefficients. However, $R^2$ measures are presented both the full and reduced data sets in all three AD/D models. We tested the relative performance of the drug only and ICD-9-CM only models with respect to their respective combined model with a J-Test.[58] This test for departures from the null hypothesis (the two models are equivalent) assessed the null against a more general model that artificially combines the two competing non-nested models. Lastly, expenditure data were adjusted for medical and drug inflation with the consumer price index (CPI) for medical commodities and services (http://stats.bls.gov/cpihome.htm). We standardized expenditures to 1995 levels, as 1995 was the last year of inclusion in the study. SAS version 6.12 software (SAS Institute, Cary, NC, USA) was used to extract the final analytical samples. Descriptive analyses, model estimations, and external validation were carried out in SAS or STATA Version 6.0 (STATA Corporation, College Station, TX, USA).

Clinical Expert Review

Univariate statistical analyses, detailed results from the initial stepwise procedures, and summaries from the bootstrap simulations were presented to a panel of stroke (three neurologists and one stroke clinical pharmacist) and AD/D clinical experts

(one geriatric internist, one pharmacologist, one psychiatrist). Clinical experts reviewed the findings and helped determine which of the variables should stay in the models and be submitted to the external validation procedure. Like Keeler during the development phase of the APACHE III, clinicians were allowed to drop factors empirically identified on sole statistical evidence but that might be unlikely predictor of the outcome studied (i.e., cost) based on clinical expertise.[59] Coefficients of the one-year AD/D and stroke cost models were subsequently re-estimated to incorporate clinicians' decisions on each of the six models.

External Model Validation

Upon clinical expert review and subsequent model re-estimations, the reduced models were 'frozen' and tested on the North Carolina Medicaid sample. The NC samples of each patient cohort were randomly divided into two sub-samples. The NC test sub-sample was used to test the performance of the GA models on an out-of-sample population, with a sample size equivalent to that of their respective GA samples. The second sub-sample, the 'holdout' sub-sample, was spared and set aside for further analysis in case the GA models would exhibit poor predictive model performance. Costs to NC Medicaid were annualized based on the number of months of survival in the one-year follow-up period. Explained variation was measured on each of the six models with the out-of-sample sum of square $R^2$:

$$\text{Predicted } R^2 = 1 - \frac{SSE}{SST} = 1 - \frac{\text{sum}\left[\left(e_i - \bar{e}\right)^2\right]}{\text{sum}\left[\left(y_i - \bar{y}\right)^2\right]}$$

where $e_i$ was error on $i^{th}$ NC observation using $\beta$-hat from the reduced GA data set and $y_i$ was observed one-year total cost to Medicaid on $i^{th}$ NC observation. A correction factor was applied to the sum of squared errors because out-of-sample errors do not necessarily

have error means of zero. Another measure of predictive $R^2$, squared correlation between actual and predicted costs, was also computed. Other researchers have used it in the past,[39,60] although it is analytically flawed as the out-of-sample correlation between actual and predicted costs is not a function of the coefficients (i.e., β-hats). Additionally, the ratios of mean total predicted payments to annualized mean total observed costs to NC Medicaid (predictive ratios) were computed for each of the six models.

Institutional Review Board was obtained from the University of Georgia Research Office (project number H980679 - CFR category 46.101 (4) - Institution Assurance number M1047).

## RESULTS

### Demographics and Eligibility

Tables 3 and 4 present demographic, eligibility, and disease-specific information for the Georgia and North Carolina Medicaid AD/D and stroke cohorts. There were a total of 4,986 and 5,000 patients in the GA training and the NC test AD/D samples. The NC AD/D holdout sub-sample contained 4,093 observations. GA patients were younger (mean ages of 75 vs. 81 years) with a smaller proportion of white patients (51% vs. 60%). Gender, Medicare eligibility, and crude one-year all-cause mortality rates (21% vs. 24%) were similar between the two AD/D patient cohorts. However, there was a smaller proportion of GA patients with aged-blind-disabled Medicaid eligibility (67% vs. 92%) and living in an ambulatory setting within two weeks prior to their index AD/D diagnosis (33% vs. 46%). Finally, one-year total cost to Medicaid post-AD/D diagnosis (in 1995 $) was nearly identical in the two cohorts ($17,234 in GA vs. $17,274 in NC).

There were a total of 4,632 and 4,500 patients in the GA training and the NC test stroke samples. The NC holdout sub-sample contained 3,248 observations. Like in the AD/D cohort, GA patients were younger (mean ages of 66 vs. 76 years) with a smaller proportion of white patients (39% vs. 50%). GA patients were more likely to be institutionalized in a nursing home at the time of treatment of their initial stroke (33% vs.

27%) but the same proportion of patients was hospitalized for their stroke (20%). Gender and Medicare eligibility were similar, but crude all-cause mortality rates at one year (23% vs. 29%) were lower in GA than in NC. Finally, one-year total cost to Medicaid post-stroke (in 1995 $) was similar between the two cohorts ($16,798 in GA vs. $16,125 in NC).

Comorbidity Burden

The prevalence of the 31 ICD-9-CM code-based comorbidities and 27 drug exposure classes in the AD/D and stroke GA Medicaid cohorts the year prior to the disease-specific index diagnosis date are presented in Table 1 and Table 2. In the stroke cohort, the most prevalent ICD-9-CM code-based conditions were hypertension (31%), diabetes (18%), chronic pulmonary disorders (12%), miscellaneous neurologic disorders (10% - e.g., epilepsy, Parkinson disease), CHF (9%), diabetes (9%), and non-organic psychotic disorders (NOPD - 8%). Hypertension (17%), NOPD (13%), cerebrovascular (9%), chronic pulmonary (8%) diseases, and other neurological disorders (7%) were more prevalent in the AD/D cohort. Classes of drugs used by most patients pre-stroke were antihypertensives (58%), cardiac (48%), acid peptic disease (31%), and chronic respiratory (22%) agents, antidepressants (20%), antiepileptics (18%), and neuroleptics (14%). Classes of drugs most frequently prescribed in AD/D patients were antihypertensives (46%), cardiac drugs (43%), neuroleptics (36%), acid peptic disease agents (28%), antidepressants (21%), chronic respiratory agents (20%), anti-Parkinson agents (19%), and antiepileptics (16%). Classification Tables 5 and 6 summarize the impact of the number of ICD-9-CM code-based comorbidities and drug exposure classes in the GA cohorts on one-year mortality and one-year cost to Medicaid. During the year prior to their index date, stroke patients had on average 1.4 ICD-9-CM code-based comorbidities (median 1) and three drug classes (median 3) and AD/D patients had 1.4 ICD-9-CM code-based comorbidities (median 0) and three drug classes (median 3). Stroke patients were more likely to receive at least one ICD-9-CM diagnosis class than

AD/D patients the year prior to their index diagnosis (57.2 % vs. 44%, respectively), whereas there was no marked difference between the two cohorts in terms of drug exposure. Nearly 88% of the patients in GA AD/D and stroke cohorts had been exposed to at least one drug class the year prior to their index date.

A circuitous J-shaped relationship emerged between ICD-9-CM comorbidity burden and drug exposure with one-year crude mortality rates in both the stroke and AD/D cohorts (Pearson $\chi^2$ test P value < 0.025 and Cochran- Armitage linear trend test P value < 0.025 – Table 5 and Table 6). Stroke and AD/D patients with no ICD-9-CM code-based comorbidity or no drug exposure had larger crude mortality rates than patients with up to four comorbidities or exposure to four drug classes. The Cuzick nonparametric test for trend across ordered groups was used to test the relationship between ordered number of drug classes, number of ICD-9-CM comorbidities and one-year cost.[61] A similar but milder J-shaped relationship was observed with ICD-9-CM code-based comorbidities and one-year cost to Medicaid for AD/D and stroke patients. Patients with no ICD-9-CM code-based comorbidity or no drug exposure had larger non-adjusted one-year total Medicaid expenditures than patients with up to two comorbidities or exposure to two drug classes. However, a straight linear relationship was observed between drug exposure and one-year cost to Medicaid in both patient cohorts. Note, a level of significance at 0.025 was specified *a priori* to control for test multiplicity, as differences at one-year follow-up were tested two ways for each outcome: once for association with drug exposure and once for association with ICD-9-CM burden.

Model Building

The variable coding for the presence of anemia was not entered in the stepwise ICD-9-CM code-based stroke and AD/D models because the number of patients presenting with this comorbidity was less than 20. For the same reason, some drug variables were excluded from the stepwise risk adjustment regression models (i.e., drugs for Alzheimer's dementia (stroke cohort only), irritable bowel disease, end stage renal

disease, bone diseases (stroke cohort only), rheumatologic conditions (dementia cohort only), migraine, and immunosuppressive agents). Also, due to the small number of patients using antiretroviral therapy in the stroke cohort, the antiretroviral dummy variable was combined with use of anti-tuberculosis agents in the drug only stroke model. Because of the overlap in certain drug classes and ICD-9-CM codes, information from the two sources was aggregated in the combined models for the stroke and AD/D cohorts in several cases: 1) second-line antihypertensives and hypertension 2) antidepressants and depression diagnosis; 3) insulins and diabetes with complications; 4) neuroleptics and NOPD; 5) antiulcer agents and ulcer; 6) antiretroviral therapy and aids (stroke cohort only).

Clinical Expert Review

Following recommendations from the clinical dementia panel, patients who presented with any claim for a diagnosis for aids (ICD-9-CM 042.X-044.9X) and/or any antiretroviral drug (i.e., protease, nucleoside, and non-nucleoside reverse transcriptase inhibitors) the year prior to the AD/D index diagnosis were discarded from the study. Aids dementia complex (ADC) is believed to be directly related to HIV infection of the brain and therefore patients with ADC have a distinct dementia etiology from that of dementia patients without aids.[62,63] An additional recommendation of the AD/D clinical panel was to test the predictive ability of place of residence around the time of AD/D diagnosis on post-AD/D one-year cost to Medicaid.

Following recommendations from the stroke clinical panel, patients who presented with an initial cerebrovascular event of transient ischemic attack (TIA) but otherwise met all inclusion criteria were discarded from the study (index primary diagnosis code of 435.xx; n = 1,049; data not presented). The clinical panel advised that mortality/cost risk factors for TIA are different enough from those for ischemic/hemorrhagic stroke to warrant the exclusion of TIA patients from the study.

## Cost Models

Of the 35, 37, and 58 potential variables tested for entry in the AD/D models, 15, 20, and 23 entered the drug, ICD-9-CM, and combined models respectively (Table 8). Similarly, of the 36, 39, and 59 potential variables tested for entry in the stroke models, 17, 24, and 30 entered the drug, ICD-9-CM, and combined models (Table 8). The coefficients of each covariate in the one-year drug, ICD-9-CM, and combined drug and ICD-9-CM GA models are presented in Table 7 and summary statistics for each of the six models in Table 8. In all three AD/D models, shrunk $R^2$ ranged from 0.18 to 0.22 in the full AD/D data set, whereas shrunk $R^2$ ranged from 0.12 to 0.17 in the stroke models. Model $R^2$ based solely on demographic information was less than 0.01 in the AD/D and stroke samples. Model $R^2$ based on demographic and place of residence information was 0.06 and 0.09 in the AD/D and stroke samples, respectively (Table 8). In the stroke cohort, the combined drug and ICD-9-CM model offers a statistically significant improvement over models using either source of information alone, whereas it did not in the AD/D cohort (Table 9).

## Individual Cost Factors

The impact of age varied between the two cohorts and between models within each patient cohort but coefficients were always negative except in the drug only stroke model. Sex was not predictive of one-year cost in the AD/D models but female sex was associated with lower predicted one-year costs in the stroke models (about -$4,850) although it was not significant in the ICD-9-CM only model. Black race was associated with lower predicted costs (about -$5,000) in the AD/D and stroke cohorts for all models containing ICD-9-CM-defined comorbidities but not in the drug only models. Patients with aged-blind-disabled Medicaid eligibility at index date had higher one-year predicted costs in the stroke cohort. Place of residence in a hospital or nursing home (base case was ambulatory setting) was a positive, strong, and consistent predictor of future health care cost in both cohorts. Residence in a nursing home, compared to a hospital, doubled

expected costs in AD/D patients the year post-diagnosis (about $14,000 vs. $7,000) across all three models. Stroke patients who resided in a nursing home still exhibited higher predicted costs than inpatients but the difference was not as marked as in the AD/D cohort (about $14,000 vs. $11,000). Lastly, stroke patients who suffered from a hemorrhagic stroke incurred about $2,500 more in costs to Medicaid than patients who experienced an ischemic stroke.

In the GA AD/D cohort, prior cardiovascular conditions (peripheral vascular or valvular disorders, CVA), endocrine or metabolic disorders (diabetes, thyroid, sudden weight loss, fluid electrolyte imbalance), rheumatologic disorders, malignancy or tumor, renal failure, and neurological/psychiatric disorders (hemiplegia, paraplegia, epilepsy, Parkinson's disease, NOPD) were consistent predictors of higher one-year post-AD/D cost to Medicaid. Similarly, exposure to four classes of cardiac drugs, two or three classes of respiratory drugs, opiates, and insulins were also strongly associated with higher one-year post-AD/D cost to Medicaid. Eight of the eleven drug classes that were predictors of higher health care costs post-index AD/D diagnosis were no longer significant in the combined drug and ICD-9-CM models, whereas ICD-9-CM code-based variables were. The coefficient of over 70% of the drug or ICD-9-CM variables present in the combined models was within 10% of their respective coefficient in the drug only and ICD-9-CM only models.

In the GA stroke cohort, prior cardiovascular conditions (peripheral vascular or valvular disorders, cardiac arrhythmia), diabetes, malignancy or tumor, renal failure, hemiplegia- paraplegia, neurological disorders, and AD/D were consistent predictors of higher one-year post-stroke cost to Medicaid. The use of four classes of cardiac drugs, two or three classes of respiratory drugs, opiates, antiepileptics, and neuroleptics were also strongly associated with higher one-year post-stroke cost to Medicaid. The use of antiretroviral therapy and/or anti-tuberculosis agents and a diagnosis for aids were associated with the largest predicted one-year cost. Again, the coefficient of over 70% of the drug or ICD-9-CM variables present in the combined models was within 10% of their

respective coefficient in the drug only and ICD-9-CM only models, with more consistency observed in the ICD-9-CM code-based covariates.

External Model Validation

The bottom rows of Table 8 present the out-of-sample sum of square $R^2$ statistics on the NC test samples for the drug, ICD-9-CM, and combined models for each of the two cohorts. Out-of-sample $R^2$ ranged from 0.09 to 0.12 in the AD/D sample and from was 0.08 in all three stroke models. $R^2$ based on the squared correlation between predicted and observed costs was 0.08 in all three stroke models and ranged from 0.11 to 0.13 in all three Ad/D models. Validation $R^2$ based on demographic information was less than 0.01 in all six models. The predictive performance of each of the AD/D models was between 0.98 and 1.05, i.e., one-year post-AD/D average predicted expenditures to NC Medicaid were between -2 and +5% of actual costs to NC Medicaid. Similarly, the predictive performance of each of the stroke models was between 1.14 and 1.17. Medicaid expenditures were overestimated in all ICD-9-CM code-based models and all models for the stroke cohort.

Models developed on the GA cohorts exhibited moderate explanatory power on the out-of-sample NC test cohort (between 0.08 to 0.12). We sought to identify whether or not this lack of explanatory power was attributable to the models themselves (i.e., comorbidity and drug exposure classes predictive of higher costs are different in GA and NC) or to a lack of calibration of the GA-derived coefficients on the NC cohort. We therefore re-estimated the coefficient weights on the NC test sample using the set of covariates that had been identified on the GA samples (Table 10). We then tested the new cost weights on the holdout AD/D and stroke NC samples (Table 11). A large number of the re-weighted coefficients were no longer significant at 10% on the NC test sample, with a larger proportion among drug exposure covariates. To one exception, newly estimated weights that were negative, e.g., fluid electrolyte, rheumatologic, and thyroid disorders in the AD/D cohort and cardiac arrhythmia and chronic pulmonary

disorders in the stroke cohort, were no longer statistically significant at 10%. Thyroid disorders in the stroke cohort was the only covariate with a negative weight that reached statistical significance. Models $R^2$, however, were very comparable or better in the training NC sample than those observed in the original GA models. $R^2$ ranged from 0.18 to 0.19 in the AD/D sample and from 0.17 to 0.19 in the stroke sample (Table 11). Split-sample validation $R^2$ on the NC holdout AD/D sample were 0.15 in the drug exposure model and 0.16 in the ICD-9-CM and combined models (Table 11). Split-sample validation $R^2$ on the NC holdout stroke sample was 0.08 in the drug exposure model and 0.12 in the ICD-9-CM and combined models (Table 11).

## DISCUSSION

Although Medicaid databases contain demographic, medical and drug utilization information for the indigent US population, no published research has developed and validated cost risk adjustment indices specific to diseases that are likely to create increasing demand for Medicaid resources. The lack of published risk adjustment models specific to AD/D and stroke population could become detrimental to Medicaid programs, as Medicaid programs cover an ever larger portion of the AD/D population and are the primary payer for long-term institutionalized services.[9,10] Indeed in 1998, Medicaid payments for nursing facility services and home health care totaled $41.3 billion for more than 3.3 million recipients of these services-an average 1998 expenditure of $12,375 per long-term care recipient. With the percentage of the US population who are elderly or disabled increasing faster than that of the younger groups, the need for long-term care is expected to increase.(http://www.hcfa.gov)

A recent study showed that the use of a non-dementia specific risk adjustment method can impair the ability to characterize comorbidity burden in AD/D Medicaid patients.[26] Therefore, one objective of this study was to provide an initial tool to Medicaid programs and health service researchers to stratify or otherwise control for varying levels of disease severity and comorbid illnesses in stroke and AD/D patient

cohorts. Ultimately, such risk adjustment indices could help predict future Medicaid costs for patients that will impose an ever-increasing burden on Medicaid resources. We explored the role of drug exposure data in predicting future health care costs to Medicaid program and assessed how well drug data can supplement commonly used ICD-9-CM code-based information.

A major issue in the development of risk adjustment models is that of independent sample validation as a risk adjustment system is only appropriate when it has been demonstrated to predict the outcome of interest in a population similar but independent to that in question.[64] Generic risk adjustment indices that have been developed in studies to examine cost outcomes for entire Medicaid populations were not independently validated or validated with a split-sample method.[39,65,66] This is the first study that developed prospective cost risk adjustment indices specific to AD/D and stroke populations and further, attempted to obtain an unbiased estimate of the true performance of the indices on an independent Medicaid population.

Model Coefficients

In a given model, the weights of individual coefficients reflect the increment in expected costs to Medicaid that is independently associated with having the condition (ICD-9-CM based) or being exposed to a particular class of drugs the year prior to the index date. A controversial finding is that race (black) was found to be associated with significantly lower predicted expenditures (from $4,332 to $5,609) in all models that contained ICD-9-CM information. The assumption that ethnicity can be used as an isolated epidemiological factor or a factor to predict future expenditures by defining clinically distinct disease subgroups remains controversial.[67] Classification around race and ethnicity changes over time due to ‘fuzzier group boundaries’ that denotes ambiguities about what constitutes groups’ identity.[16] Suggesting that African-Americans are likely to incur lower future expenditures and therefore may commend lower capitated payments at a provider level is an artifact of the model. The inconsistent

role of race may reflect the fact that ICD-9-CM models were not able to account for all patient characteristics such that sources of unmeasured (unexplained) variations in patient outcomes are confounded with race. This confounding would most likely originate from an interaction between comorbidity burden and race, as race was not a predictor of cost in drug only models. In retrospect, it would have been more appropriate not to adjust for a patient attribute such as race in our prospective cost models. Sex had no predictive power on future Medicaid costs in the inception AD/D cohort whereas females tended to have lower predicted expenditures in the stroke cohort. Although sex was a statistically significant predictor in two stroke models, suspicion about "gender bias in patient treatment need further exploration."[16] Sex could confound with disease severity and/or likelihood of post-stroke survival as females patients had a 10 to 25% increased in odds of survival controlling for prior comorbidities and drug exposure. (Refer to Chapter 4: "Prospective Mortality Risk Adjustment Indices for Stroke Using Administrative Data") The impact of age varied between the two cohorts and between models within each patient cohort but coefficients were negative in five out of six models. In the GA AD/D and stroke cohorts, 7 and 15% of the patients were not Medicare eligible. Some of the direct medical expenditures of dual Medicaid-Medicare eligible are covered by Medicare (inpatient stay and office visits), whereas all expenditures of non-dual eligible are assumed by Medicaid. As Medicare eligible patients were 15 and 17 years older in the GA stroke and AD/D cohorts respectively (T-tests $p<0.001$), a larger fraction of older patients' total direct medical expenditures was not covered by GA Medicaid. Difference in dual program eligibility created a model artifact where the older the patient the less his/her Medicaid predicted expenditures, controlling for all demographics, comorbidity burden, and drug exposure information.

Place of residence in a nursing home in the two weeks prior to the index diagnosis of AD/D or at the time of stroke treatment was a consistent predictor of increased future expenditures to Medicaid (from $13,000 to $15,000 in all six models). Place of residence may be correlated with a higher likelihood of transferring to or remaining in a long-term

care facility post-index date. As noted earlier, AD/D comprise the most important diagnoses in nursing home populations,[9] half of the cost being borne by Medicaid programs.[10] Also, 30% of stroke survivors require assistance in their activities of daily living and 15% are institutionalized.[15] Systematic higher predicted costs for nursing home residents underline an urgent need for state and federal authorities for the provision of appropriate services for these patient populations,[10] as their number will skyrocket in a near future and their impact on limited Medicaid resources will increase accordingly. Similarly, patients who were hospitalized had higher predicted expenditures than ambulatory patients, though coefficients were 45 to 70% higher in the stroke than in the AD/D inception cohort. Higher predicted costs in the stroke cohort may reflect the resource-intensive acute treatment phase of a severe stroke, which corroborates with the higher predicted expenditures associated with hemorrhagic versus ischemic stroke. Our models suggest that place of residence can help reflect expected cost in disease specific populations more accurately.

Comorbidity and drug exposure burden between the GA AD/D and stroke cohorts exhibit common characteristics, as well as striking differences. Both cohorts included a large proportion of patients 65 years of age or older that presented with comorbidities and drug classes frequently encountered in the elderly. For instance, hypertension, chronic pulmonary disorders, diabetes, and miscellaneous neurologic disorders were quite prevalent in both cohorts, as well as the use of antihypertensives, acid peptic disease, cardiac, and chronic respiratory agents. However, it is interesting to note that GA AD/D patients are characterized by a lower comorbidity burden than stroke patients even though they were 10 years older. It remains to be determined if "demented patients may paradoxically be considered healthier,"[68,69] or if it is a claims coding artifact, as almost twice as many AD/D as stroke patients resided in a nursing home around the time of their initial diagnosis/event. An earlier study with GA Medicaid AD/D patients found that nursing homes customarily code a single ICD-9-CM code per recipient claim and only bill GA Medicaid once a month. For patients who used nursing homes as their primary

source of care, a limited array of ICD-9-CM codes could result in the systematic undercoding of prevalent comorbid conditions.[26] Other differences between the two cohorts reside in their drug exposure the year prior to their index date. A larger proportion of stroke patients used antihypertensives and cardiac agents, even though they were 10 years younger. Hypertension and cardiac conditions, such as myocardial infarct, are known risk factors for stroke.[70,71] Conversely, twice as many AD/D as stroke patients were using neuroleptics and anti-Parkinson agents.

As noted by Kronick, the most frequently occurring diagnoses in our models tended to have the lowest additional costs associated with them, in many cases between $1,000 and $2,000 per year, if statistically significant at all (e.g., hypertension, diabetes, chronic pulmonary diseases).[1] This finding is also verified with drug exposure, e.g., antihypertensives, acid peptic disease agents, antidepressants. Conversely, the presence of certain rare and serious conditions, such as renal failure, aids (stroke cohort only), sudden weight loss, valvular disorders, or infrequent exposure to opiates had a substantial incremental effect on one-year cost post-index date. The absence of key pharmaceutical classes such as antineoplastic agents is explained by the fact that Medicaid claims databases do not include prescription drugs delivered in an inpatient setting. Higher predicted payments for cancer patients were a function of the type of cancer (solid metastatic tumors vs. any malignancy) and not the choice of therapy, as the covariate for antineoplastic agents did not reach statistical significance in any drug model. The relationship between cancer diagnoses and exposure to antineoplastic agents supports our decision to employ an *a priori* hierarchical approach to operationalize certain drug exposure and comorbidities in order to screen out some of the possible redundancy inherent to drug and ICD-9-CM based information. Indeed, "a payment model should not be sensitive to every diagnostic code (or exposure to every drug class) recorded because this will result in poorly specified coefficients and unstable estimates."[39] For instance, a patient with diagnosis codes for 'diabetes with complications' may also present with codes for 'diabetes'. A regression model that separately assigns cost

increment for each of those diagnoses will have confounded parameter estimates. Additionally, such system would reward plans that engage into "diagnosis discovery" in the hope to increase future payments. Therefore, we assigned hierarchies to constrain comorbidity and drug exposure assignments (see footnotes of Table 1 and Table 2). The hierarchical classification also reduces potential for collinearity, making explanatory variables more orthogonal and increases statistical precision and estimated coefficients of serious condition/drug categories.[39] For instance, a consistent linear trend was observed with the respiratory drug classes hierarchy, where the larger the number of classes the higher the predicted expenditures in the stroke and AD/D cohorts. In the AD/D drug only model, exposure to one, two, and three respiratory drug classes the year prior to the index AD/D diagnosis was associated with incremental predicted costs of $922, $1996, and $3852, respectively. Patients with 'insulin' had higher predicted costs than patients on 'oral hypoglycemiants' only, so did patients with a diagnosis code for 'metastatic solid tumor' as opposed to those with only a diagnosis code for 'any malignancy', or patients with a diagnosis of 'diabetes with complications' as opposed to 'diabetes' only.

Model Performance

Our cost models based on demographics data performed poorly ($R^2 < 0.01$), as observed by other researchers.[39,72,73,74] Age and sex are "poor proxies of permanent health and therefore poor predictors of future health care expenditures."[60] Our study shows, however, that adding place of residence around the time of diagnosis can help achieve significant improvements in model performance, i.e., $R^2$ increased several folds from 0.01 to 0.06 and 0.09 in the stroke and AD/D cohorts. Place of residence could be a surrogate marker for patient functionality (lower if a patient resides in nursing home) or disease severity (greater if a patient is hospitalized for his/her stroke). Future studies that develop cost models for elderly patient groups (e.g., Medicare recipients) may increase model performance by adding a variable coding for place of residence. Information about place of residence for setting prospective capitation payment rates could induce

undesirable behaviors. Patients with borderline health status could be directed toward the type of facility that commend larger payments (nursing homes), therefore undermining efforts to keep these patients out of long-term care facilities and penalizing health plans that promote alternative lower cost systems of care.

Models based on drug exposure and/or ICD-9-CM information performed best with shrunk $R^2$ from 0.18 to 0.22 in the AD/D full cohort and shrunk $R^2$ from 0.12 to 0.17 in the stroke cohort. External predictive $R^2$ on the NC sample were also higher in the AD/D (0.09 to 0.12) than in the stroke cohort (0.08). Expenditures within medically defined groups should be more predictable than among populations with many non-users. As such, models for patients with a specific condition (AD/D diagnosis or stroke event) should achieve higher $R^2$ than models with heterogeneous subgroups of patients.[1] The maximum predictable $R^2$ for prospective cost models based on prior expenditure levels has been estimated to be about 20%.[72,75] The predictive performance declined sharply in the out-of-sample cohorts, as it dropped by 33 to 60% in the NC test sample when predicted with out-of-sample $R^2$, and by 28 to 52% when assessed with the squared correlation between observed and predicted costs. Despite such as sharp decline, these models performed well in comparison to other prospective payments models that achieved split-sample validation $R^2$ between 5.5 and 8.6% and largely exceeded the performance of models based on demographic information only ($R^2$ < 1%).[76] The performance of our models underperformed that of the ACG-HCC model which achieved a split-sample validation $R^2$ of 0.23 in a Medicaid only population. Dual Medicare-Medicaid eligible recipients were however excluded from the latter study, making the sample more homogeneous and payments insensitive to Medicare reimbursement coverage plolicies.[39] To more adequately compare the performance of our models to that of published ones, we re-estimated the weights of each coefficients on the NC test sample and obtained split-sample $R^2$ on the holdout AD/D and stroke NC samples. To the exception of the drug only models, performance of ICD-9-CM only and combined models increased by 50% in the stroke cohort ($R^2$=0.12) and by 77% in the AD/D cohort

($R^2$=0.16). This shows that split-sample validation tends to overestimate model performance, even though in our case, we did not seek to maximize NC model performance as included covariates were selected based on the GA cohort characteristics.

Several factors may have been detrimental to the homogeneity of our cohorts and thus, negatively impacted predictive model performance. First, we attempted to predict population-based Medicaid cost for inception cohorts of stroke and AD/D patients. Doing so may have led to the inclusion of patients presenting with different risk factors and disease etiology than the majority of their reference group, e.g., inclusion of patients with vascular dementia (VaD) in the AD/D cohort.[41] Additionally, patients with a prior diagnosis of non-organic psychotic disorders and alcohol abuse exhibited very distinct odds of death.[77;78] (Refer to Chapter 5: "Prospective Mortality Risk Adjustment Indices for Alzheimer's Disease and Related Dementias Using Administrative Data") Further, patients with no prior comorbidities had higher one-year crude mortality rates and non-adjusted Medicaid expenditures as patients with up to four and two comorbidities, respectively. As observed in the GA stroke cohort, patients with no comorbidity conditions the year prior to the index stroke had fewer medical encounters, which could have caused a lower reporting in pre-stroke ICD-9-CM comorbidity burden, and resulted in a 21% lower pre-stroke total annual costs to Medicaid. As Iezzoni suggested, it is possible that patients with "more regular contacts with doctors have their acute illnesses identified at earlier stages or at a lower severity," thus potentially improving their relative risk of death after an acute event such as stroke.[16] (Refer to Chapter 4: "Prospective Mortality Risk Adjustment Indices for Stroke Using Administrative Data")

AD/D and stroke models underpredicted future annualized Medicaid costs by 8 to 14% and 7 to 10%, respectively. To further investigate the predictive performance of ICD-9-CM and drug exposure models, we tested the relative performance of the ICD-9-CM and drug only models vis-à-vis that of the combined models. Models were non-nested therefore the *F* test was not an appropriate measure of relative performance. We applied the J-Test developed by Davidson and MacKinnon to detect whether or not

combined models outperformed models based on either source of information alone.[58] In the stroke cohort, the combined model did outperform models based on drug or ICD-9-CM information alone (Table 9). The J-Test was inconclusive in the AD/D cohort as adding information from the drug only model to the combined model and from the combined model to the drug only model improved the performance of each model, likewise with the ICD-9-CM only and combined models. The fact that the combined stroke model was superior to either model alone is somewhat surprising as its $R^2$ was equal to that of the ICD-9-CM only model ($R^2$ = 0.17), and it had the same model performance on the NC test sample ($R^2$ = 0.08).

When developing the models with the GA cohorts, the outcome variable was defined as total Medicaid paid expenses. Expenses were annualized for patients who died during the one-year follow-up and their variance was weighted accordingly in each GA model. Post-index total Medicaid expenses were also annualized in the NC validation samples. Larger one-year all-cause crude mortality rates were observed in NC than in GA, +15 and +25% in the dementia and stroke cohorts, respectively. Controlling for early censoring by annualizing cost in the test sample helped limit the decline in model performance in the validation NC cohorts. Indeed, in the presence of a terminal illness, "the spending rate rises in the penultimate month of life, and it rises still further in the last month of life."[72] GA AD/D and stroke patients who died early had monthly expenditures 30 and 100% greater than patients who survived the entire 12-month period (T-test p values < 0.001). Van Vliet showed that "even with the most extensive administrative information (including demographics, Diagnostic Cost Groups, total costs in the last years of life), costs of decedents are largely unpredictable."[79] Therefore, as observed with our indices, a large proportion of the excess costs incurred in the last year of life remain unpredictable. Thus, higher mortality rates in the GA and NC stroke cohorts compared the GA and NC AD/D cohorts may account for the lower model performance observed in the stroke GA models, independent NC validation models, and NC split-sample validation models.

Potential for Gaming the System with Drug Data

The role of a cost risk adjustment model intended to calculate future payments, is "to effectively predict costs from data that should be present in any healthcare delivery system, while limiting the rewards for undesirable behavior with respect to either treatment or reporting."[39] Implied is the concern that payment methods can create incentives for health care providers to engage in behaviors that reap undue economic surplus by "gaming" the system. For instance, a capitated environment encourages doing less, a fee-for-service environment doing more, and flat-rate capitated payments to enroll healthy people and do as little as required to keep them enrolled.[39] Risk adjustment models based on ICD-9-CM codes may encourage "diagnosis" discovery. We tried to address this issue by applying a hierarchical classification when possible, and by submitting variables selected on a basis of statistical evidence to the review of stroke and AD/D clinical panels.

At first glance, it would seem that models based on ICD-9-CM information are less conducive to a 'gaming ' behavior than models based on drug exposure information. An ICD-9-CM code-based model may more readily convey the concept that a more critical condition, associated with higher health care resource use, should commend higher predicted costs and/or reimbursements. For instance, in our models, the presence of a diagnosis for aids, metastatic solid tumors, valvular disorders, or renal failures is a predictor of large increases in future health care costs. The 'dominant' position of ICD-9-CM code-based over drug exposure information in the development of prospective predictive cost models is summarized in a single finding. Nearly 90% of the ICD-9-CM code-based covariates included in the ICD-9-CM only models were still included in the combined models. Conversely, as few as 20% of the drug covariates included in the drug only models were included in the combined models.

A strong argument against the use of predictive cost models based on drug exposure data is that in general the cost of providing a given drug for an entire year is less

than its model coefficient. For instance in the AD/D drug only model, the coefficient for exposure to one class of respiratory drugs was $922. Acquisitions costs for such agents, where there is a strong generic intrusion, could be as low as $50 for an entire year, creating an 'apparent' opportunity for an excess profit of $872. However, in a drug only model, not only does the coefficient for drug exposure cover the drug acquisition cost, but also the cost of care associated with the clinical management of a particular condition. In our example, chronic pulmonary disease could be associated with utilization related to the initial diagnosis, pharmacotherapy, follow-up visits, and eventual emergency room visits or hospitalizations.

In order to increase the predictive power of cost risk adjustment models, health service researchers need to examine the potential of inexpensive and readily available sources of information. We would argue that once a few safeguards are put in place, drug exposure data have a lesser potential for 'gaming' the system than ICD-9-CM codes. Indeed, assigning a diagnosis code of type II diabetes (e.g., ICD-9-CM 250.00) to a patient with borderline glucose levels and send that patient home with dietary and/or physical exercise recommendations and/or schedule a follow-up visit requires little effort on the part of the health care provider. Actively starting that patient on an oral hypoglycemiant regimen and monitor his/her blood glucose level would be more resource consuming. Still, in our AD/D models, a code for 250.00 commends a higher payment than exposure to an oral hypoglycemiant. We would argue that the use of simple *a priori* decision rules ('safeguards') could altogether greatly reduce the 'gaming' potential when developing drug-based cost risk adjustment models. First, a few drug classes may present a clear potential for abuse and they should be excluded from a drug-based model. Such drugs or classes of drugs share some characteristics: safe side effect profile, large therapeutic window, low price, wide use, and often found over-the-counter (e.g., $H_2$-receptor antagonists). Other drugs that should not be included in the development of cost risk adjustment indices are drugs whose use may characterize a lifestyle choice, such as hair loss products. The latter are rarely, if at all, reimbursed by Medicaid programs.

Therefore, in retrospect, we should have been more restrictive with at least one of our 31 drug classes, by excluding $H_2$-receptor antagonist from the drug class targeted at acid peptic diseases. Second, employ an *a priori* hierarchical approach to operationalize certain drug exposure classes to gain some insight about the disease severity (cardiac drugs, respiratory drugs for chronic conditions, insulins and oral hypoglycemiants, etc.). Third, if using both drug and ICD-9-CM data information, combine the two sources in a clinically meaningful manner whenever possible.

All that said practical considerations could get in the way of our empirical findings on cost models. Nowadays, drug claims are adjudicated on-line and information about drug exposure is available to health plans on a weekly, and even, daily basis. Therefore, information necessary to build cost drug exposure models for year T+1 is readily and fully available at the end of year T. Information on ICD-9-CM data, however, is not yet collected and adjudicated as quickly as that for drug information. It is not rare for a plan to have to wait six to 12 months before 95% of physician, outpatient, and inpatient claims are available. Hospital claims, the ICD-9-CM rich claims, take the longest time to reach health plans and health care payers. Given the state of the information technology today, future research could examine how well ICD-9-CM code-based cost risk adjustment models for year T+1 perform based on ICD-9-CM information from the Year T-1.

## Limitations

There are several limitations to this study. Patients were selected on the presence of a primary diagnosis ICD-9-CM code reflecting AD/D or ischemic/hemorrhagic stroke. Because of the lack of biological markers for dementias, the perception on the differential diagnosis between AD/D and VaD has become blurred.[68] Therefore, although we excluded all patients with any diagnosis for non-AD/D, it is possible that our ICD-9-CM-defined AD/D population also included patients with mixed AD/D - VaD and/or patients

with VaD only. A mixed cohort would result in an AD/D sample with a lower homogeneity, constraining a model's predictive power.

Similarly, in an effort to assess mortality risk for a cohort of newly diagnosed stroke patients, we discarded patients who had any claim for a cerebrovascular condition during the year prior to their index date. Therefore, an artifact of our study design is that we discarded patients with a prior TIA and/or stroke. TIA and stroke are known risk factors for subsequent stroke, with a recurrence risk of 5 to 25% a year.[80] Consequently, these cost indices are not applicable to patients with a known stroke or TIA event in the last year prior to their index date, unless and until the models are re-estimated for a broader stroke population.

'Frozen' models had modest to moderate performance when tested in the independent NC sample. Calibration is the ability to predict the outcome across all ranges of risk. Age differences were important between the GA and NC AD/D and stroke patient cohorts and age is highly correlated with the number and complexity of comorbidities.[81] Like in Ash study, it might have been beneficial to test age-interacted condition categories.[39] However, we intended to use the same candidate variables in the mortality and cost risk adjustment models, therefore the overall number of candidate variables was limited by the total number of events (deaths) in each cohort. We were therefore not able to test age-interacted condition categories with drug exposure and ICD-9-CM code-based covariates. (Refer to Chapter 4 and Chapter 5) The continuous age variable may have been better modeled with the help of statistical smoothing techniques, such as splines, or by categorizing it into a series of mutually exclusive age groups. Future studies with larger sample sizes may be more adequately powered to test important age-interacted condition categories.

Lastly, our inclusion period spanned several years (1991 to 1995). We attempted to control for inflation by using the published consumer price index (CPI) for medical commodities and services. However, the CPI can only control for price inflation and not for policy and fiscal changes as well as medical advances that may have affected the

reimbursement of medical acts across a five-year period and across two Medicaid programs.

A goal of this study was to provide a tool to Medicaid programs and health service researchers to initially stratify or otherwise control for varying levels of disease severity and comorbid illnesses for inception cohorts of patients with disease states of particular relevance to Medicaid, namely patients with a stroke or Alzheimer's dementia and related dementias. The study showed that a model based on drug exposure data alone can perform as well as models based on ICD-9-CM information. Combining information from the two sources does not meaningfully increase model performance, although it may provide some complementary information, in terms of disease specificity and severity. An unexpected finding of the study is that place of residence at time of AD/D diagnosis and place of treatment at time of index stroke greatly increase model performance. This simple measure (hospital, nursing home, ambulatory) should be tested in further studies developing cost risk adjustment models for elderly patient groups. We advocate that drug information can be as useful a predictor in the development of cost risk adjustment models as the more commonly employed ICD-9-CM code-based data. We present a series of recommendations to limit 'gaming' opportunities with drug exposure information. The long-term goal for cost risk adjustment indices is to help predict future Medicaid costs for two patient populations that will impose an ever-increasing burden on Medicaid resources. However, further refinements and independent testing of our models, mostly for the stroke models, with larger samples are needed before they can reliably and accurately predict future levels of resource needs.

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- Dr. David C. Hess, neurologist (Medical College of Georgia, Augusta, GA).

* Alzheimer's Dementia Panel:

- Dr.. Tom Jackson, internist (Director of the Center for Senior Health, Medical College of Georgia, Augusta, GA);
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- Alvin V. Terry, Ph.D, pharmacologist (University of Georgia College of Pharmacy and Medical College of Georgia Alzheimer's Research Center, Augusta, GA).

TABLE 1: ICD-9-CM code-based Comorbidities One Year Prior to AD/D and Stroke and their Operational Definitions

| ID-9-CM Comorbidities | AD/D Patients (%) | Stroke Patients (%) | ICD-9-CM Codes |
|---|---|---|---|
| 1. Congestive heart failure | 267 (5.4%) | 409 (8.8%) | 389.91, 402.11, 402.91,404.11, 404.13, 404.91, 404.93, 428.0-428.9 |
| 2. Myocardial infarction | 53 (1.1%) | 93 (2.0%) | 410-410.9, 412, 429.71, 429.79 |
| 3. Cardiac arrhythmia | 131 (2.6%) | 208 (4.5%) | 426.10, 426.11, 426.13, 426.2-426.53, 426.6-426.89, 427.0, 427.2, 427.31, 427.60, 427.9, 785.( V45.0, V53.3 |
| 4. Valvular disease | 120 (2.4%) | 158 (3.4%) | 093.20-093.24, 394.0-397.1, 424.0-424.91, 746.3 746.6, V42.2, V43.3 |
| 5. Pulmonary circulation disorders | 24 (0.5%) | 34 (0.7%) | 416.0-416.19, 417.9 |
| 6. Peripheral vascular disorders | 198 (4.0%) | 210 (4.5%) | 440.0-440.9, 441.2, 441.4, 441.7, 441.9, 443.1-443.9, 447.1, 557.1, 557.9, 785.4, V43.4 |
| 7. Hypertension (complicated and uncomplicated) | 871 (17.5%) | 1,432 (30.9%) | 401.1, 401.9, 402.10, 402.90, 404.10, 404.90, 405.11, 405.19, 405.91, 405.99 |
| 8. Hemiplegia / paraplegia | 108 (2.2%) | 99 (2.1%) | 342.0-344.9 |
| 9. Other neurological disorders | 337 (6.8%) | 465 (10.0%) | 331.9, 332.0, 333.4, 333.5, 334.0-335.9, 340, 341.1-341.9, 345.00-345.11, 345.40-345.51, 345.80-345.91, 348.1, 348.3, 780.3, 784.3 |
| 10. Chronic pulmonary disease | 381 (7.6%) | 560 (12.1%) | 490-492.8, 493.00-493.91, 494, 495.0-505, 506.4 |
| 11. Diabetes, uncomplicated | 244 (4.9%) | 470 (10.1%) | 250.00 - 250.33 |
| 12. Diabetes, complicated | 186 (3.7%) | 355 (7.7%) | 250.40 - 250.73, 250.90-250.93 |
| 13. Hypothyroidism | 61 (1.2%) | 86 (1.9%) | 243-244.2, 244.8, 244.9 |
| 14. Renal failure and chronic disorders | 97 (1.9%) | 146 (3.2%) | 403.11, 403.91, 404.12, 404.92, 582-582.9, 583-583.7, 585, 586, 588-588.9, V42.0, V45.1, V56.0 V56.8 |
| 15. Liver disease | 36 (0.7%) | 73 (1.6%) | 070.32, 070.33, 070.54, 456.0, 456.1, 456.20, 456.21, 571.0, 571.2, 571.3, 571.40-571.49, 571.5 571.6, 571.8, 571.9, 572.3, 572.8, V42.7 |
| 16. Peptic ulcer disease | 81 (1.6%) | 128 (2.8%) | 531-534.9, V12.71 |
| 17. Aids | 0 (0.0%) | 30 (0.6%) | 042-044.9 |
| 18. Any malignancy, including leukemia and lymphoma | 83 (1.7%) | 144 (3.1%) | 140.0-172.9, 174.0-175.9, 179-195.8, 200.00-202.38, 202.50-203.01, 203.8-203.81, 238.6, 273. V10.00-V10.9 |
| 19. Metastatic solid tumor | 46 (0.9%) | 51 (1.1%) | 196.0-199.1 |
| 20. Rheumatoid arthritis / collagen vascular disease | 51 (1.0%) | 88 (1.9%) | 701.0, 710.0-710.9, 714.0-714.9, 720.0-720.9, 72 |
| 21. Coagulopathy | 36 (0.7%) | 50 (1.1%) | 286.0-286.9, 287.1, 287.3-287.5 |
| 22. Obesity | 33 (0.7%) | 67 (1.4%) | 278.0 |
| 23. Weight loss / malnutrition | 37 (0.7%) | 35 (0.8%) | 260-263.9 |
| 24. Fluid and electrolyte disorders | 49 (1.0%) | 39 (0.8%) | 276.0-276.9 |
| 25. Anemias | 0 (0.0%) | 0 (0.0%) | 280.0-281.9, 285.9 |
| 26. Alcohol abuse | 168 (3.4%) | 204 (4.4%) | 291.1, 291.2, 291.5, 291.8, 291.9, 303.90-303.93, 305.00-305.03, V11.3 |
| 27. Drug abuse | 28 (0.6%) | 46 (1.0%) | 292.0, 292.82-292.89, 292.9, 304.00-304.93, 305.20-305.93 |
| 28. NOPD | 662 (13.3%) | 379 (8.2%) | 295.00-298.9, 299.10-299.11 |
| 29. Depression | 118 (2.4%) | 142 (3.1%) | 300.4, 301.12, 309.0, 309.1, 311 |
| 30. Cerebrovascular disease | 466 (9.3%) | 0 (0.0%) | 430-438 |
| 31. Dementia / Alzheimer | 0 (0.0%) | 164 (3.5%) | 290-290.9, 331-331.9, 797, 294.9 |

ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification.
Aids: Acquired Immune Deficiency Syndrome; NOPD, Non-organic psychotic disorders.

Note on Operational Definitions: In order to account for the fact that additional diagnoses within a category more likely reflect additional diagnosis of the same underlying condition rather than additional severity of illness a hierarchy counting was developed for the following comorbidities.[48] If both uncomplicated diabetes and complicated diabetes are present, count only complicated diabetes. If both malignancies without metastasis and metastatic solid tumors are present, count only metastatic cancers. This hierarchy helped reduce multicollinearity as many patients were expected to present uncomplicated and complicated diabetes or tumor without metastasis and metastatic solid tumor simultaneously.

TABLE 2: Drug Exposure Classes One Year Prior to AD/D and Stroke and their Operational Definitions

| Drug Classes | AD/D Patients (%) | Stroke Patients (%) | Therapeutic / Drug Classes |
|---|---|---|---|
| 1. Cardiac agents | 887 (17.8%) | 915 (19.8%) | (1) Antiarrythmic, inotropic, cardiac vasopressor agents |
| | 762 (15.3%) | 995 (21.5%) | (2) ACE inhibitors or angiotensin II antagonists |
| | 786 (15.8%) | 815 (17.6%) | (3) Antianginal agents |
| | 1,035 (20.8%) | 1,152 (24.9%) | (4) Loop diuretics |
| 2. Antiparkinson agents | 967 (19.4%) | 524 (10.3%) | Antiparkisonian agents (anticholinergic, dopamine agonists, and miscellaneous) |
| 3. Coagulation modifiers | 534 (10.7%) | 690 (14.9%) | Coagulation modifiers (anticoagulants, antiplatelet agents, heparin antagonists, thrombolytics, miscellaneous coagulation modifiers) |
| 4. Antihypertensives | 815 (16.2%) | 334 (7.2%) | (1) First-line antihypertensive drugs (β-adrenergic blocking agents; potassium-sparing, thiazide, and miscellaneous diuretics) |
| | 1,901 (38.1%) | 2,359(50.2%) | (2) Second-line antihypertensive drugs (peripherally and centrally antiadrenergic agents; calcium channel blocking agents; antihypertensive combinations; vasodilators agents) |
| 5. Respiratory agents | 404 (8.1%) | 461 (10.0%) | (1) Adrenergic bronchodilatators, asthma vasopressors, and bronchodilatator combinations |
| | 649 (13.0%) | 643 (13.9%) | (2) Methylxanthines |
| | 299 (6.0%) | 371 (8.0%) | (3) Respiratory inhalants, leukotrien asthma agents, antiasthmatic combinations |
| 6. Drugs for NID diabetes | 453 (9.1%) | 444 (9.6%) | Oral hypoglycemiant agents |
| 7. Insulins | 386 (7.7%) | 676 (14.6%) | Insulins |
| 8. Antineoplastics (cancer) | 172 (3.4%) | 142 (3.1%) | Antineoplastics (alkylating, antibiotics/antineoplastics, antimetabolites, hormones/antineoplastics, miscellaneous antineoplastics, mitotic inhibitors, colony stimulating factors) and 5HT3 antagonists |
| 9. Antiepileptics / anticonvulsants | 808 (16.2%) | 852 (18.4%) | Anticonvulsants (hydantoin, succinimide, barbiturate, oxazolidinedione, certain benzodiazepine, and miscellaneous anticonvulsants) |
| 10. Acid peptic disease agents | 1,372 (27.5%) | 1,443 (31.2%) | H2 antagonists, proton pomp inhibitors, sucralfate, and antibiotherapy cocktails |
| 11. Glaucoma | 259 (5.2%) | 236 (5.1%) | Ophthalmic glaucoma agents |
| 12. Antigout agents | 145 (2.9%) | 204 (4.4%) | Allopurinol, colchicine, probenecid, and miscellaneous |
| 13. Anti-hyperlipidemia, hypercholesterolemia | 165 (3.3%) | 236 (5.1%) | HMG-CoA reductase inhibitors, fibrates, sequestrants, probucol, and miscellaneous |
| 14. Antiretrovirals (aids) | 0 (0.0%) | 15 (0.3%) | Protease, nucleoside, and non-nucleoside reverse transcriptase inhibitors |
| 15. Thyroid agents | 330 (6.6%) | 271 (5.9%) | Levothyroxine and thyroid replacement agents |
| 16. Narcotic analgesics | 86 (1.7%) | 108 (2.3%) | Narcotic analgesics |
| 17. Antidepressants | 1,070 (21.5%) | 929 (20.1%) | SSRI, tricyclic, MAO, and miscellaneous antidepressants |
| 18. Neuroleptics | 1,799 (36.1%) | 629 (13.6%) | Phenothiazine, trazodone, and miscellaneous antipsychotics |
| 19. Dementia agents | 0 (0.0%) | 7 (0.2%) | Donepezil and tacrine |
| 20. Antituberculosis agents | 33 (0.7%) | 17 (0.4%) | Ethambutol, isoniazid, rifampin, pyrazinamide, and miscellaneous |

TABLE 2: Drug Exposure Classes One Year Prior to AD/D and Stroke and their Operational Definitions

| Drug Classes | AD/D Patients (%) | Stroke Patients (%) | Therapeutic / Drug Classes |
|---|---|---|---|
| 21. Drug for rheumatologic conditions | 15 (0.3%) | 25 (0.5%) | Gold salts and hydroxychloroquin |
| 22. Systemic steroids | 361 (7.2%) | 459 (9.9%) | Systemic adrenal cortical steroids |
| 23. Drug for Irritable bowel disease | 3 (0.1%) | 3 (0.1%) | Mesalamine, olsalazine, infliximab |
| 24. End stage renal disease | 3 (0.1%) | 7 (0.2%) | Hematopoietic agents (marrow stimulants, erythropoietin) |
| 25. Immunosuppressive agents | 2 (0.0%) | 6 (0.1%) | Azathioprine, basiliximab, cyclosporine, daclizumab, muromonab-CD3, mycophenolate mofetil, and tacrolimus |
| 26. Antimigraine agents | 2 (0.0%) | 6 (0.1%) | Triptans, ergotamines, and miscellaneous combinations |
| 27. Drugs for bone diseases (Padget's disease, osteoporosis) | 25 (0.5%) | 12 (0.3%) | Alendronate, etidronate, pamidronate, risedronate, tiludronate, raloxifene, cacitonin, and calcium carbonate products (with or without added vitamin D) |

ACE inhibitors, angiotensin converting enzyme inhibitors; HIV, Human Immunodeficiency Virus; MAO, monoamine oxydase inhibitors; NID Diabetes, non insulin-dependent diabetes; SSRI, selective serotonin reuptake inhibitors. Note that angiotensin II antagonist and non-nucleoside reverse transcriptase inhibitors were not yet commercialized at the time of the study.

Note on Operational Definitions: Before comorbidity variables were tested for entry in the models, a hierarchy was developed between certain therapeutic classes.[34,49] If both non insulin-dependent and insulin-dependent diabetes drugs were present, we counted only insulin-dependent diabetes drugs. If both first- and second-line antihypertensive drugs were present, we counted only second-line antihypertensive drugs.[82]

If drugs from only one therapeutic respiratory illnesses were found for a given patient, then the dummy RESPIRATORY-1 variable was set to 1, 0 elsewhere; if two classes were found then RESPIRATORY-2 was set 1, 0 elsewhere; likewise for the RESPIRATORY-3 variable. A similar coding system was used for the therapeutic classes from the cardiac conditions for the definition of the CARDIAC-1 to CARDIAC-4 variables.

TABLE 3: Demographics, Eligibility, and Dementia-Related Information - GA and NC Medicaid Recipients Aged 50 and over with an Alzheimer's Dementia or Related Dementias Diagnosis Claim between 1991 and 1995.

| **Patient Group** | **Georgia Medicaid** | **North Carolina Medicaid**** |
|---|---|---|
| Number of patients | 4,986 | 5,000 |
| Demographic Information | | |
| Age in years (mean; std) | 75.2 (12.3) | 81.2 (10.0) |
| Age range in years | 50 – 105 | 50 – 108 |
| Gender: female (%) / male (%) | 3,729 (75%) / 1,257 (25%) | 3,862 (77%) / 1,138 (23%) |
| Race: black (%) / white (%) / other (%) | 2,036 (41%) / 2,543 (51%) / 397 (8%) | 1,470 (29%) / 2,990 (60%) / 540 (11%) |
| Eligibility Information | | |
| Medicare eligible: yes (%) / no (%) | 4,645 (93%) / 341 (7%) | 4,670 (93%) / 330 (7%) |
| Age-blind-disabled (%) / Other (%) | 3,337 (67%) / 1,649 (33%) | 4,591 (92%) / 409 (8%) |
| Dementia-Specific Information | | |
| Residence at time of diagnosis: inpatient hospital (%) / nursing home (%) / ambulatory setting (%) | 447 (9%) / 2,885 (58%) / 1,654 (33%) | 608 (12%) / 2,077 (42%) / 2,315 (46%) |
| One-year all-cause mortality | 1,063 (21%) | 1,190 (24%) |
| Total one-year Medicaid expenditures (mean; std)* | $17,234 (12,457) | $17,274 (13,974) |

Std: standard deviation. *: Adjusted for medical and drug inflation in 1995 $
** NC Test Sample 1

TABLE 4: Demographics, Eligibility, and Stroke-Related Information - Georgia and North Carolina Medicaid Recipients Aged 40 and over with a Cerebrovascular Event between 1991 and 1995.

| **Patient Group** | **Georgia Medicaid** | **North Carolina Medicaid**** |
|---|---|---|
| Number of patients | 4,632 | 4,500 |
| Demographic Information | | |
| Age in years (mean; std) | 65.6 (14.4) | 75.9 (12.5) |
| Age range in years | 40 – 105 | 40 – 110 |
| Gender: female (%) / male (%) | 3,311 (72%) / 1,321 (28%) | 3,240 (72%) / 1,260 (28%) |
| Race: black (%) / white (%) / other (%) | 2,376 (51%) / 1,793 (39%) / 463 (10%) | 1,728 (38%) / 2,266 (50%) / 890 (12%) |
| Eligibility Information | | |
| Medicare eligible: yes (%) / no (%) | 3,924 (85%) / 708 (15%) | 3,879 (86%) / 621 (14%) |
| Age-blind-disabled / other: yes (%) / no (%) | 4,126 (89%) / 506 (11%) | 3,678 (82%) / 822 (18%) |
| Stroke-Specific Information | | |
| Ischemic stroke (%) / intracranial hemorrhage stroke (%) | 4,349 (94%) / 283 (6%) | 4,256 (95%) / 244 (5%) |
| Place of treatment: hospital (%) / nursing home (%) / ambulatory (%) | 937 (20%) / 1,525 (33%) / 2,170 (47%) | 885 (20%) / 1,212 (27%) / 2,403 (53%) |
| One-year all-cause mortality | 1,054 (23%) | 1,284 (29%) |
| Total one-year Medicaid expenditures (mean; std)* | $16,798 (15,546) | $16,125 (15,919) |

Std: standard deviation. *: Adjusted for medical and drug inflation in 1995 $
** NC Test Sample 1

TABLE 5: ICD-9-CM Code-Based Comorbidity Count One Year Prior to Stroke or Dementia and One-Year Mortality Rates and Cost to Medicaid in Georgia Medicaid Patients

| Number of Comorbidities | AD/D Patient Cohort | | | Stroke Patient Cohort | | |
|---|---|---|---|---|---|---|
| | Number (%) Patients | % Expired at One Year | One-year Cost | Number (%) Patients | % Expired at One Year | One-year Cost |
| 0 | 2,788 (55.9%) | 22.5% | $17,057 | 1,983 (42.8%) | 25.5% | $17,183 |
| 1 | 1,096 (22.0%) | 21.5% | $15,977 | 978 (21.1%) | 21.5 % | $13,692 |
| 2 | 393 (7.9%) | 12.2% | $15,072 | 683 (14.7%) | 17.0% | $14,783 |
| 3-4 | 455 (9.1%) | 18.0% | $19,219 | 700 (15.1%) | 20.6% | $19,215 |
| 5-6 | 184 (3.7%) | 28.8% | $22,847 | 233 (5.0%) | 25.8% | $22,723 |
| > 6 | 70 (1.4%) | 25.7% | $28,432 | 55 (1.2%) | 32.7% | $27,119 |
| **Total** | **4,986** | **21.3%** | **$17,234** | **4,632** | **22.8%** | **$16,798** |

For one-year mortality in AD/D and stroke cohorts, P value of Pearson $\chi^2$ test < 0.025 and P value of Cochran-Armitage linear trend test < 0.025.*
For one-year cost, P value of Cuzick linear trend test < 0.025 for AD/D and stroke patients.*[61]
* P value of 0.025 was chosen *a priori* to control for test multiplicity

TABLE 6: Drug Exposure Classes Count One Year Prior to Stroke or Dementia and One-Year Mortality Rates and Cost to Medicaid in Georgia Medicaid Patients

| Number of Drug Classes | AD/D Patient Cohort | | | Stroke Patient Cohort | | |
|---|---|---|---|---|---|---|
| | Number (%) Patients | % Expired at One Year | One-year Cost | Number (%) Patients | % Expired at One Year | One-year Cost |
| 0 | 653 (13.1%) | 21.3% | $15,579 | 523 (11.3%) | 23.1% | $14,769 |
| 1 | 662 (13.3%) | 19.0% | $16,422 | 579 (12.5%) | 20.7 % | $15,000 |
| 2 | 935 (18.8%) | 19.7% | $16,858 | 839 (18.1%) | 22.9% | $15,905 |
| 3-4 | 1,751 (35.1%) | 20.4% | $17,307 | 1,709 (36.9%) | 22.4% | $17,143 |
| 5-6 | 786 (15.8%) | 24.7% | $18,325 | 807 (17.4%) | 23.8% | $18,590 |
| > 6 | 199 (4.0%) | 31.7% | $22,163 | 175 (3.8%) | 26.3% | $21,460 |
| **Total** | **4,986** | **21.3%** | **$17,234** | **4,632** | **22.8%** | **$16,798** |

For one-year mortality in AD/D and stroke cohorts, P value of Pearson $\chi^2$ test < 0.025 and P value of Cochran-Armitage linear trend test < 0.025.*
For one-year cost, P value of Cuzick linear trend test < 0.025 for AD/D and stroke patients.*[61]
* P value of 0.025 was chosen *a priori* to control for test multiplicity

Table 7: One-Year Cost Models Robust Regression Coefficients by Study Cohort and Index Type

| | AD/D Cohort | | | Stroke Cohort | | |
|---|---|---|---|---|---|---|
| Candidate Variables | RX | ICD-9-CM | Combined | RX | ICD-9-CM | Combined |
| Intercept | 27,109 | 12,640 | 12,227 | 5,597 | 9,831 | 12,872 |
| Age | -385 | -45 | -44 | 184 | -31 | -85 |
| Female | | | | -4,838 | | -4,860 |
| Black | | -5,609 | -4,774 | | -4,966 | -4,332 |
| Age square | 2 | | | -2 | | - |
| Age * Female | | | | 71 | | 72 |
| Age * Black | | 67 | 57 | | 64 | 58 |
| Age-Blind-Disabled | | | | 3,350 | 2,794 | 2,496 |
| Hospital | 7,869 | 6,298 | 6,558 | 11,443 | 10,719 | 11,056 |
| Nursing Homes | 14,443 | 14,457 | 14,319 | 12,973 | 15,016 | 14,484 |
| Hemorrhagic stroke | N/A | N/A | N/A | 2,174 | 2,725 | 2,734 |
| | | | | | | |
| **Drug-based covariates** | | | | | | |
| Aids - tuberculosis | N/A | | N/A | 15,842 | | * |
| Two classes of cardiac drugs | 822 | | - | | | |
| Four classes of cardiac drugs | 3,619 | | - | 5,291 | | 2,927 |
| Oral Hypoglycemiants | 1,388 | | - | | | |
| Antiepileptics | 1,396 | | - | 2,590 | | 1,633 |
| Insulins | 4,401 | | * | 1,822 | | * |
| Neuroleptics | | | * | 3,345 | | * |
| Opiates | 6,385 | | 5,917 | 4,581 | | 3,428 |
| Coagulation modifiers | 1,405 | | - | | | |
| One class of respiratory drugs | 922 | | - | | | |
| Two classes of respiratory drugs | 1,996 | | 1,620 | 1,917 | | 2,065 |
| Three classes of respiratory drugs | 3,852 | | 3,778 | 4,324 | | 4,438 |
| Acid peptic disease drugs | 1,065 | | * | 1,623 | | * |

Table 7: One-Year Cost Models Robust Regression Coefficients by Study Cohort and Index Type

| | AD/D Cohort | | | Stroke Cohort | | |
|---|---|---|---|---|---|---|
| Candidate Variables | RX | ICD-9-CM | Combined | RX | ICD-9-CM | Combined |
| **ICD-9-CM code-based covariates** | | | | | | |
| Aids | | N/A | N/A | | 9,074 | * |
| Alcohol abuse | | | | | 2,895 | 2,630 |
| Cardiac arrhythmia | | | | | 5,079 | 5,260 |
| Cerebrovascular accidents | | 2,872 | 2,945 | | N/A | N/A |
| Chronic Pulmonary Disorders | | | | | 1,790 | - |
| Dementia Alzheimer | | N/A | N/A | | 6,450 | 6,162 |
| Diabetes | | 2,581 | 1,608 | | 1,951 | - |
| Diabetes with complications | | 5,602 | * | | 3,973 | * |
| Fluid electrolyte disorders | | 5,072 | 4,905 | | | |
| Hemiplegia – Paraplegia | | 2,798 | 2,869 | | 6,385 | 6,445 |
| Any malignancy | | 2,517 | 2,568 | | 3,059 | 3,093 |
| Other neurological disorders | | 2,038 | 2,191 | | 3,482 | 2,228 |
| Pulmonary circulation disorders | | | | | 6,660 | 7,074 |
| Peripheral vascular disorders | | 6,261 | 6,767 | | 5,189 | 5,194 |
| NOPD | | 974 | * | | | * |
| Renal failure and chronic disorders | | 9,020 | 9,278 | | 15,615 | 16,543 |
| Rheumatologic disorders | | 5,831 | 5,939 | | | |
| Thyroid disorders | | 4,837 | 4,766 | | 3,330 | 3,373 |
| Metastatic solid tumor | | 5,128 | 4,121 | | 8,422 | 7,802 |
| Valvular disorders | | 8,071 | 7,948 | | 5,646 | 5,753 |
| Sudden weight loss | | 6,658 | 6,819 | | 8,126 | - |
| **Covariates based on drug class and ICD-9-CM information** | | | | | | |
| Antiretroviral - aids | | | N/A | | | 7,849 |
| Insulin – diabetes w/ complications | | | 2,975 | | | 1,884 |
| NOPD - neuroleptics | | | 624 | | | 2,015 |
| Ulcers - acid peptic disease drugs | | | | | | 941 |

Aids: Acquired Immune Deficiency Syndrome; NOPD, Non-organic psychotic disorders.

* represents a variable that was included in the ICD-9-CM or drug based model and that was combined with its counterpart in the combined model.

- represents a variable that was included in the ICD-9-CM or drug based model but that failed to enter its respective combined model.

Table 8: Model Summary Statistics by Study Cohort and Index Type

| | AD/D Cohort | | | Stroke Cohort | | |
|---|---|---|---|---|---|---|
| **GA Training Sample** | | | | | | |
| | Drugs | ICD-9-CM | Combined | Drugs | ICD-9-CM | Combined |
| Number of patients | 4,985 | | | 4,632 | | |
| Maximum number of covariates | 35 | 37 | 58 | 36 | 39 | 59 |
| Included covariates | 15 | 20 | 23 | 17 | 24 | 30 |
| $R^{2\,a}$ | < 0.01 | | | < 0.01 | | |
| $R^{2\,b}$ | 0.06 | | | 0.09 | | |
| $R^{2\,c}$ | 0.18 | 0.22 | 0.22 | 0.12 | 0.17 | 0.17 |
| $R^2$ 95% CI[d] | 0.26 – 0.32 | 0.32 – 0.38 | 0.32 – 0.38 | 0.11 – 0.16 | 0.15 – 0.22 | 0.16 – 0.23 |
| **NC Test Sample (1)** | | | | | | |
| Number of patients | 5,000 | | | 4,500 | | |
| $R^{2\,a}$ | < 0.01 | | | < 0.01 | | |
| $R^2$ | 0.12 | 0.09 | 0.09 | 0.08 | 0.08 | 0.08 |
| $R^{2\,e}$ | 0.13 | 0.11 | 0.11 | 0.08 | 0.08 | 0.08 |
| Annualized total one-year expenditures (mean; std) | $19,617 (15,667) | | | $20,385 (25,305) | | |
| Predicted total one-year expenditures (mean; std) | $16,868 (7,017) | $18,096 (7,018) | $18,139 (7,628) | $18,342 (7,247) | $18,949 (8,175) | $18,984 (8,253) |
| Predictive Ratios[f] | 0.86 | 0.92 | 0.92 | 0.90 | 0.93 | 0.93 |

Std: standard deviation

[a] Include age, sex, race, age square, interactions between age and race, and age and sex.

[b] Include demographic variables above and place of residence at time of diagnosis

[c] Original sample (full samples). $R^2$ was adjusted for shrinkage, correcting for the number of candidate predictors that were initially tested according to the formula by Van Houwelingen and Le Cessie.[57] Model $R^2$ for the AD/D reduced data set were 0.28, 0.34, and 0.34 for the drug only, ICD-9-CM only, and combined models respectively.

[d] Confidence interval over 1,000 bootstraps (reduced AD/D samples).

[e] Defined as the squared correlation between actual and predicted costs

[f] Predictive ratios are the ratio of mean total predicted payments to annualized mean total observed costs to Medicaid

Table 9: J-Test Model Performance for Non-Nested Models in the GA Cohorts[58]

| | **Source Model** | **Information Added from** | **AD/D Cohort** | | | **Stroke Cohort** | | |
|---|---|---|---|---|---|---|---|---|
| | | | t-value | p-value | Outcome | t-value | p-value | Outcome |
| 1 | Drug Only Model (A) | Combined | 11.193 | 0.001 | A < B | 12.171 | 0.001 | A < B |
| 2 | Combined Model (B) | Drug Only | 3.400 | 0.001 | B < A | 1.587 | 0.741 | B > A |
| | | | | | | | | |
| 3 | ICD-9-CM Only Model (C) | Combined | 5.453 | 0.001 | C < B | 5.986 | 0.001 | C < B |
| 4 | Combined Model (B) | IDC-9-CM Only | 3.349 | 0.001 | B < C | 0.762 | 0.446 | B > C |

1: Adding information from combined model to drug only model
2: Adding information from drug only model to combined model
3: Adding information from combined model to ICD-9-CM only model
4: Adding information from ICD-9-CM only model to combined model

TABLE 10: One-Year Cost Models Robust Regression Coefficients by Study Cohort and Index Type on NC Test Sample with Significant Covariates from Respective GA Models

| | **AD/D Cohort** | | | **Stroke Cohort** | | |
|---|---|---|---|---|---|---|
| Candidate Variables | RX | ICD-9-CM | Combined | RX | ICD-9-CM | Combined |
| Intercept | 53,435 | 12,360 | 11,622 | 39,979 | 8,480 | 3,719[a] |
| Age | -1,059 | 5[b] | 14[b] | -949 | -12[b] | 39[a] |
| Female | | | | 7,988 | | 5,936[a] |
| Black | | 1,509[b] | 1,839[b] | | 5,299[a] | 5,801[a] |
| Age square | 7 | | | 7 | | |
| Age * Female | | | | -103 | | -70[a] |
| Age * Black | | -22[b] | -26[a] | | -56[a] | -60[a] |
| Age-Blind-Disabled | | | | 5,609 | 5,687 | 4,894 |
| Hospital | 4,158 | 3,860 | 3,870 | 5,538 | 5,943 | 5,990 |
| Nursing Homes | 12,395 | 12,428 | 12,298 | 15,054 | 15,809 | 15,557 |
| Hemorrhagic stroke | N/A | N/A | N/A | 5,278 | 5,212 | 5,257 |
| **Drug-based covariates** | | | | | | |
| Aids - tuberculosis | N/A | | N/A | 10,148 | | * |
| Two classes of cardiac drugs | 70[b] | | - | | | |
| Four classes of cardiac drugs | 866[b] | | - | -312[b] | | 20[b] |
| Oral Hypoglycemiants | -198[b] | | - | | | |
| Antiepileptics | 1,857 | | - | 1,325 | | 711[a] |
| Insulins | 4,205 | | * | 4,037 | | * |
| Neuroleptics | | | * | 1,206 | | * |
| Opiates | 3,209 | | 3,658 | 1,963[a] | | 1,771[a] |
| Coagulation modifiers | 1,378 | | - | | | |
| One class of respiratory drugs | 1,129 | | - | | | |
| Two classes of respiratory drugs | 94[b] | | 464[a] | 191[b] | | 7[b] |
| Three classes of respiratory drugs | 2,379[a] | | 2,869[b] | 2,861[a] | | 3,028[a] |
| Acid peptic disease drugs | 1,913 | | | 1,253 | | * |

TABLE 10: One-Year Cost Models Robust Regression Coefficients by Study Cohort and Index Type on NC Test Sample with Significant Covariates from Respective GA Models

| | **AD/D Cohort** | | | **Stroke Cohort** | | |
|---|---|---|---|---|---|---|
| Candidate Variables | RX | ICD-9-CM | Combined | RX | ICD-9-CM | Combined |
| **ICD-9-CM code-based covariates** | | | | | | |
| Aids | | N/A | N/A | | 10,566 [a] | * |
| Alcohol abuse | | | | | 5,022 | 5,603 |
| Cardiac arrhythmia | | | | | -96 [b] | 44 [b] |
| Cerebrovascular accidents | | 3,210 | 3,235 | | N/A | N/A |
| Chronic Pulmonary Disorders | | | | | -907 [a] | - |
| Dementia Alzheimer | | N/A | N/A | | 4,943 | 4,889 |
| Diabetes | | 1,410 | -384 [b] | | 462 [b] | - |
| Diabetes with complications | | 5,145 | * | | 9,789 | * |
| Fluid electrolyte disorders | | -3,411 [a] | -3,476 [a] | | | |
| Hemiplegia – Paraplegia | | 4,467 | 4,478 | | 6,133 | 6,270 |
| Any malignancy | | 1,672 [a] | 1,763 [a] | | 4,470 | 4,447 |
| Other neurological disorders | | 2,542 | 2,761 | | 840 [a] | 702 [b] |
| Pulmonary circulation disorders | | | | | 4,682 [a] | 4,250 [a] |
| Peripheral vascular disorders | | 1,788 | 1,769 | | 2,639 | 2,928 |
| NOPD | | 838 [a] | * | | | * |
| Renal failure and chronic disorders | | 3,158 | 3,441 | | 2,195 | 3,217 |
| Rheumatologic disorders | | -1,252 [a] | -1,224 [a] | | | |
| Thyroid disorders | | -902 [a] | -749 [b] | | -3,117 | -3,660 |
| Metastatic solid tumor | | 486 [b] | -1 [b] | | 8,729 | 8,303 |
| Valvular disorders | | -725 [b] | -693 [b] | | 1,171 [a] | 1,593 [b] |
| Sudden weight loss | | 4,687 | 4,839 | | 5,735 | - |
| **Covariates based on drug class and ICD-9-CM information** | | | | | | |
| HIV - aids | | | N/A | | | 10,138 [a] |
| Insulin – diabetes w/ complications | | | 3,892 | | | 3,915 |
| Schizophrenia - neuroleptics | | | 706 | | | 1,533 |
| Ulcers - acid peptic disease drugs | | | | | | 1,591 |

* represents a variable that was included in the ICD-9-CM or drug based model and that was combined with its counterpart in the combined model.

- represents a variable that was included in the ICD-9-CM or drug based model but that failed to enter its respective combined model.

a) $0.10 < p < 0.50$

b) $p \geq 0.50$

TABLE 11: Model Statistics by Study Cohort and Index Type Using the NC Test Sample to Derive Weights and the NC Holdout Sample to Test the Predictive Performance of the Models

| **NC Test Sample (1)** | | | | | | |
|---|---|---|---|---|---|---|
| | AD/D Cohort | | | Stroke Cohort | | |
| | Drugs | ICD-9-CM | Combined | Drugs | ICD-9-CM | Combined |
| Number of patients | 5,000 | | | 4,500 | | |
| $R^2$ | 0.18 | 0.19 | 0.19 | 0.17 | 0.18 | 0.19 |
| **NC Test Holdout Sample (2)** | | | | | | |
| Number of patients | 4,903 | | | 3,248 | | |
| $R^2$ | 0.15 | 0.16 | 0.16 | 0.08 | 0.12 | 0.12 |
| $R^{2\,a}$ | 0.15 | 0.16 | 0.16 | 0.09 | 0.12 | 0.12 |

Std: standard deviation

[a] Defined as the squared correlation between actual and predicted costs

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CHAPTER SEVEN

# PROSPECTIVE RISK ADJUSTMENT INDICES FOR MORTALITY AND COST OUTCOMES USING ADMINISTRATIVE DATA IN AMBULATORY POPULATIONS[1]

[1] Ricci, JF., J. H. Dorfman, and B. C. Martin. To be submitted to Health Care Financing Review, 2001.

ABSTRACT

***Background and Purpose*** – Due to an expansion of its covered population and services, Medicaid has recently experienced a very rapid growth in expenditures, with outlays forecasted at $285 billion in fiscal year 2005. In response, Medicaid has been moving away from its traditional fee-for-service payment system toward a managed care health delivery system. However, unlike for the Medicare population, little information has been published and few risk adjustment models developed specifically for Medicaid populations. This research describes the development and independent validation of prospective mortality and cost risk adjustment indices for ambulatory Medicaid recipients based on automated pharmacy and medical claims data.

***Methods*** **–** A retrospective review of Georgia (training cohort) and North Carolina (test and holdout samples) claims Medicaid data for eight years (1990 to 1997) was used to identify ambulatory recipients between the ages of 15 and 50 years. ICD-9-CM code-based comorbidities and drug exposure were collected the year prior to an arbitrary index date along with demographic information. Three types of models were developed to predict total cost to Medicaid and survival outcomes post-index date: models with drug exposure data, models with ICD-9-CM codes, and models with combined drug exposure and ICD-9-CM information. Cox proportional hazards regression was used to model seven-year survival and weighted linear regression with Huber-White robust estimator of the variance to model one-year cost to Medicaid. Risk factors, identified on statistical empirical evidence in the GA sample, were subsequently submitted to a clinical panel for validation. Clinically validated GA models were then re-estimated, 'frozen', and prospectively validated on the external NC Medicaid cohort.

***Results –*** We identified cohorts of 273,970 and 120,000 GA and NC Medicaid recipients, with mean ages of 28 and 29 years and mean annual expenditures of $2,954 and $2,353 (1996 $), respectively. In the GA cohort, c-statistic for Cox proportional hazards models ranged from 0.85 to 0.88 and $R^2$ from 0.10 to 0.15 in the three cost models. Female gender, blind-disabled Medicaid eligibility, prior exposure to opiates, cardiac and respiratory drugs, antiretroviral therapy, a prior diagnosis for aids, tumors/cancers, cardiac and organ diseases (CHF, renal failure, liver diseases), and sudden weight loss were associated with the largest increases in odds of death and one-year cost to Medicaid. Recipients with chronic mental/psychiatric conditions (depression and non-organic psychotic disorders) or with a prior exposure to antidepressants or neuroleptics had greater likelihood of survival. In general, drug exposure and ICD-9-CM comorbidity provided complementary information. $R^2$ for the combined one-year cost model was 45% higher than the $R^2$ for the drug only model and 16% higher than the $R^2$ for the ICD-9-CM only model. When GA 'frozen' models were prospectively tested on the external NC sample, c-statistic ranged from 0.87 to 0.90 and $R^2$ for cost models from 0.04 to 0.09, with a better model performance observed in the combined model. Combined and ICD-9-CM cost models outperformed the drug exposure cost model, whereas there was no difference in discriminative ability between the three mortality models.

***Conclusions*** – The study showed that models based on drug exposure data alone provide valuable information regarding survival and future health expenditures of an ambulatory Medicaid population. With a cohort of more than 270,000 recipients, we were able to provide detailed information on the prevalence of diseases and the use of drugs in an ambulatory population. Both drugs and ICD-9-CM codes can help characterize the comorbidity burden of an ambulatory population, but used in conjunction, the two sources of information increased the sensitivity to disease prevalence. Our models provide a tool to Medicaid programs and health service researchers to initially stratify or otherwise control for varying levels of disease severity

and comorbid illnesses for ambulatory Medicaid patients. The long-term goal for our prospective cost risk adjustment models is to forecast resources commensurate with actual needs of a large segment of the Medicaid population. However, further refinements and independent testing of our cost models are needed before they can reliably and accurately predict future levels of resource needs.

Key Words: Medicaid; Risk Adjustment; Case Mix Measure; Comorbidity; Mortality; Cost; ICD-9-CM; Drugs; Administrative Data.

INTRODUCTION

Recent shifts in medical care from inpatient to outpatient settings have increased the interests of the medical community and health care payers about issues related to ambulatory patient populations. Practitioners, health plan managers, private health care payers and the government have felt a greater need for ambulatory measures for different reasons.[1] However, as Berlowitz noted, a large number of ambulatory care measures have been developed for acute care settings, "addressing issues surrounding a discrete medical episode that generates large amount of data." Information for the ambulatory setting itself is scarce and often solely applicable for the setting it was initially developed, e.g., health maintenance organizations, multi-specialty group practices. A global ambulatory measure requires the ability to follow patients across years and different settings, such as physicians, outpatient hospitals, emergency rooms, dentists, pharmacies, etc. Although, Medicaid is rapidly moving away from its traditional fee-for-service payment system toward a mostly capitated managed care health delivery system, very little research has been published on the development and validation of population-based Medicaid-specific risk adjustment indices.[2,3]

Capitation of health insurers involves the payment of a fixed amount per person covered. Costs incurred by the insurer are a function of a person's health status. Therefore, chronic component of health status if accounted for should help increase the ability to predict future health care costs. In the literature several classification systems have been proposed for ambulatory populations.[4] Only one of them was specifically developed for a subset of the Medicaid population. Kronick devised a system of diagnostic categories that Medicaid programs can adapt to adjust capitation payments to health plans that enroll people with disability.[2] Another system, the Diagnostic Cost Groups (DCGs), has been re-weighted and tested on a Medicaid patient population and for privately insured persons.[3] DCGs use age, sex, and diagnoses generated from patient encounters to infer which medical problems are present for each individual and their

likely effect on health care costs for a population. DCGs were initially developed in the late 1980's for inpatient admission type of encounters in Medicare populations.[5,6,7]

The conceptual development of risk adjustment indices with administrative databases has been described previously. (Refer to Chapter 4: "Prospective Mortality Risk Adjustment Indices for Stroke Using Administrative Data") In summary, it mostly relied on diagnosis codes, most often ICD-9-CM codes.[8,9,10,11,12] ICD-9-CM code-based measures, however, present with a potential for omission bias in coding comorbidities in the context of longitudinal studies. Therefore, there exists a need to complement ICD-9-CM code-based measures with another source of comorbidity information. Medical records represent an invaluable source of such information, containing data on vital signs, patient risk factors, and diagnostic and test results.[13,14] Unfortunately, the information needed to code for clinical indicators is usually not recorded in administrative databases such as Medicaid, making their use in large-scale studies almost impossible and prohibitively expensive on the scale needed to develop and validate population-based indices.[11] As a research team from the Group Health Cooperative of Pudget Sound, Seattle, WA showed with the Chronic Disease Score (CDS), detailed prescription files can serve as an inexpensive source of information on patients' health status.[15,16] Until recently, however, few published studies have incorporated the CDS or prescription durgs as a health status indicator.[17,18,19]

Although Medicaid databases contain demographic, medical, and drug utilization information for the indigent US population necessary to perform longitudinal studies, little published research has developed and/or validated risk adjustment indices specific to ambulatory Medicaid populations.[2,3] The nature of the Medicaid databases is one of the major reasons why risk adjustment methods for such a large segment of the US population (more than 40 million enrollees in 1999) have not been studied. Their sheer-size, complexity, and lower visibility than Medicare files "may have caused some analysts to despair and decide that Medicaid data are hopeless."[20] Furthermore, the lack of consistency of data across states has impaired researchers' ability to formulate research

models from one state and to validate these models in other states. Therefore, the objectives of the study were twofold:

1) To develop population-based risk adjustment indices for ambulatory cohorts of Medicaid recipients based on ICD-9-CM codes and drug exposure separately, and combined ICD-9-CM codes and drug exposure data to predict one-year cost to Medicaid and seven-year patient survival.

2) To test the predictive ability of the new indices on an independent external Medicaid ambulatory population from another state.

## METHODS

Data sources have already been described elsewhere. (Refer to Chapter 4, Methods, Data Sources: "Prospective Mortality Risk Adjustment Indices for Stroke Using Administrative Data")

### Cohort Definition

To be included in the ambulatory cohort, Medicaid recipients had to be continuously eligible for a minimum of 24 months (12 months of observation and 12 months of follow-up unless they expired during follow-up) between 1990 and 1997. The index date (first day of follow-up post-observation year) was arbitrarily set to the first day of the calendar year, i.e., 1 January 1991, 1992, 1993, 1994, 1995, or 1996. Consequently, the follow-up time period varied from two years (observation year in 1995 and index date of January 1 1996) to seven years (observation year in 1990 and index date of 1 January 1991). Medicaid recipients continuously eligible for several years were randomly assigned to an index date. For example, a Medicaid recipient who was continuously eligible from November 1990 to September 1995 could have been assigned to one of three index dates (1 January 1992, 1 January 1993, and 1 January 1994), with a corresponding 12-month observation period starting on 1 January 1991, 1 January 1992, and 1 January 1993.

Medicaid recipients also had to be 15 to 50 years of age at the beginning of the observation period. With this age requirement, researchers sought to assemble a broad and yet uniform cross-section of important Medicaid recipients where age would be less likely to be a single risk factor explaining a significant portion of the model variance. Additionally, Medicaid recipients who presented a nursing home claim and/or stayed for more than 30 consecutive days in an inpatient facility during the one-year period prior to their index date were excluded. Thus, we opted to discard recipients who suffered from a serious condition that warranted a long-term stay in a hospital and patients who may have needed enough help in their activity of daily living to be institutionalized. We collected all outpatient pharmacy and medical claims for the 12-month observation period and the entire follow-up period (up to seven years).

Definitions of Comorbidities and Drug Exposure

To develop the list of potential ICD-9-CM code-based comorbidity markers, we combined elements of the Deyo's adaptation of the Charlson Index[9] and the updated set of comorbidity measures published by Elixhauser.[12] Details on the adaptation of the Charlson and Elixhauser methods have been described elsewhere. (Refer to Chapter 4, "Prospective Mortality Risk Adjustment Indices for Stroke Using Administrative Data") Given the age range (15 to 50 years) and the predominant female nature of the Medicaid population, our cohort included many women of childbearing age. We therefore added two "comorbidity" definitions: 'complications during pregnancy' and 'complications at delivery and/or post delivery'. The final set of 33 comorbidities along with their ICD-9-CM codes is displayed in Table 1. The Chronic Disease Score (CDS) developed by Von Korff,[15] and revised by Clark,[21] and the rationale supporting it, served as the foundation of our drug classification that includes 27 drug exposure categories (Table 2). All drug claims during the one-year observation period pre-index date were sorted by National Drug Code number and assigned to a therapeutic class using a classification algorithm

(http://www.multum.com). As the CDS was developed in 1992, we updated different drug classes to reflect the availability of newer pharmacological classes and agents.

In addition to comorbidity and drug class definitions described above, a set of covariates was tested for entry in all six prospective models. Covariates included information on demographic, Medicaid (blind or disable) and Medicare eligibility, a quadratic term for age, and interaction terms (e.g., age and gender, age and race).

Seven-Year Survival and One-Year Cost Models

The prevalence of ICD-9-CM code-based comorbidities and drug exposure, as defined in Tables 1 and 2, was checked in the Georgia Medicaid cohort (n = 273,970). Covariates for condition or drug exposure classes with low prevalence (fewer than 100 patients) were merged with other covariates in a clinically meaningful manner or dropped. (See Chapter 4: "Prospective Mortality Risk Adjustment Indices for Stroke Using Administrative Data").

We assessed seven-year survival prognostic factors with Cox proportional hazards regression models.[22] Hazard rate ratios (R.R.) and corresponding 90% confidence intervals were derived from the final models. Measure of model discrimination was obtained using the c-statistic.[23]

Costs to GA and NC Medicaid were annualized based on the number of months of survival in the one-year follow-up period. Weighted least squares regression was used to model the continuous one-year total cost outcome to Medicaid and to estimate the amount of additional expenditures in a given year associated with a person having a given diagnosis claim or exposure to a drug in the previous year. Weights for individual standard error estimates for each observation were set equal to the ratio of 12 over the number of months each recipient was of eligibility in the one-year follow-up, so that recipients with the fewer number of months eligible were assigned a larger variance weight in the GA training sample.[5] We checked for the presence of outliers and/or influential observations; none was identified. In order to better correct model estimates

for the presence of heteroskedasticity, we used Huber-White corrected standard errors.[24] We tested the relative performance of the drug only and ICD-9-CM only models with respect to that of the combined model with a J-Test.[25] This test for departures from the null hypothesis (the two models are equivalent) assessed the null against a more general model that artificially combines the two competing non-nested models. Lastly, expenditure data were adjusted for medical and drug inflation with the consumer price index for medical commodities and services (http://stats.bls.gov/cpihome.htm). We standardized expenditures to 1996 levels, as 1996 was the last year of inclusion in the study.

The significance of all potential covariates in all six models was first tested in a stepwise weighted backward regression procedure at a significance level for staying in the models of 0.10.[26] The 10% significance level required for a variable to remain in a model helped limit the inclusion of noise variables in our indices.[27,28] As stepwise variable selection processes can lead to model overfitting, $R^2$ was adjusted for shrinkage, thus correcting for the number of candidate predictors that were initially tested.[29] SAS version 6.12 software (SAS Institute, Cary, NC, USA) was used to extract the final analytical samples. Descriptive analyses, model estimations, and external validation were carried out in SAS or STATA Version 6.0 (STATA Corporation, College Station, TX, USA).

## Clinical Expert Review

Univariate statistical analyses and detailed results from the initial stepwise procedures were presented to an internist and a clinical pharmacist. They reviewed the findings and helped determine which of the variables should stay in the models and be submitted to the external validation procedure. Like Keeler during the development phase of the APACHE III, clinicians were allowed to drop factors empirically identified on sole statistical evidence but that might be unlikely predictor of the outcome studied (i.e., survival and cost) based on clinical expertise.[30] Coefficients of seven-year survival

and one-year cost models were subsequently re-estimated on the GA cohort to incorporate clinicians' decisions on each of the six models.

External Models Validation

Upon clinical expert review and subsequent model re-estimations, the reduced models were 'frozen' and tested on the North Carolina Medicaid cohort. The NC cohort was randomly divided into two sub-samples. The NC test sub-sample was used to test the performance of the GA models on an out-of-sample population (n = 120,000). The second sub-sample, the 'holdout' sub-sample (n = 85,097), was spared and set aside for further analysis in case the GA models would exhibit poor predictive ability or model performance. Correct probability of prediction of death (or external predictive discrimination) in the final three survival reduced models was assessed by the c-statistic.[23] Due to large cohort sizes and a resource intensive computer algorithm, a 20% random GA sample (n = 54,794) and a 50% NC random sample (n = 60,000) were used to compute the c-statistic. . Costs to NC Medicaid were annualized based on the number of months of survival in the one-year follow-up period. Explained variation on each of the three cost models was measured with the out-of-sample sum of square $R^2$:

$$\text{Predicted } R^2 = 1 - \frac{SSE}{SST} = 1 - \frac{\text{sum}\left[\left(e_i - \bar{e}\right)^2\right]}{\text{sum}\left[\left(y_i - \bar{y}\right)^2\right]}$$

where $e_i$ was error on $i^{th}$ NC observation using $\beta$-hat from truncated GA model and $y_i$ was observed one-year total cost to Medicaid on $i^{th}$ NC observation. A correction factor was applied to the sum of squared errors because out-of-sample errors do not necessarily have error means of zero. Another measure of predictive $R^2$, squared correlation between actual and predicted costs, was also computed. Other researchers have used it in the past,[3,31] although it is analytically less conservative, as out-of-sample correlation between actual and predicted costs is not a function of coefficient estimates (i.e., $\beta$-hats).

Additionally, the predictive ratios (P.R.) of mean total predicted payments to mean total observed costs to NC Medicaid were computed for each of the three cost models.

Institutional Review Board was obtained from the University of Georgia Research Office (project number H980679 - CFR category 46.101 (4) - Institution Assurance number M1047).

## RESULTS

### Demographics and Eligibility

Table 3 presents demographic and eligibility information on the Georgia and North Carolina Medicaid cohorts. There were a total of 273,970 and 120,000 recipients in the GA and the NC test samples. The NC holdout sub-sample contained 85,097 recipients and was not used in this study. GA and NC cohorts had the same proportion of females (75%) and had similar age (28.1 vs. 28.5 years). A larger number of GA recipients were black (66 vs. 55%), dual Medicaid-Medicare eligible (24 vs. 8%), had blind-disabled Medicaid eligibility (31 vs. 20%), and died (2.8 vs. 1.5%) during the seven-year follow-up period. Finally, one-year total direct medical costs to Medicaid post-index date (in 1996 $) were 25% higher in the GA than in the NC cohort ($2,954 vs. $2,353).

### Comorbidity and Drug Exposure Burden

The prevalence of the 33 ICD-9-CM code-based comorbidities and 27 drug exposure classes in the GA Medicaid cohort the year prior to the index date (observation year) are presented in Table 1 and Table 2. The most prevalent ICD-9-CM conditions were hypertension (6.9%), chronic pulmonary diseases (6.4%), non-organic psychotic disorders (NOPD – 6.2%), complications at or post-delivery (4.5%), depression (3.4%), and other neurological disorders (e.g., epilepsy – 3.0%). Classes of drugs used by most recipients were antihypertensives (11.2%), chronic respiratory agents (11.0%),

antidepressants (10.9%), acid peptic disease agents (10.7%), anti-Parkinson agents (8.9%), neuroleptics (6.7%), systemic steroids (6.3%), and cardiac agents (5.7%).

Classification Table 4 summarizes the impact of the number of ICD-9-CM code-based comorbidities and drug exposure classes in the GA cohorts on seven-year mortality and one-year direct medical costs to Medicaid. During the year prior to their index date, GA recipients had on average 0.5 ICD-9-CM code-based comorbidity (median 0) and 0.9 drug class (median 0). Nearly two-thirds (65%) of the recipients did not present with any of the 33 comorbidity classes and 57% were not exposed to any drug class the year prior to their index date. A straight linear relationship emerged between ICD-9-CM comorbidity burden and drug exposure with respect to seven-year crude mortality (Pearson $\chi^2$ test P value < 0.025 and Cochran- Armitage linear trend test P value < 0.025 – Table 4). Fewer than 2% of recipients with no drug exposure and/or ICD-9-CM code-based comorbidities expired within seven years. However, more than 20% of recipients who received six or more drug classes and/or nearly one in three who had six or more ICD-9-CM code-based comorbidities expired during follow-up period.

The Cuzick nonparametric test for trend across ordered groups was used to test the relationship between ordered number of drug classes, ordered number of ICD-9-CM comorbidities, and one-year costs.[32] There was a direct linear relationship between one-year Medicaid costs and prior comorbidity burden ($p<0.025$) and number of drug classes ($p<0.025$). Recipients with exposure to no drug class or no comorbidity cost on average less than $2,000 to Medicaid in the follow-up year. Conversely, recipients with exposure to 6 or more drug classes cost more than $11,000 and recipients with 6 or more code-based comorbidities cost more than $20,000 to Medicaid in the follow-up year. Note, a level of significance at 0.025 was specified *a priori* for all tests to control for test multiplicity, as differences at one-year follow-up were tested two ways for each outcome: once for association with drug exposure and once for association with ICD-9-CM burden.

## Model Building

The variable coding for the presence of anemia was not entered in the stepwise risk adjustment regression models because the number of recipients presenting with this comorbidity was less than 100. Three drug classes were excluded for the same reason (drugs for end stage renal disease, drugs for bone diseases, and drugs for Alzheimer's dementia). Because of the overlap in certain drug classes and ICD-9-CM codes, information from the two sources was aggregated in the combined model in several cases: 1) antiepileptics and other neurological disorders 2) antidepressants and depression diagnosis; 3) insulins and diabetes with complications; 4) neuroleptics and NOPD; 5) antiulcer agents and ulcer; 6) antiretroviral therapy and aids diagnosis. Overlap was defined when 65% of the patients or more had both a drug exposure and an ICD-9-CM code for a condition.

## Cost and Mortality Models

The coefficients of each covariate in the one-year cost and seven-year survival drug, ICD-9-CM, and combined models are presented in Table 5 and summary statistics for each of the six models in Table 6. Of the 38, 40, and 64 potential covariates tested for entry in the drug, ICD-9-CM, and combined models, 27, 29, and 34 entered the seven-year Cox proportional hazards models and 34, 38, and 56 entered the weighted linear cost models (Table 6). There were 7,558 recorded deaths (events) in the seven-year follow-up in the GA cohort. Therefore, the largest event-to-variable ratio was observed in the seven-year drug model ($199{:}1 \approx 7{,}558{:}27$) and the smallest event-to-variable ratio in the combined model ($118{:}1 \approx 7{,}558{:}34$).

In all survival models, c-statistic ranged from 0.852 to 0.878 with the largest discriminative ability observed in the combined model (Table 6). Cost model $R^2$ based

solely on demographic information was around 0.01 and model $R^2$ based on demographic and Medicaid and Medicare eligibility information was 0.03 (Table 6). $R^2$ ranged from 0.10 to 0.15 in the drug, ICD-9-CM, and combined models with the largest model performance observed in the combined model. $R^2$ for the combined one-year cost model was 45% higher than $R^2$ for the drug only model and 16% higher than $R^2$ for the ICD-9-CM only model. However, model performance was not significantly different, as the J-Tests were inconclusive with both drug and ICD-9-CM models when compared to the combined model (Table 7).

Individual Mortality Factors

The impact of age was constant across all models, for a one-year increase in age at index date, risk of death during follow-up time increased by 11% (Table 5). Males were about twice as likely to die than their counterparts. Recipients who were 'disabled-blind' Medicaid eligible were three times as likely to expire in the seven-year follow up, whereas Medicare eligibility increased the odds of death by 40 to 50%. Black race was also associated in the ICD-9-CM and combined models with a marginal 6 to 11% increase in odds of death.

Among all drug-based variables tested, the use of antiretroviral therapy was the stronger predictor of death (with a 9- and 10-fold increase in the drug and combined models). The hierarchical classification used to operationalize cardiac and respiratory drug classes allows for a comparison of the regression coefficients within each model. A similar linear relationship was observed in the two drug models with both cardiac and respiratory drugs as patients exposed to a larger number of cardiac (or respiratory) classes of drugs experienced higher risk of death than recipients who were exposed to fewer classes of cardiac (or respiratory) drugs. For instance, in the drug only model, R.R. were

1.36, 2.11, 3.51, and 5.36 for patients who were exposed to one, two, three, and four classes of cardiac drugs, respectively. Prior exposure to neuroleptics, antidepressants, and antihyperlipidmics were associated with lower odds of death by 13, 16, and 26%.

Among all ICD-9-CM code-based variables tested, a prior diagnosis of aids (R.R. = 12) and metastatic solid tumor (R.R. = 11) were the largest predictors of death. Diagnoses for malignancies, liver and renal diseases, congestive heart failure, and sudden weight loss the observation year prior to the index date were associated with twofold or greater increase in odds of death (R.R. > 2) in the ICD-9-CM and combined models. The presence of a diagnosis for hypertension, depression, and NOPD were associated with lowered odds of death by 9, 15, and 30%, respectively.

In the combined model, R.R were very similar to that of their respective drug and ICD-9-CM models. Of note, however, is the reduction in the magnitude of the R.R. for cardiac conditions and cardiac drugs when they are combined in a single model. A similar phenomenon was observed with antineoplastics and a prior diagnosis for solid metastic tumors. A prior diagnosis of NOPD or exposure to neuroleptics was associated with a 14% reduction in odds of death, the use of antidepressants and/or a prior diagnosis for depression with a 15% reduction, a prior diagnosis of hypertension and exposure to antihyperlipidemics with a 24% reduction in odds of death.

Individual Cost Predictors

Age coefficients were always negative, between –$93 to –$74 for each additional year at index date (Table 5). Male sex was associated with a lower one-year cost to Medicaid by about $2,400. Black race was associated with higher predicted costs (about +$300) in the two models containing ICD-9-CM-defined comorbidities but was not significant in the drug only model. Recipients with blind-disabled Medicaid eligibility at index date had higher one-year predicted costs by over of $1,000 whereas Medicare eligibility was not constant, alternating between a lower predicted cost in the combined and drug models and a higher predicted cost in the ICD-9-CM only model.

Prior exposure to antiretroviral therapy, immunosuppressive, antituberculosis, PVD agents, opiates, and several classes of cardiac drugs were associated with the largest predicted costs to Medicaid (> +$3,000). Other non-negligible drug agents ($1,500 < $3,000) included antineoplastic, insulins, neuroleptics, antiepileptics, several classes of respiratory drugs, and drugs for irritable bowel disease. A prior diagnosis of aids, renal failure, metastatic solid tumor, sudden weight loss, hemiplegia-paraplegia, diabetes with complications, coagulopathy, congestive heart failure, and liver and pulmonary chronic diseases were associated with the largest predicted costs to Medicaid (> +$3,000). Other non-negligible prior conditions ($1,500 < $3,000) included complications of pregnancy, Alzheimer's dementia, malignancies, myocardial infarct, and other neurological disorders (including epilepsy).

Most of the drug classes and comorbidities that were predictors of higher health care costs post-index date in the drug only and ICD-9-CM only models were still associated with significantly higher Medicaid expenditures in the combined model. As in the survival models, a reduction in the magnitude of the coefficients for cardiac conditions and drugs, and respiratory conditions and drugs was observed when drug and ICD-9-CM covariates were combined into a single model.

External Model Validation

The bottom rows of Table 8 present predictive discrimination (c-statistic for survival) and predictive model performance (out-of-sample sum of square $R^2$ for cost) statistics on the NC test sample (n = 120,000 recipients) for the drug, ICD-9-CM, and combined models. C-statistic ranged between 0.870 and 0.894 with increasing discriminative ability observed from the drug only, ICD-9-CM only, to the combined model. Out-of-sample $R^2$ ranged from 0.04 to 0.09 with increasing performance observed from the drug only, IDC-9-CM only, to the combined models. $R^2$ based on the squared correlation between predicted and observed costs ranged from 0.06 to 0.10. Validation $R^2$ based on demographic information was less than 0.01. The predictive

performance of each of the cost models was around 1.5, i.e., one-year costs to NC Medicaid were overestimated on average by 50%.

## DISCUSSION

Medicaid was initially formulated as a medical care extension of Federally funded programs providing cash income assistance for the poor, with an emphasis on dependent children and their mothers, the disabled, and the elderly. Legislation in the late 1980s assured Medicaid coverage to an expanded number of low-income pregnant women, poor children, and to some Medicare beneficiaries who are not eligible for any cash assistance program. Medicaid programs are now assuming health care coverage of over 40 million people across the US (http://www.hcfa.gov). In an effort to better control ever rising expenses, Medicaid has been rapidly moving away from its traditional fee-for-service payment system toward a managed care health delivery system. The number of Medicaid beneficiaries enrolled in some form of managed care program grew from 14 percent in 1993 to 54 percent in 1998 (http://www.hcfa.gov). Under managed care systems, HMOs, prepaid health plans, or comparable entities agree to provide a specific set of services to Medicaid enrollees, usually in return for a predetermined periodic payment per enrollee. As in the case of Medicare, there is a need for risk adjustment models that could help predict capitation payments to health care providers for Medicaid enrollees based on demographics and health status indicators.

Risk adjustment indices not specific to indigent populations have been used in studies that examined cost and resource utilization outcomes for Medicaid recipients.[33,34,35,36] These studies showed that risk adjustment indices may not always be consistent predictors of the outcomes of interest,[33] albeit they can help explain a proportion of variation of the outcome.[35] Besides the paucity of the number of the studies using risk adjustment methods in Medicaid populations, little research has formally developed and externally validated Medicaid-specific cost or mortality models for these populations. Indeed, a major issue in the development of risk adjustment models is that

of independent sample validation as a risk adjustment system is only appropriate when it has been demonstrated to predict the outcome of interest in a population similar but independent to that in question.[37] This is the first set of published risk adjustment indices specific to a large Medicaid population that attempts to predict both cost and mortality outcomes. Indices were externally validated with an independent cohort to test their validity. Administrative data were chosen because this type of data allow a detailed description of prescription drugs, ambulatory physician, inpatient hospital, outpatient hospital, nursing homes, and other outpatient services utilization. The Georgia Medicaid data has been used to describe the impact of other types of conditions and various policy analyses.[38,36] Additionally, administrative data of this type have been found valid for economic and epidemiological investigations.[39,40,41]

Comorbidity and Drug Exposure Burden

Comorbidity and drug exposure burden was low with an average of 0.5 ICD-9-CM code-based comorbidity (median 0) and 0.9 drug class (median 0). In fact nearly two-thirds of the recipients did not present with any of the 33 comorbidity classes and 57% were not exposed to any drug class the year prior to their index date. Studying a cohort of more than 270,000 recipients helped provide detailed information on the prevalence of diseases and the use of drugs in an ambulatory population. The two most prevalent conditions were hypertension and chronic pulmonary diseases, both with prevalence at about 1 in 15 individuals. One out of 12 women suffered from complications at or post-delivery. Interestingly, the next three most prevalent conditions were psychiatric/mental ailments, i.e., non-organic psychotic disorders (NOPD – 6.2%), depression (3.4%), and other neurological disorders (e.g., epilepsy, Parkinson – 3.0%). The prevalence of NOPD is much larger than that observed in the general population, a likely consequence of the population studied, as NOPD may entitle an individual to Medicaid benefits. Classes of drugs most frequently used were in general indicated for the treatment of the most prevalent conditions: antihypertensives (11.2%), chronic

respiratory agents (11.0%), antidepressants (10.9%), anti-Parkinson agents (8.9%), neuroleptics (6.7%), and cardiac agents (5.7%). The fact that drug use prevalence was in general larger than the prevalence of a condition itself can be explained by several factors. First, most drugs can be indicated for several conditions, e.g., antidepressants. Second, physicians may not report all comorbid conditions present in an individual but only the most severe one or the one for to the reason of visit. Third, physicians may choose not to code for conditions, such as mental illnesses, that carry a social stigma. Conversely, conditions that are rare or for which there exists no specific drug treatment seem to be more accurately captured with ICD-9-CM codes than with drug exposure (e.g., hemiplegia/paraplegia, renal failure, fluid electrolyte disorders, Alzheimer's dementia, weight loss/malnutrition). Both drugs and ICD-9-CM codes can help characterize the comorbidity burden of an ambulatory population, but used in conjunction, the two sources of information seem to increase the sensitivity to disease prevalence. Information on disease prevalence is invaluable for identifying opportunities for selecting, implementing, and evaluating the effectiveness of disease management programs.[3]

Mortality Model Coefficients

Low economic status has been linked to excess mortality rates.[42] Epstein (1989) noted that uninsured or Medicaid patients in Massachusetts were significantly more likely than privately insured patients to be hospitalized for potentially avoidable causes.[43] Such patients often have a higher risk of death, increased chance of complications, impaired recuperative abilities; all these factors negatively affect their longevity.[44,45] This is the first study to examine the prospective impact of comorbidities and drug exposure on mortality for a large ambulatory Medicaid population. The effect of comorbidity can depend on the time frame of follow-up but little systematic information is available on long term patient risks for conditions other than cancer.

The impact of age was constant across all models. Risk of death during the seven-year follow-up time increased by 11% for a one-year increase in age at index date, by a threefold for a 10-year age difference, and a 39-fold for a 35-year difference (age range of the cohorts). Males were twice as likely to die as women. This excess hazard rate exceeds lifetables mortality estimates where males' survival is slightly inferior to that of females until age 50 (http://www.cdc.gov). A majority of Medicaid eligible women between the ages of 15 and 40 qualify for Medicaid benefits through the "Aid to Family with Dependent Children" program. Therefore, women recipients in this age class tend to qualify because of a combination of a low income and a status of child support. Men in this age class rarely qualify to AFDC but are more likely to become Medicaid eligible because of a poor health condition. This difference in eligibly status may explain the two-fold increase in mortality observed in men. Patients with a blind-disabled Medicaid and Medicare eligibility were respectively three and 1.5 times more likely to expire. Again, difference in mortality reflects a difference in eligibility status. The maximum age of our cohort was 50, so patients who were dually eligible were individuals with a disability or chronic kidney disease. Nearly four out of five Medicare eligible recipients also qualified for a Medicaid disabled eligibility status.

Exposure to antiretroviral therapy, a prior diagnosis of aids and metastatic solid tumors were the strongest risk factors for death (R.R. > 8) in our relatively young population. The use of a hierarchical classification for drugs and ICD-9-CM codes added a sense of disease severity to our models. The larger the number of cardiac and respiratory drug classes, treatment with insulin over oral hypoglycemiant only, and a diagnosis of diabetes with complications over uncomplicated diabetes only were associated with higher odds of death. Among all 44 risk factors identified in the final three models, a few drug exposure classes and ICD-9-CM comorbidities were associated with lower odds of death, in the drug only or ICD-9-CM only models, but also in the combined model. These factors were exposure to antidepressants and a prior diagnosis of depression, a prior diagnosis of hypertension, and exposure to antihyperlipidemics. As

Iezzoni suggested, patients with "chronic conditions (e.g., hypertension) have more regular contacts with doctors and thus may have their acute illnesses identified at earlier stages or at a lower severity."[4] Also, patients with several chronic comorbidities are less likely to receive a code for a lesser severe chronic conditions, such as hypertension. The combination of these two factors can make a non-life threatening comorbidity appear to have a protective effect on survival in patients who present no other comorbidity. This is most likely the case in relatively young populations with exposure to antidepressants, a diagnosis of depression or hypertension, or exposure to antihyperlipidemics. Patients exposed to neuroleptics or with a diagnosis of NOPD also had lower risk of death across all models. The study unfortunately cannot provide an explanation regarding this finding. This 'apparent' protective effect of a prior NOPD diagnosis on survival in a large ambulatory cohort needs to be investigated further in other Medicaid populations. It may be due to a confounding effect between NOPD and Medicare / Medicaid disable eligibility, as NOPD (schizophrenia particularly) is a major reason for Medicare eligibility in adults younger than 65 years.

Cost Model Coefficients

In a given cost model, the weights of individual coefficients reflect the increment in expected costs to Medicaid that is independently associated with having the condition (ICD-9-CM based) or being exposed to a particular class of drugs the year prior to the index date. A controversial finding is that race (black) was found to be associated with relatively higher predicted expenditures (from $308 to $321) in all models that contained ICD-9-CM information. The inconsistent role of race may reflect the fact that ICD-9-CM models were not able to account for all patient characteristics such that sources of unmeasured (unexplained) variations in patient outcomes are confounded with race. The relative weights of the race coefficients were almost negligible, albeit statistically significant, as race weights were lower than weights for any of the nearly 50 drug exposure and comorbidity covariates present in the final models. In retrospect, it would

have been more appropriate not to adjust for a patient attribute such as race in our prospective cost models, as the assumption that ethnicity can be used as an isolated epidemiological factor by defining clinically distinct disease subgroups remains controversial.[46] Conversely, sex had a strong predictive power on future Medicaid costs, as males tended to have lower predicted expenditures by about $2,300. Age had a constant negative impact in all three models (-$93 to -$74). In the GA cohort, 24% of the recipients were dual Medicaid-Medicare eligible. Some of the direct medical expenditures of dual eligible are covered by Medicare (inpatient stay and office visits), whereas all expenditures of non-dual eligible are assumed by Medicaid. As Medicare eligible patients were 10 years older (T-test $p<0.001$), a larger fraction of older patients' total direct medical expenditures was not covered by GA Medicaid. Difference in dual program eligibility created a model artifact where the older the patient the less his/her Medicaid predicted expenditures, controlling for all demographics, comorbidity burden, and drug exposure information.

All statistically significant comorbidity and drug exposure covariates increased future predicted Medicaid costs. Almost any prior exposure to a drug class or any prior comorbidity predicted some of the expected cost to Medicaid in an ambulatory population. Conversely, increment in expected mortality was predicted by fewer covariates as only 50 to 70% of the non-demographic and non-eligibility variables remained in the final Cox survival models whereas 85 to 94% of the same variables remained in the final one-year cost models. All covariates included in the final survival models were also present in the cost models.

As noted by Kronick, the most frequently occurring diagnoses, and drug exposure classes in our models, tended to have the lowest additional costs associated with them. In many cases, the incremental cost was less than $1,000 per year, if statistically significant at all (e.g., hypertension or exposure to oral hypoglycemiants, antihypertensive agents, systemic steroids, and one class of respiratory and cardiac drugs).[2] Conversely, the presence of certain rare and serious conditions, such as renal failure, aids, metastatic solid

tumors, sudden weight loss, hemiplegia/paraplegia, coagulopathy or infrequent exposure to antiretroviral therapy, antituberculosis agents, and four classes of cardiac drugs had a substantial incremental effect on one-year cost post-index date (>+$5,000). Therefore, the parameter estimates appear reasonable in size and they seem to exhibit good face validity. The conditions that most clinicians would judge to be more serious have larger expenditures associated with them than the conditions that most would judge to be less serious.[2]

Higher predicted payments for cancer and diabetes patients were function of the type of cancer (solid metastatic tumors vs. any malignancy) and diabetes (diabetes with or without complications). This supports our decision to employ an *a priori* hierarchical approach to operationalize certain drug exposure and comorbidities in order to screen out some of the possible redundancy inherent to drug and ICD-9-CM code-based information. Indeed, "a payment model should not be sensitive to every diagnostic code (or exposure to every drug class) recorded because this will result in poorly specified coefficients and unstable estimates."[3] Such system would reward plans that engage into "diagnosis discovery" in the hope to increase future payments. Therefore, we assigned hierarchies to constrain comorbidity and drug exposure assignments (see footnotes of Table 1 and Table 2). The hierarchical classification also reduces potential for collinearity, making explanatory variables more orthogonal and increases statistical precision and estimated coefficients of serious condition/drug categories.[3] For instance, a linear trend was observed with both the respiratory and cardiac drug classes hierarchy, where the larger the number of drug classes the higher the predicted expenditures. In the drug only model, exposure to one, two, and three respiratory drug classes was associated with incremental predicted costs of $458, $1073, and $3242, respectively.

In the GA ambulatory cohort, after combining information from the two sources (drug exposure and ICD-9-CM codes), predicted cost weights associated with exposure to cardiac drugs were 50% lower in the combined models than in the drug only models. A similar trend was observed for respiratory and diabetes drugs. Likewise, cost coefficients

for hypertension and cardiac, diabetes, and respiratory conditions were lower in the combined than in the ICD-9-CM only models. In sort, combining the information from the two sources sorted out what proportion of the incremental cost was due to the mere presence of a diagnosis and to the severity of the condition: number of classes of drugs or type of drugs used, e.g., insulins vs. oral hypoglycemiants.

Model Performance

Our cost models based on demographics data performed poorly ($R^2 < 0.01$), as observed by other researchers.[3,6,7,47] Age and sex are "poor proxies of permanent health and therefore poor predictors of future health care expenditures."[31] Our study shows the addition of eligibility status (Medicare, blind-disabled Medicaid) tripled model performance, i.e., $R^2$ increased from 0.01 to 0.03, as eligibility status is a surrogate marker for disability (blind, disabled, renal failure).

The model based on drug exposure and/or ICD-9-CM information performed best with a shrunk $R^2$ of 0.15. External predictive $R^2$ on the NC sample was also higher in the combined model ($R^2$ of 0.09). Based on previous research, "20% is generally considered the current upper bond of explainable variation; the rest simply may be random or unforeseeable (such as expenditures related to accidents)."[47,48] Thus, our models explained 50 to 75% of the variation considered predictable in the GA cohort and 20 to 45% in the NC validation cohort. The demographic risk adjusters currently used in Medicare explain about 1% of the variation, whereas other widely used Medicare models have not exceeded 9%.[48] Two studies have developed Medicaid-specific risk adjustment models. Kronick developed a system of diagnostic categories, Disability Payment System (DPS), for health plans that enroll Medicaid patients with disability.[2] In prospective payment models, DPS model $R^2$ was 0.17 for a 5-state sample, and ranged from 0.16 to 0.22 by state in the disable patients group, but the DPS was not externally validated. Kroncik showed, however, that individual expenditures are 7 to 10 times more predictable for patients with a disability than enrollees with Aid to Families with

Dependent Children eligibility. He further argues that for ratesetting purposes, a large State, such as New York, "might estimate regression coefficients using its own data, whereas a smaller State might make more reliable predictions by averaging estimates from its own data with estimates from a multistate sample, adjusted to its own expenditure levels."

Ash expanded the use of the Diagnostic Cost Groups Hierarchical Condition Category (DCG/HCC) Medicare models to a Medicaid population.[3] DCG/HCC, developed over a 10-year period, use a proprietary categorization of ICD-9-CM codes into 118 Condition Categories. Ash et al. achieved with the DCG/HCC a split-sample validation $R^2$ of 0.23, with most of the data used in the development sample and the rest used for measuring model performance. Their $R^2$ performance measure was based on the correlation between observed payments and predicted costs to Medicaid, where dual Medicare-Medicaid eligible were excluded. With the same performance measure, explained variation of our out-of-sample models was between to 0.06 and 0.10, i.e., explaining between 30 and 50% of the variation considered predictable in the NC cohort.

The disadvantage of using an external validation sample versus a random split-sample is that observed average one-year costs in the development and validation samples are less likely to be equal. Indeed, NC one-year expenditures were 20% lower than GA expenditures. Recalibration of the NC expenditures might have helped improved out-of-sample $R^2$, however when predictions are recalibrated, they lose their value as an external standard.[4] To minimize the loss, we could have recalibrated the one-year NC post-index date expenditures with the ratio of GA to NC one-year pre-index date expenditures. However, Kronick showed that average annual expenditures are poorly predicted by expenditures in the previous year in the general Medicaid population.[2] While $R^2$ is one way to examine performance of cost models, it may not be the most important. $R^2$ is a measured of explained variation among enrollees. However, in a capitation environment, a more relevant measure is how well the model works for groups, as the management of risk is based on revenues for groups.[48] We therefore computed the

predictive ratios (P.R.) of mean total predicted payments to mean total observed costs to NC Medicaid for each of the three models. One-year Medicaid expenditures were overpredicted by nearly 50% as all three P.R. were between 1.43 and 1.51. Overprediction was most important for recipients with no or few prior comorbidities or exposure to drug classes (Table 8). For patients with 2 or more prior drug classes or 3 or more prior comorbidities, P.R. was inferior to 1.20, and was even undepredicted for recipients with six or more comorbidities. Twice as many NC as GA recipients did have no Medicaid expenditures in the prediction-year (15 vs. 7%) contributed to the overprediction of the models, as prospective models never predict zero costs, because no one as zero expected future health care costs.[3]

Whereas predictive ability and calibration limited the external performance of our three cost models, the true predictive power of the mortality models was not overestimated in the GA training cohort compared to the independent NC validation cohort. The large sample size and lower variability in intrinsic mortality risk factors (such as age) may explain why models performed equally well in the development and external samples, with c-statistic approaching 90% in out-of-sample NC cohort. Although we defined an homogeneous population so that age information alone would be less likely to be a single risk factor explaining a significant portion of the model variance, model with age and other demographic information achieved a c-statistic of 0.77. The addition of prior drug exposure and/or comorbidity information increased the predictive ability of our survival models by 33%. The performance of our survival models cannot be compared to that of others, as we were unable to identify a single study in the published literature that examined prospective risk factors for ambulatory populations.

Potential for Gaming the System with Drug Data

The role of a cost risk adjustment model intended to calculate future payments, is "to effectively predict costs from data that should be present in any healthcare delivery system, while limiting the rewards for undesirable behavior with respect to either

treatment or reporting."[3] Implied is the concern that payment methods can create incentives for health care providers to engage in behaviors that reap undue economic surplus by "gaming" the system. At first glance, it would seem that models based on ICD-9-CM information are less conducive to a 'gaming ' behavior than models based on drug exposure information. Arguments against and in favor of using drug exposure to risk adjust future health care expenditures have been presented previously, along with a set of specific recommendations to decrease 'gaming' opportunities. (Refer to Chapter 6: "Prospective Cost Risk Adjustment Indices for Stroke and Alzheimer's Dementia Using Administrative Data") In brief, recommendations were to not include certain drugs or therapeutic classes in the development of a risk adjustment index, to employ an *a priori* hierarchical approach to operationalize certain drug exposure classes, and to combine, whenever possible, information drug and ICD-9-CM codes a clinically meaningful manner.

Limitations

There are several limitations to this study. Our inclusion period spanned several years (1991 to 1996). We attempted to control for inflation by using the published consumer price index (CPI) for medical commodities and services. However, the CPI can only control for price inflation and not for policy and fiscal changes as well as medical advances that may have affected the reimbursement and coding of medical acts across a six-year period and across two Medicaid programs. Differences in coverage and payment systems between the two Medicaid states may also contribute to the larger number of Medicare and Medicaid blind-disabled eligible in the GA cohort.

Variables in the GA models were initially chosen by stepwise techniques, which can make the resulting models more sensitive to the characteristics of the population from which there were derived and more sensitive to overfitting.[23] However, we were careful to screen drug exposure and ICD-9-CM code-based candidate variables from prior studies that had established their relevance as potential markers of health status.[8,12,15]

Second, we used a population with a large sample size (n > 270,000) and submitted our models to the most rigorous validation procedure: external validation with an entirely independent data set, which "provides the strongest test of predictive validity."[4] We are not aware of any published risk adjustment instrument that has gone through the rigor of an external validation process for an ambulatory cohort.

Our mortality risk adjustment models were developed for use with large populations for health service research purposes, and not to guide clinical decision making at a patient level. They could now help controlling confounding by comorbidity and drug exposure burden in other Medicaid studies. When comparing physician's practices or regional health care delivery systems, patient profiles can be aggregated to describe the various mixes of medical problems most often encountered by providers. In longitudinal studies examining treatment effectiveness or quality of care, covariates identified in our mortality models could be used to control for comorbid illnesses that may affect the outcome studies.

The study showed that a model based on drug exposure data alone can provide valuable information regarding survival and future health expenditures of an ambulatory Medicaid population. With a cohort of more than 270,000 recipients, we were able to provide detailed information on the prevalence of diseases and the use of drugs in an ambulatory population. Both drugs and ICD-9-CM codes can help characterize the comorbidity burden of an ambulatory population, but used in conjunction, the two sources of information increased the sensitivity to disease prevalence. Our models provide a tool to Medicaid programs and health service researchers to initially stratify or otherwise control for varying levels of disease severity and comorbid illnesses for ambulatory Medicaid patients. The long-term goal for our prospective cost risk adjustment models is to forecast resources commensurate with actual needs of a large segment of the Medicaid population. However, further refinements and independent testing of our cost models are needed before they can reliably and accurately predict future levels of resource needs.

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TABLE 1: ICD-9-CM-based Comorbidities One Year Prior to Inclusion in the GA Ambulatory Cohort and their Operational Definitions

| Comorbidities | Recipients n (%) | ICD-9-CM Codes |
|---|---|---|
| 1. Congestive heart failure | 1,783 (0.7%) | 389.91, 402.11, 402.91,404.11, 404.13, 404.91, 404.93, 428.0-428.9 |
| 2. Myocardial infarction | 502 (0.2%) | 410-410.9, 412, 429.71, 429.79 |
| 3. Cardiac arrhythmia | 2,319 (0.8%) | 426.10, 426.11, 426.13, 426.2-426.53, 426.6-426.89, 427.0, 427.2, 427.31, 427.60, 427.9, 785.0, V45.0, V53.3 |
| 4. Valvular disease | 2,831 (1.0%) | 093.20-093.24, 394.0-397.1, 424.0-424.91, 746.3-746.6, V42.2, V43.3 |
| 5. Pulmonary circulation disorders | 306 (0.1%) | 416.0-416.19, 417.9 |
| 6. Peripheral vascular disorders | 937 (0.3%) | 440.0-440.9, 441.2, 441.4, 441.7, 441.9, 443.1-443.9, 447.1, 557.1, 557.9, 785.4, V43.4 |
| 7. Hypertension (complicated and uncomplicated) | 18,949 (6.9%) | 401.1, 401.9, 402.10, 402.90, 404.10, 404.90, 405.11, 405.19, 405.91, 405.99 |
| 8. Hemiplegia / paraplegia | 2,436 (0.9%) | 342.0-344.9 |
| 9. Other neurological disorders | 8,282 (3.0%) | 331.9, 332.0, 333.4, 333.5, 334.0-335.9, 340, 341.1-341.9, 345.00-345.11, 345.40-345.51, 345.80-345.91, 348.1, 348.3, 780.3, 784.3 |
| 10. Chronic pulmonary disease | 17,579 (6.4%) | 490-492.8, 493.00-493.91, 494, 495.0-505, 506.4 |
| 11. Diabetes, uncomplicated | 6,167 (2.3%) | 250.00 - 250.33 |
| 12. Diabetes, complicated | 2,604 (1.0%) | 250.40 - 250.73, 250.90-250.93 |
| 13. Hypothyroidism | 2,555 (0.9%) | 243-244.2, 244.8, 244.9 |
| 14. Renal failure and chronic disorders | 1,277 (0.5%) | 403.11, 403.91, 404.12, 404.92, 582-582.9, 583-583.7, 585, 586, 588-588.9, V42.0, V45.1, V56.0, V56.8 |
| 15. Liver disease | 874 (0.3%) | 070.32, 070.33, 070.54, 456.0, 456.1, 456.20, 456.21, 571.0, 571.2, 571.3, 571.40-571.49, 571.5, 571.6, 571.8, 571.9, 572.3, 572.8, V42.7 |
| 16. Peptic ulcer disease | 4.035 (1.5%) | 531-534.9, V12.71 |
| 17. Aids | 2,355 (0.9%) | 042-044.9 |
| 18. Any malignancy, including leukemia and lymphoma | 4,456 (1.6%) | 140.0-172.9, 174.0-175.9, 179-195.8, 200.00-202.38, 202.50-203.01, 203.8-203.81, 238.6, 273.3, V10.00-V10.9 |
| 19. Metastatic solid tumor | 537 (0.2%) | 196.0-199.1 |
| 20. Rheumatoid arthritis / collagen vascular disease | 2,087 (0.8%) | 701.0, 710.0-710.9, 714.0-714.9, 720.0-720.9, 725 |
| 21. Coagulopathy | 940 (0.3%) | 286.0-286.9, 287.1, 287.3-287.5 |
| 22. Obesity | 5,357 (2.0%) | 278.0 |
| 23. Weight loss / malnutrition | 257 (0.1%) | 260-263.9 |
| 24. Fluid and electrolyte disorders | 499 (0.2%) | 276.0-276.9 |
| 25. Anemias | 0 (0.0%) | 280.0-281.9, 285.9 |
| 26. Alcohol abuse | 4,790 (1.7%) | 291.1, 291.2, 291.5, 291.8, 291.9, 303.90-303.93, 305.00-305.03, V11.3 |
| 27. Drug abuse | 5,173 (1.9%) | 292.0, 292.82-292.89, 292.9, 304.00-304.93, 305.20-305.93 |
| 28. NOPD | 17,069 (6.2%) | 295.00-298.9, 299.10-299.11 |
| 29. Depression | 9,321 (3.4%) | 300.4, 301.12, 309.0, 309.1, 311 |
| 30. Cerebrovascular disease | 1,930 (0.7%) | 430-438 |
| 31. Dementia / Alzheimer | 714 (0.3%) | 290-290.9, 331-331.9, 797, 294.9 |
| 32. Complications during pregnancy | 4,180 (1.5%) | 630-639.9, 642.4-642.9 |
| 33. Complications at delivery and/or post-delivery | 12,281 (4.5%) | 660-669.9, 670-670.4, 671.3, 671.4, 671.5, 673-673.84, 674-674.94 |

ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification.
Aids: Acquired Immune Deficiency Syndrome; NOPD, Non-organic psychotic disorders.

Note on Operational Definitions: In order to account for the fact that additional diagnoses within a category more likely reflect additional diagnosis of the same underlying condition rather than additional severity of illness a hierarchy counting was developed for the following comorbidities.[12] If both uncomplicated diabetes and complicated diabetes are present, count only complicated diabetes. If both malignancies without metastasis and metastatic solid tumors are present, count only metastatic cancers. This hierarchy helped reduce multicollinearity as many patients were expected to present uncomplicated and complicated diabetes or tumor without metastasis and metastatic solid tumor simultaneously.

TABLE 2:Drug Exposure Classes One Year Prior to Inclusion in the GA Ambulatory Cohort and their Operational Definitions

| Drug Classes | Patients n (%) | Therapeutic Classes |
|---|---|---|
| 1. Cardiac agents | 2,392 (0.9%) | (1) Antiarrythmic, inotropic, cardiac vasopressor agents |
| | 7,446 (2.7%) | (2) ACE inhibitors or angiotensin II antagonists |
| | 2,751 (1.0%) | (3) Antianginal agents |
| | 2,603 (2.8%) | (4) Loop diuretics |
| 2. Antiparkinson agents | 24,293 (8.9%) | Antiparkisonian agents (anticholinergic, dopamine agonists, and miscellaneous) |
| 3. Coagulation modifiers | 2,408 (0.9%) | Coagulation modifiers (anticoagulants, antiplatelet agents, heparin antagonists, thrombolytics, miscellaneous coagulation modifiers) |
| 4. Antihypertensives | 8,327 (3.0%) | (1) First-line antihypertensive drugs (β-adrenergic blocking agents; potassium-sparing, thiazide, and miscellaneous diuretics) |
| | 22,304 (8.1%) | (2) Second-line antihypertensive drugs (peripherally and centrally antiadrenergic agents; calcium channel blocking agents; antihypertensive combinations; vasodilators agents) |
| 5. Respiratory agents | 18,403 (6.7%) | (1) Adrenergic bronchodilatators, asthma vasopressors, and |
| | 6,949 (2.5%) | bronchodilatator combinations |
| | 14,906 (5.4%) | (2) Methylxanthines |
| | | (3) Respiratory inhalants, leukotrien asthma agents, antiasthmatic combinations |
| 6. Drugs for NID diabetes | 3,355 (1.2%) | Oral hypoglycemiant agents |
| 7. Insulins | 5,226 (1.9%) | Insulins |
| 8. Antineoplastics (cancer) | 1,948 (0.7%) | Antineoplastics (alkylating, antibiotics/antineoplastics, antimetabolites, hormones/antineoplastics, miscellaneous antineoplastics, mitotic inhibitors, colony stimulating factors) and 5HT3 antagonists |
| 9. Antiepileptics / anticonvulsants | 17,008 (6.2%) | Anticonvulsants (hydantoin, succinimide, barbiturate, oxazolidinedione, certain benzodiazepine, and miscellaneous anticonvulsants) |
| 10. Acid peptic disease agents | 29,386 (10.7%) | H2 antagonists, proton pomp inhibitors, sucralfate, and antibiotherapy cocktails |
| 11. Anti-glaucoma agents | 990 (0.4%) | Ophthalmic glaucoma agents |
| 12. Antigout agents | 1,382 (0.5%) | Allopurinol, colchicine, probenecid, and miscellaneous |
| 13. Anti-hyperlipidemia, hypercholesterolemia | 2,483 (0.9%) | HMG-CoA reductase inhibitors, fibrates, sequestrants, probucol, and miscellaneous |
| 14. Antiretrovirals (aids) | 1,383 (0.5%) | Antiretrovirals: Protease, nucleoside, and non-nucleoside reverse transcriptase inhibitors |
| 15. Thyroid agents | 4.073 (1.5%) | Levothyroxine and thyroid replacement agents |
| 16. Narcotic analgesics | 4,659 (1.7%) | Narcotic analgesics |
| 17. Antidepressants | 29,771 (10.9%) | SSRI, tricyclic, MAO, and miscellaneous antidepressants |
| 18. Neuroleptics | 18,390 (6.7%) | Phenothiazine, trazodone, and miscellaneous antipsychotics |
| 19. Dementia agents | 2 (0.0%) | Donepezil and tacrine |
| 20. Antituberculosis agents | 789 (0.3%) | Ethambutol, isoniazid, rifampin, pyrazinamide, and miscellaneous |
| 21. Drug for rheumatologic conditions | 1,126 (0.4%) | Gold salts and hydroxychloroquin |
| 22. Systemic steroids | 17,330 (6.3%) | Systemic adrenal cortical steroids |
| 23. Drugs for irritable bowel disease | 155 (0.1%) | Mesalamine, olsalazine, infliximab |
| 24. End stage renal disease | 65 (0.0%) | Hematopoietic agents (marrow stimulants, erythropoietin) |

TABLE 2:Drug Exposure Classes One Year Prior to Inclusion in the GA Ambulatory Cohort and their Operational Definitions

| Drug Classes | Patients n (%) | Therapeutic Classes |
|---|---|---|
| 25. Immunosuppressive agents | 331 (0.1%) | Azathioprine, basiliximab, cyclosporine, daclizumab, muromonab-CD3, mycophenolate mofetil, and tacrolimus |
| 26. Antimigraine agents | 1,065 (0.4%) | Triptans, ergotamines, and miscellaneous combinations |
| 27. Drugs for bone diseases (Padget's disease, osteoporosis) | 95 (0.0%) | Alendronate, etidronate, pamidronate, risedronate, tiludronate, raloxifene, cacitonin, and calcium carbonate products (with or without added vitamin D) |

ACE inhibitors, angiotensin converting enzyme inhibitors; HIV, Human Immunodeficiency Virus; MAO, monoamine oxydase inhibitors; NID Diabetes, non insulin-dependent diabetes; SSRI, selective serotonin reuptake inhibitors. Note that angiotensin II antagonist and non-nucleoside reverse transcriptase inhibitors were not yet commercialized at the time of the study.

Note on Operational Definitions: Before comorbidity variables were tested for entry in the models, a hierarchy was developed between certain therapeutic classes.[15],[21]. If both non insulin-dependent and insulin-dependent diabetes drugs were present, we counted only insulin-dependent diabetes drugs. If both first- and second-line antihypertensive drugs were present, we counted only second-line antihypertensive drugs.[50]

If drugs from only one therapeutic respiratory illnesses were found for a given patient, then the dummy RESPIRATORY-1 variable was set to 1, 0 elsewhere; if two classes were found then RESPIRATORY-2 was set 1, 0 elsewhere; likewise for the RESPIRATORY-3 variable. A similar coding system was used for the therapeutic classes from the cardiac conditions for the definition of the CARDIAC-1 to CARDIAC-4 variables.

TABLE 3: Demographics and eligibility information – Ambulatory Georgia and North Carolina Medicaid recipients aged 15 to 50 years between 1991 and 1995

| **Patient Group** | **Georgia Medicaid** | **North Carolina Medicaid** |
|---|---|---|
| Number of patients | 273,970 | 120,000 |
| Demographic Information | | |
| Age in years (mean; std) | 28.1 (10.1) | 28.5 (9.8) |
| Age range in years | 15 – 50 | 15 - 50 |
| Gender: female (%) | 205,999 (75%) | 91,398 (76%) |
| Race: black (%) / white (%) / other (%) | 180,830 (66%) / 80,692 (30%) / 12,448 (4%) | 65,588 (55%) / 46,314 (39%) / 8,098 (6%) |
| Eligibility Information | | |
| Medicare eligible: yes (%) | 66,560 (24%) | 9,533 (8%) |
| Blind-disabled / Other: yes (%) | 83,820 (31%) | 23,563 (20%) |
| Outcomes-Related Information (post-observation period) | | |
| One year total direct medical costs – in 1996 dollars | | |
| Mean (std) | $2,954 ($6,562) | $2,353 ($6,901) |
| Median | $785 | $571 |
| $99^{th}$ percentile | $28,127 | $29,377 |
| Maximum | $293,170 | $506,704 |
| Percent with zero prediction-year costs | 7% | 15% |
| Expired within 7 years (%) | 7,558 (2.8%) | 1,837 (1.5%) |
| Seven-year follow-up time in months (mean; std) | 32.4 (18.5) | 32.6 (16.9) |

Std: standard deviation.

TABLE 4: ICD-9-CM-Based Comorbidity Count and Drug Exposure Classes Count One Year Prior to Index Date – Seven-Year Mortality Rates and One-Year Cost to Medicaid in Georgia Medicaid Ambulatory Recipients

| Counts | ICD-9-CM Code-Based Comorbidity | | | Drug Exposure | | |
|---|---|---|---|---|---|---|
| | Number (%) of Patients | Seven-Year Mortality | One-Year Cost | Number (%) of Patients | Seven-year Mortality | One-Year Cost |
| 0 | 179,770 (65%) | 1.6% | $1,974 | 155,693 (57%) | 1.1% | $1,843 |
| 1 | 62,806 (23%) | 3.3% | $3,751 | 52,898 (19%) | 2.5% | $2,955 |
| 2 | 19,706 (7%) | 5.8% | $5,502 | 29,125 (10%) | 4.2% | $4,203 |
| 3-4 | 9,916 (4%) | 10.9% | $8,408 | 26,810 (10%) | 7.1% | $5,924 |
| 5-6 | 1,531 (1%) | 21.6% | $11,403 | 7,495 (3%) | 13.5% | $8,275 |
| > 6 | 241 (0%) | 32.8% | $20,969 | 1,949 (1%) | 21.6% | $11,669 |
| **Total** | **273,970 (100%)** | **2.8%** | **$2,954** | **273,970 (100%)** | **2.8%** | **$2,954** |

For seven-year mortality, P value of Pearson $\chi^2$ test < 0.025 and P value of Cochran-Armitage linear trend test < 0.025*

For one-year cost, P value of Cuzick linear trend test < 0.025 with both ICD-9-CM and drug exposure counts* [32]

* P value of 0.025 was chosen *a priori* to control for test multiplicity

Table 5: Regression Coefficients by Index Type and Outcome

| | Seven-year Cox Proportional Hazards Models (Hazard Ratios) | | | One-year Robust Regression Cost Models (in 1996 $) | | |
|---|---|---|---|---|---|---|
| Candidate Variables | RX | ICD-9-CM | Combined | RX | ICD-9-CM | Combined |
| Intercept | - | - | - | 3,624 | 3,276 | 3,357 |
| Age | 1.12 | 1.11 | 1.11 | -93 | -74 | -92 |
| Black | | 1.06 | 1.11 | | 308 | 321 |
| Male | 1.79 | 2.07 | 1.98 | -2,455 | -2,251 | -2,288 |
| Age square | 0.99 | 0.99 | 0.99 | 1 | 1 | 1 |
| Age * Black | | | | | -23 | -16 |
| Age * Male | | 0.99 | 0.99 | 61 | 50 | 54 |
| Blind-Disabled | 3.09 | 3.03 | 2.87 | 1,356 | 1,333 | 1,052 |
| Medicare eligible | 1.38 | 1.55 | 1.41 | -175 | 233 | -96 |
| **Drug-based covariates** | | | | | | |
| Aids (antiretrovirals) | 8.59 | | * | 8,215 | | * |
| Rheumatologic conditions | | | | 1,080 | | |
| Cancer drugs | 2.08 | | 1.72 | 2,512 | | 1,978 |
| One class of cardiac drugs | 1.36 | | 1.37 | 725 | | 327 |
| Two classes of cardiac drugs | 2.11 | | 1.95 | 2,341 | | 841 |
| Three classes of cardiac drugs | 3.51 | | 2.87 | 4,317 | | 1,883 |
| Four classes of cardiac drugs | 5.36 | | 4.75 | 5,004 | | 2,149 |
| IBD drugs | | | | 1,795 | | 1,762 |
| Antidepressants | 0.84 | | * | 1,142 | | * |
| Oral Hypoglycemiants | | | | 386 | | |
| Antiepileptics | 1.49 | | * | 2,047 | | * |
| Antigout agents | 1.59 | | 1.54 | 567 | | |
| Glaucoma agents | | | | | | 514 |
| First-line antihypertensives | 1.19 | | 1.20 | 454 | | 170 |
| Second-line antihypertensives | 1.13 | | 1.17 | 896 | | 495 |
| Insulins | 1.82 | | * | 3,108 | | * |
| Antihyperlipidemics | 0.74 | | 0.76 | 614 | | 384 |
| Neuroleptics | 0.87 | | * | 1,993 | | * |
| Opiates | 2.27 | | 1.93 | 3,157 | | 2,718 |
| Antiparkinson agents | | | | 637 | | 668 |
| PVD agents | 1.58 | | 1.51 | 3,754 | | 2,262 |
| One class of respiratory drugs | 1.15 | | 1.15 | 458 | | 269 |
| Two classes of respiratory drugs | 1.30 | | 1.29 | 1,073 | | 735 |
| Three classes of respiratory drugs | 1.51 | | 1.71 | 3,242 | | 2,928 |
| Systemic steroids use | 1.31 | | 1.22 | 675 | | 493 |
| Immunosuppressives | | | | 3,249 | | 3,394 |
| Tuberculosis agents | 2.52 | | 1.82 | 6,638 | | 5,408 |
| Acid peptic disease drugs | 1.13 | | | 1,223 | | * |

Table 5: Regression Coefficients by Index Type and Outcome

| | Seven-year Cox Proportional Hazards Models (Hazard Ratios) | | | One-year Robust Regression Cost Models (in 1996 $) | | |
|---|---|---|---|---|---|---|
| **ICD-9-CM code-based covariates** | | | | | | |
| Aids | | 11.56 | * | | 7,915 | * |
| Alcohol abuse | | 1.26 | 1.39 | | 1,253 | 1,299 |
| Cardiac arrhythmia | | 1.27 | | | 1,306 | 947 |
| Cerebrovascular accidents | | | | | 1,209 | 1,013 |
| Congestive heart failure | | 2.46 | 1.37 | | 3,949 | 3,080 |
| Coagulopathy | | 1.65 | 1.43 | | 6,415 | 5,610 |
| Complications of pregnancy | | | | | 1,498 | 1,512 |
| CPD | | 1.19 | | | 1,244 | 857 |
| Dementia Alzheimer | | 1.25 | 1.30 | | 1,568 | 1,626 |
| Depression | | 0.85 | * | | 1,266 | * |
| Diabetes | | 1.17 | | | 1,437 | 368 |
| Diabetes with complications | | 1.71 | * | | 4,556 | * |
| Illicit drug use | | | | | 2,010 | 1,950 |
| Hemiplegia – Paraplegia | | 1.55 | 1.58 | | 6,380 | 6,279 |
| Hypertension | | 0.91 | 0.76 | | 855 | 442 |
| Liver diseases | | 2.26 | 2.04 | | 4,067 | 3,796 |
| Malignancy (any) | | 2.69 | 2.52 | | 2,276 | 2,130 |
| MI | | | | | 2,102 | 1,487 |
| Obesity | | | | | 209 | |
| Other neurological disorders | | 1.56 | * | | 2,396 | * |
| PCD | | 1.63 | 1.37 | | 4,008 | 3,246 |
| PVD | | 1.28 | | | 4,285 | 4,001 |
| NOPD | | 0.70 | * | | 2,092 | * |
| Renal failure and chronic disorders | | 2.72 | 2.37 | | 10,379 | 9,900 |
| Rheumatologic disorders | | 1.39 | 1.30 | | 1,770 | 1,322 |
| Thyroid disorders | | | | | 405 | 311 |
| Metastatic solid tumor | | 11.28 | 9.64 | | 9,574 | 8,545 |
| Ulcer diseases | | | | | 1,418 | * |
| Valvular disorders | | | | | 1,191 | 809 |
| Sudden weight loss | | 2.55 | 2.72 | | 6,958 | 6,621 |
| **Combined ICD-9-CM comorbidities and drug information** | | | | | | |
| Aids | | | 10.3 | | | 6,845 |
| Depression - antidepressants | | | 0.85 | | | 800 |
| Other neurological disorders - antiepileptics | | | 1.55 | | | 1,896 |
| Insulin – diabetes with complications | | | 1.73 | | | 2,646 |
| NOPD - neuroleptics | | | 0.86 | | | 1,831 |
| Ulcers - acid peptic disease drugs | | | 1.06 | | | 911 |

Aids: Acquired Immune Deficiency Syndrome; CPD: Chronic pulmonary disorders; IBD: Irritable Bowel Disease; MI: Myocardial infarction; NOPD: Non-organic psychotic disorders; PCD: Pulmonary circulation disorders; PVD Peripheral vascular disorders;

* represents a variable that was included in the ICD-9-CM or drug based model and that was combined with its counterpart in the combined model.
- represents a variable that was included in the ICD-9-CM or drug based model but that failed to enter its respective combined model.

Table 6: Model Statistics by Index Type and Outcome

| **GA Training Cohort (N=273,970)** | | | | | | |
|---|---|---|---|---|---|---|
| | Seven-Year Cox Proportional Hazards Models | | | One-Year Robust Regression Cost Models | | |
| | Drugs | ICD-9-CM | Combined | Drugs | ICD-9-CM | Combined |
| Number of patients | 273,970 | 273,970 | 273,970 | 273,970 | 273,970 | 273,970 |
| Maximum number of covariates | 38 | 40 | 64 | 38 | 40 | 64 |
| Included covariates | 27 | 29 | 34 | 34 | 38 | 56 |
| Event-to-variable ratio | 199:1 | 189:1 | 118:1 | - | - | - |
| $R^{2\,a}$ | - | | | 0.01 | | |
| $R^{2\,b}$ | - | | | 0.03 | | |
| Shrunk $R^{2\,c}$ | - | - | - | 0.100 | 0.126 | 0.146 |
| c-statistic [d] (20% sample) | 0.777 | | | - | | |
| c-statistic (20% sample) | 0.852 | 0.863 | 0.878 | - | - | - |
| **NC Validation Cohort (N=120,000)** | | | | | | |
| | Seven-Year Cox Proportional Hazards Models | | | One-Year Cost Models | | |
| | Drugs | ICD-9-CM | Combined | Drugs | ICD-9-CM | Combined |
| $R^{2\,a}$ | - | | | < 0.01 | | |
| $R^{2\,c}$ | - | - | - | 0.04 | 0.08 | 0.09 |
| $R^{2\,e}$ | - | - | - | 0.06 | 0.08 | 0.09 |
| c-statistic (50% sample) | 0.870 | 0.887 | 0.894 | - | - | - |
| Annualized total one-year expenditures (mean; std) | - | | | $2,399 (7,748) | | |
| Predicted total one-year expenditures (mean; std) | - | - | - | $3,623 (2,607) | $3,421 (2,589) | $3,516 (2,882) |
| Predictive Ratio [f] | - | - | - | 1.51 | 1.43 | 1.47 |

[a] Includes age, sex, race, age square, interactions between age and race, and age and sex.
[b] Includes demographic variables above and Medicaid and Medicare eligibility status
[c] Based on out-of-sample $R^2$ formula
[d] Includes age, sex, race, age square, interactions between age and race, and age and sex.
[e] Squared correlation coefficient between predicted expenditures and actual costs
[f] Predictive ratios are the ratio of mean total predicted payments to mean total observed annualized costs to Medicaid
- Statistics not applicable to the type of model

Table 7: J-Test Model Performance for Non-Nested Models in the GA Cohorts (Davidson)

| | **Base Model** | **Information Added from Model** | **One-Year Cost Models** | | |
|---|---|---|---|---|---|
| | | | **t-value** | **p-value** | **Outcome** |
| 1 | Drug Only Model (A) | Combined | 41.0 | 0.001 | A < B |
| 2 | Combined Model (B) | Drug Only | 4.9 | 0.001 | B < A |
| 3 | ICD-9-CM Only Model (C) | Combined | 44.8 | 0.001 | C < B |
| 4 | Combined Model (B) | IDC-9-CM Only | 11.2 | 0.001 | B < C |

1: Adding information from combined model to drug only model
2: Adding information from drug only model to combined model
3: Adding information from combined model to ICD-9-CM only model
4: Adding information from ICD-9-CM only model to combined model

Table 8: Predictive Ratios for Drug only, ICD-9-CM only, and Combined Models on NC out-of-sample Cohort

| **Burden Count** | 0 | 1 | 2 | 3-4 | 5-6 | >6 |
|---|---|---|---|---|---|---|
| **P.R. by count of drug classes** | | | | | | |
| %Patients | 64% | 16% | 8% | 7% | 2% | 3% |
| Drug only model | 1.99 | 1.53 | 1.40 | 1.19 | 1.14 | 1.08 |
| Combined model | 1.90 | 1.49 | 1.39 | 1.17 | 1.13 | 1.09 |
| **P.R. by count of ICD-9-CM code-based comorbidities** | | | | | | |
| %Patients | 70% | 20% | 6% | 3% | <1% | <1% |
| ICD-9-CM only model | 1.76 | 1.34 | 1.13 | 1.09 | 1.15 | 0.81 |
| Combined model | 1,80 | 1.40 | 1.17 | 1.12 | 1.14 | 0.79 |

P.R.: Predictive ratios are the ratio of total predicted payments to total observed annualized costs to NC Medicaid

Group “0”, “1”, “2”, “3 or 4”, “5 or 6”, “> 6” represent the number of drug-based comorbidities and ICD-9-CM-based comorbidities in the ICD-9-CM only models.

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# CHAPTER EIGHT

# CONCLUSIONS

The objective of this research was to develop a set of linear risk additive adjustment models specific to various Medicaid populations, while improving upon existing risk adjustment techniques. More specifically, we developed and tested the predictive ability of disease-specific risk adjustment indices for cost and mortality outcomes in patients with a stroke event and a diagnosis of Alzheimer's dementia or related dementias (AD/D). We also developed and tested risk adjustment case mix models for ambulatory Medicaid patients between the ages of 15 and 50. Administrative claims data containing prescriptions dispensed and diagnoses coded at provider visits during the year prior to the index date along with demographic and eligibility information were used to develop and validate prospective models. The study tested two research hypotheses:

1) Risk adjustment models based on drug exposure information can perform as well as the traditional models based on ICD-9-CM disease information.
2) Risk adjustment models based on combined information (ICD-9-CM diagnosis and drug exposure) can outperform models based on the use of either source of information alone and bridge some of their shortcomings.

This type of combined (drug- and diagnosis-based) risk adjustment indices represented a new venue in the field of risk adjustment. Also, very few risk adjustment models had been specifically developed and/or validated for Medicaid populations. The most stringent test of a risk adjustment model is a true external validation: the application of a 'frozen' model to a new population. Without an external validation, investigators may remain unaware that some factors represent spurious associations with the outcome

because of 'noise' in the data or multiple comparisons. Therefore, to assess whether or not the study proved or disproved our two research hypotheses, we developed our indices on the GA Medicaid training sample and tested the performance of the models on the NC out-of-sample patient cohorts. The remainder of the conclusion will only refer to the performance of the models on the NC sample, unless otherwise specified.

Hypothesis 1: Performance of drug exposure models equates that of ICD-9-CM code-based models

Unlike models in the AD/D and ambulatory cohorts, mortality models for the stroke cohort based on ICD-9-CM codes outperformed models based on drug exposure by 2 percentage points, at all three follow-up times. This is equivalent to a 15% gain in external predictive ability in favor of the ICD-9-CM models in the stroke cohort. ICD-9-CM models achieved better model performance, higher $R^2$ values, than the drug exposure model in the stroke cohort but not in the AD/D cohort.

In the AD/D cohort, the one-year predictive drug exposure cost model outperformed the model based on ICD-9-CM information by 33% whereas the two models were not different in the stroke cohort. An opposite relationship was observed in the ambulatory cohort where the ICD-9-CM code-based models outperformed the drug exposure model by 100% ($R^2$ of 0.08 and 0.04, respectively). Interestingly, ICD-9-CM models in the development sample (GA cohorts) consistently achieved a higher $R^2$ than models based on drug exposure.

In general results are variable. The performance of drug exposure models sometimes approaches or slightly exceeds that of ICD-9-CM code-based models. However, more often than not, drug exposure models underperfrom ICD-9-CM code-based models, depending on the population or the outcome studied. For instance, drug exposure models suffer a lower loss of predictive discriminative ability when switching from a development to a prediction sample in small, well-defined patient populations (i.e., AD/D and stroke). However, performance of a drug exposure model does not

equate that of an ICD-9-CM model when predicting cost outcomes in a large ambulatory cohort.

Hypothesis 2: Performance of combined models exceeds that of drug exposure and ICD-9-CM code-based models alone.

With this hypothesis, we specifically sought to test whether or not the addition of drug exposure data to an ICD-9-CM code-based model would enhance model performance or predictive ability. Overall, it did not, so that we cannot reject the null hypothesis. In all 21 mortality models developed for the three patient cohorts, combined models marginally outperformed ICD-9-CM models, if at all. In the ambulatory cohort, the combined cost model outperformed the ICD-9-CM only models by a narrow margin but outperformed the drug exposure model by more than 100%. Interestingly, in the AD/D and stroke patient cohorts, the performance of the combined one-year cost models was at par with that of ICD-9-CM only models, but did underperform that of the drug exposure model by 25% in the AD/D cohort. Again, this contrasts with the fact that combined cost models achieved higher performance than drug exposure models in the GA development sample.

Potential of Drug Exposure Information in Risk Adjustment: Is there a Future?

Mortality models based on drug exposure information had in most cases similar predictive ability than ICD-9-CM code-based models. Adding information from drug only to ICD-9-CM only models and vice versa did not meaningfully improve the predictive ability of either model alone. Although model performance was not affected, combining the information from the two sources using hierarchical categorization of certain drug exposure classes (e.g., chronic cardiac and respiratory drugs) was valuable. It helped sort out what proportion of the incremental risk of death was due to the presence of a disease (as measured by the diagnosis code) and to the severity of the condition (as measured by the number and type of drug classes). It is usually very difficult for

researchers, if not impossible, to control for disease severity in retrospective studies, unless researchers can directly access clinical information, e.g., patient clinical charts or tests results. The combination of the drug and ICD-9-CM information using simple categorization algorithms is a step toward a better sense of severity of chronic prevalent conditions such as cardiovascular, respiratory diseases, diabetes, and to a lesser extent, cancers.

The performance of cost models was variable in the sense that drug exposure models outperformed combined and ICD-9-CM only models in the AD/D cohort but not in the stroke cohort. However, an opposite relationship was observed in the ambulatory cohort. Given the paucity of disease-specific risk-adjustment models for stroke and ambulatory cohorts, our drug exposure cost models are a valuable contribution to health service researchers and Medicaid risk adjusters. We would however caution the use of drug-based models in ambulatory population where they underperformed ICD-9-CM only models by 50%.

All that said practical considerations could get in the way of our empirical findings on cost models for the ambulatory cohort. Nowadays, drug claims are adjudicated on-line and information about drug exposure is available to health plans on a weekly, and even, daily basis. Therefore, information necessary to build cost drug exposure models for year T+1 is readily and fully available at the end of year T. Information on ICD-9-CM data, however, is not yet collected and adjudicated as quickly as that for drug information. It is not rare for a plan to have to wait six to 12 months before 95% of physician, outpatient, and inpatient claims are available. Hospital claims, the ICD-9-CM rich claims, take the longest time to reach health plans and health care payers. Given the state of the information technology today, future research could examine how well ICD-9-CM code-based cost risk adjustment models for year T+1 perform based on ICD-9-CM information from the Year T-1.

<u>How useful are our Models? How and when can they be used?</u>

Mortality models based on drug exposure, ICD-9-CM codes, and combined information exhibit similar predictive abilities at a given follow-up time within the AD/D, stroke, and ambulatory cohorts. Therefore, if a researcher or a health system only had access to ICD-9-CM or drug exposure data, the predicted models would only loose/gain little incremental predictive ability. Our mortality models increase the depth of the current published models by providing tools that can help monitor outcome of care across regional providers or various health delivery systems for patients with a first diagnosis of AD/D or a first stroke event. Current models have mostly focused on outcomes of acute care hospitalizations as they were driven by hospitals' internal decisions to institute severity measurement.

Cost models in the AD/D and stroke cohorts exhibited moderate to large losses in their performance when tested on an external sample, although we showed that losses were minimized in the split-sample validation. Also, predicted $R^2$ value were always much larger than that for models based solely on demographic data. Actuaries and policy makers consider models with $R^2$ values of 0.05 useful. One example of policy research would be assessing differences in cost outcomes of AD/D or stroke patients insured by Medicaid and private pay systems. We would however recommend using these models with caution if trying to predict future capitated payment for providers with a large stroke or AD/D patient population. Recalibrating the models would allow making the average of the expected outcome equal to the actual average outcomes in their population, although recalibrated predictions lose their value as an external standard.

The combined cost model in the ambulatory population outperformed the drug only and ICD-9-CM only models. To date, there is no published cost model that has been specifically developed and validated for an ambulatory Medicaid population. The only model that has been tested for this population is the Diagnostic Cost Groups Hierarchical Condition Category model (DCG/HCC). DCG/HCC is based on a proprietary categorization of ICD-9-CM codes. One troubling issue in the choice of a risk adjustment methodology is that of transparency. There is often a lot of reluctance on a

vendor's part to provide complete information concerning their method's logic, typically due to proprietary considerations. According to Dr. Robert Brook, "If I were a purchaser, I would look for a system that is in the public domain … Purchasers should have an absolute right to know what is in the severity adjustment model – that should not be kept proprietary. It would be like saying, 'Take this drug to get better, but I am not going to tell you its name or its chemical compound.'"[1] We would therefore advocate that our combined ambulatory model is a good place to start for a Medicaid program that seeks to assess future capitation payments.

In conclusion, both drug exposure or ICD-9-CM codes can characterize the comorbidity burden of ambulatory, AD/D, and stroke patient populations independently, but used in conjunction with a hierarchical classification, the two sources of information increased the sensitivity to disease burden. Our prospective mortality risk adjustment models provide a tool to Medicaid programs and health service researchers to initially stratify or otherwise control for varying levels of disease severity and comorbid illnesses. A long-term goal for our prospective cost risk adjustment models is to forecast resources commensurate with actual needs of a large segment of the Medicaid population or for patient cohorts that will exact an increasing toll on Medicaid resources. However, further refinements (re-calibration) and independent testing of our disease-specific cost models is needed before they can reliably and accurately predict future levels of resource needs in Medicaid cohorts. Drug exposure represents a new venue of information in risk adjustment that should enhance the quality and performance of health service research studies.

[1] Woolsey,C. "Buyer's Guide to Outcome Management Systems," Business Insurance, June 28, 1993, 23.

# APPENDICES

# APPENDIX A

## LETTER TESTIFYING TRANSFER OF NC MEDICAID DATA FROM THE NC DEPARTMENT OF MEDICAL ASSISTANCE TO THE UNIVERSITY OF GEORGIA

North Carolina Department of Health and Human Services
**Division of Medical Assistance**
1985 Umstead Drive - Post Office Box 29529 - Raleigh, N.C. 27626-0529
Courier Number 56-20-06

James B. Hunt, Jr., Governor
H. David Bruton, M.D., Secretary

Paul R. Perruzzi, Director

September 24, 1998

TO WHOM IT MAY CONCERN:

Jean-Francois Ricci, Ph.D Candidate, College of Pharmacy, University of Georgia, first approached us as the State Medicaid agency to acquire North Carolina Title XIX paid claims and recipient and provider eligibility data as well as all pricing files in July 1997. We initially provided file descriptions and data element definitions in order that he might develop a formal data request to the Division Deputy Director. Computer technical staff of the University of Georgia and the State of North Carolina Information Processing Center coordinated tape hardwares resources of both installations. It was agreed that M. Ricci would supply cartridge tapes initialized on the University of Georgia computer hardware. Twenty (20) tapes were sent in January 1998. Test tapes were created and mailed in February 1998. Upon confirmation that the data tapes could be read, additional cartridge tapes were provided by M. Ricci and the process of copying North Carolina Title XIX datasets began. Title XIX claims as paid January 1990 – April 1998 were copied removing or encripting confidential information. Pricing files and provider files have been copied. Eligibility files are still be copied as of this date. North Carolina staff remains in email and telephone contact with M. Ricci as he pursues completion of his project.

Daphne O. Lyon
Deputy Director

Patricia C. Slaughter
Statistician
Information Services

# APPENDIX B

## INSTITUTIONAL REVIEW BOARD APPROVAL

The University of Georgia

Office of the Vice President for Research
DHHS ASSURANCE ID NO.: M1047

Institutional Review Board
Human Subjects Office
606A Graduate Studies Research Center
Athens, Georgia 30602-7411
(706) 542-6514; 542-3199
FAX No. (706) 542-5638

# STATUS REPORT FORM FOR RENEWALS/CHANGES

Date Renewal/Change Request Received: 9/16/98 Project Number: H980679CI

Major Investigator: Mr. Jean-Francois Ricci Soc. Sec. No.: 469-21-9176

Co-Investigator(s): Dr. Bradley Martin Soc. Sec. No.: 300-56-5790

Dept./Bldg./Phone: Clinical & Administrative Sciences / Pharmacy Bldg / 2-5111

Off-Campus Address:

TITLE OF STUDY: Development and Cross-Validation of Comorbidity Indexes Based on Prescription Drugs and Medical Utilizations in the Georgia and North Carolina Medicaid Populations

45 CFD 46 Category: CR- XM X Renew NO Change(s):
Was 46.101(4)
for period: 6/23/98 - 9/30/98

Modifications:

Reviewer: Alexander -

RENEWAL OF APPROVAL PERIOD WITH NO CHANGES:

Approved: 9-18-98 (date study approved) for the period 10-1-98 (date can begin data collection) to 6-22-99 (date to end data collection)

NOTE: *Any research conducted before the approval date or after the end data collection date shown above is not covered by IRB approval, and cannot be retroactively approved.*

| Number Assigned by Sponsored Programs: | NA | Funding Agency: | NA | Form 310 Provided: | No |
|---|---|---|---|---|---|

**Your request for approval of renewal and/or changes has been approved as indicated under IRB ACTION above. If you will need to extend your approval period again or to make additional changes to your study please follow the same procedures as before.**

**For your convenience in obtaining approval of changes, extending the approval period, or closing your file we are providing you with a second copy of this form. Detach the second copy** *(RETURN COPY stamped in red)*, **complete the form as appropriate, sign and date it, then return the form to the IRB Office. Keep this original copy for your records.**

Julia Alexander

Julia Alexander, M.A.,
Chairperson, Institutional Review Board

Copy: Dr. Jeffrey Kotzan

(Rev.1/98)

# APPENDIX C

## DRUG THERAPEUTIC CLASSES

| Class | Drug Class Description | Source (1) |
|---|---|---|
| 0 | nonsense NDC | Added by Investigator |
| 1 | antibiotics | Expanded by Multum |
| 2 | amebicides | |
| 3 | anthelmintics | |
| 4 | antifungals | |
| 5 | antimalarial agents | |
| 6 | antituberculosis agents | |
| 7 | antiviral agents | Expanded by Multum |
| 8 | carbapenems | |
| 9 | cephalosporins | Expanded by Multum |
| 10 | leprostatics | |
| 11 | macrolides | |
| 12 | miscellaneous antibiotics | |
| 13 | penicillins | |
| 14 | quinolones | |
| 15 | sulfonamides | |
| 16 | tetracyclines | |
| 17 | urinary anti-infectives | |
| 18 | aminoglycosides | |
| 19 | antihyperlipidemic agents | Expanded by Multum |
| 20 | antineoplastics | Expanded by Multum |
| 21 | alkylating agents | |
| 22 | antibiotics/antineoplastics | |
| 23 | antimetabolites | |
| 24 | hormones/antineoplastics | |
| 25 | miscellaneous antineoplastics | |
| 26 | mitotic inhibitors | |
| 27 | radiopharmaceuticals | |
| 28 | biologicals | |
| 29 | allergenic extracts | |
| 30 | antitoxins and antivenins | |
| 31 | bacterial vaccines | |
| 32 | colony stimulating factors | |
| 33 | immune serums | |
| 34 | in vivo diagnostic biologicals | |
| 35 | rabies prophylaxis products | |
| 36 | recombinant human erythropoietins | |
| 37 | toxoids | |
| 38 | viral vaccines | |
| 39 | miscellaneous biologicals | |
| 40 | cardiovascular agents | Expanded by Multum |
| 41 | agents for hypertensive emergencies | |
| 42 | angiotensin converting enzyme inhibitors | |
| 43 | antiadrenergic agents, peripherally acting | |
| 44 | antiadrenergic agents, centrally acting | |
| 45 | antianginal agents | |
| 46 | antiarrhythmic agents | |
| 47 | beta-adrenergic blocking agents | |
| 48 | calcium channel blocking agents | |

| Class | | Drug Class Description | Source (1) |
|---|---|---|---|
| 49 | | diuretics | Expanded by Multum |
| 50 | | inotropic agents | |
| 51 | | miscellaneous cardiovascular agents | |
| 52 | | peripheral vasodilators | |
| 53 | | vasodilators | |
| 54 | | vasopressors | Expanded by Investigator |
| 55 | | antihypertensive combinations | |
| 56 | | angiotensin II inhibitors | |
| 57 | | central nervous system agents | Expanded by Multum |
| 58 | | analgesics | Expanded by Multum |
| 59 | | miscellaneous analgesics | |
| 60 | | narcotic analgesics | |
| 61 | | nonsteroidal antiinflammatory agents | |
| 62 | | salicylates | |
| 63 | | analgesic combinations | |
| 64 | | anticonvulsants | Expanded by Multum |
| 65 | | antiemetic/antivertigo agents | Expanded by Multum |
| 66 | | antiparkinson agents | Expanded by Multum |
| 67 | | anxiolytics, sedatives, and hypnotics | Expanded by Multum |
| 68 | | barbiturates | |
| 69 | | benzodiazepines | |
| 70 | | miscellaneous anxiolytics, sedatives and hypnotics | |
| 71 | | CNS stimulants | |
| 72 | | general anesthetics | |
| 73 | | muscle relaxants | Expanded by Multum |
| 74 | | neuromuscular blocking agents | |
| 75 | | psychotherapeutic agents | Expanded by Multum |
| 76 | | miscellaneous antidepressants | |
| 77 | | miscellaneous antipsychotic agents | |
| 78 | | miscellaneous psychotherapeutic agents | |
| 79 | | psychotherapeutic combinations | |
| 80 | | miscellaneous central nervous system agents | Expanded by Investigator |
| 81 | | coagulation modifiers | |
| 82 | | anticoagulants | |
| 83 | | antiplatelet agents | Expanded by Investigator |
| 84 | | heparin antagonists | |
| 85 | | miscellaneous coagulation modifiers | |
| 86 | | thrombolytics | |
| 87 | | gastrointestinal agents | Expanded by Multum |
| 88 | | antacids | |
| 89 | | anticholinergics/antispasmodics | |
| 90 | | antidiarrheals | |
| 91 | | digestive enzymes | |
| 92 | | gallstone solubilizing agents | |
| 93 | | GI stimulants | |
| 94 | | H2 antagonists | |
| 95 | | laxatives | |
| 96 | | miscellaneous GI agents | Expanded by |

| Class | | Drug Class Description | Source (1) |
|---|---|---|---|
| | | | Investigator |
| 97 | | hormones | Expanded by Multum |
| 98 | | adrenal cortical steroids | |
| 99 | | antidiabetic agents | Expanded by Multum |
| 100 | | miscellaneous hormones | Expanded by Investigator |
| 101 | | sex hormones | Expanded by Multum |
| 102 | | oral contraceptives | |
| 103 | | thyroid drugs | |
| 104 | | immunosuppressive agents | |
| 105 | | miscellaneous agents | Expanded by Multum |
| 106 | | antidotes | |
| 107 | | chelating agents | |
| 108 | | cholinergic muscle stimulants | |
| 109 | | local injectable anesthetics | |
| 110 | | miscellaneous uncategorized agents | |
| 111 | | psoralens | |
| 112 | | radiocontrast agents | |
| 113 | | urinary tract products | |
| 114 | | illicit (street) drugs | |
| 115 | | nutritional products | Expanded by Multum |
| 116 | | iron products | |
| 117 | | minerals and electrolytes | Expanded by Investigator |
| 118 | | oral nutritional supplements | |
| 119 | | vitamins | |
| 120 | | vitamin and mineral combinations | Expanded by Investigator |
| 121 | | intravenous nutritional products | |
| 122 | | respiratory agents | Expanded by Multum |
| 123 | | antihistamines | |
| 124 | | antitussives | |
| 125 | | bronchodilators | Expanded by Multum |
| 126 | | methylxanthines | |
| 127 | | decongestants | |
| 128 | | expectorants | |
| 129 | | miscellaneous respiratory agents | Expanded by Investigator |
| 130 | | respiratory inhalant products | |
| 131 | | antiasthmatic combinations | |
| 132 | | upper respiratory combinations | |
| 133 | | topical preparations | Expanded by Multum |
| 134 | | anorectal preparations | |
| 135 | | antiseptic and germicides | |
| 136 | | dermatologicals | Expanded by Multum |
| 137 | | topical antiinfectives | |
| 138 | | topical steroids | |
| 139 | | local anesthetics | |
| 140 | | miscellanous topical agents | |
| 141 | | topical steroid and antiinfective combinations | |
| 143 | | acne products | |

| Class | Drug Class Description | Source (1) |
|---|---|---|
| 144 | antipsoratics | |
| 146 | mouth and throat products | |
| 147 | ophthalmic products | Expanded by Multum |
| 148 | otic preparations | Expanded by Multum |
| 149 | spermicides | |
| 150 | sterile irrigating solution | |
| 151 | vaginal preparations | |
| 152 | miscellaneous skin preparations | |
| 153 | plasma expanders | |
| 154 | loop diuretics | |
| 155 | potassium-sparing diuretics | |
| 156 | thiazide diuretics | |
| 157 | carbonic anhydrase inhibitors | |
| 158 | miscellaneous diuretics | |
| 159 | first generation cephalosporins | |
| 160 | second generation cephalosporins | |
| 161 | third generation cephalosporins | |
| 162 | fourth generation cephalosporins | |
| 163 | ophthalmic antiinfectives | |
| 164 | ophthalmic glaucoma agents | |
| 165 | ophthalmic steroids | |
| 166 | ophthalmic steroid and antiinfective combinations | |
| 167 | ophthalmic nonsteroidal antiinflammatory agents | |
| 168 | ophthalmic lubricants and irrigations | |
| 169 | miscellaneous ophthalmic agents | |
| 170 | otic antiinfectives | |
| 171 | otic steroid and antiinfective combinations | |
| 172 | miscellaneous otic agents | |
| 173 | HMG-CoA reductase inhibitors | |
| 174 | miscellaneous antihyperlipidemic agents | Expanded by Investigator |
| 175 | protease inhibitors | |
| 176 | reverse transcriptase inhibitors | |
| 177 | miscellaneous antivirals | |
| 178 | skeletal muscle relaxants | |
| 179 | skeletal muscle relaxant combinations | |
| 180 | adrenergic bronchodilators | |
| 181 | bronchodilator combinations | |
| 182 | androgens and anabolic steroids | |
| 183 | estrogens | |
| 184 | gonadotropins | |
| 185 | progestins | |
| 186 | sex hormone combinations | |
| 187 | miscellaneous sex hormones | |
| 191 | narcotic analgesic combinations | |
| 192 | antirheumatics | |
| 193 | antimigraine agents | |
| 194 | antigout agents | |
| 195 | 5HT3 receptor antagonists | |
| 196 | phenothiazine antiemetics | |

| Class | Drug Class Description | Source (1) |
|---|---|---|
| 197 | anticholinergic antiemetics | |
| 198 | miscellaneous antiemetics | |
| 199 | hydantoin anticonvulsants | |
| 200 | succinimide anticonvulsants | |
| 201 | barbiturate anticonvulsants | |
| 202 | oxazolidinedione anticonvulsants | |
| 203 | benzodiazepine anticonvulsants | |
| 204 | miscellaneous anticonvulsants | |
| 205 | anticholinergic antiparkinson agents | |
| 206 | miscellaneous antiparkinson agents | |
| 207 | dopamine agonists | |
| 208 | SSRI antidepressants | |
| 209 | tricyclic antidepressants | |
| 210 | phenothiazine antipsychotics | |
| 211 | platelet aggregation inhibitors | |
| 212 | glycoprotein platelet inhibitors | |
| 213 | sulfonylureas | |
| 214 | non-sulfonylureas | |
| 215 | insulin | |
| 900 | other hyperlipidemics (sequestrant, probucol, etc.) (from class 174) | Added by Investigator |
| 901 | fibrates and niacin at more that 250 mg (from class 174) | Added by Investigator |
| 902 | niacin < 250 mg (from class 174) | Added by Investigator |
| 96A | pomp inhibitors | Added by Investigator |
| 96B | antibiotherapy - triple coktail | Added by Investigator |
| 96C | Chron's disease | Added by Investigator |
| 96D | sucralfate | Added by Investigator |
| 96E | other gastrointestinal agents | Added by Investigator |
| 80A | antidementia - Alzheimer | Added by Investigator |
| 80B | other central nervous system agents | Added by Investigator |
| 910 | osteoporosis miscellaneous hormones (from class 100) | Added by Investigator |
| 911 | misellaneous hormones (from class 100) | Added by Investigator |
| 920 | calcium carbonate (from class 117) | Added by Investigator |
| 921 | other minerals and electrolytes (from class 117) | Added by Investigator |
| 925 | calcium carbonate and vitamin D (from class 120) | Added by Investigator |
| 926 | other vitamin and mineral combinations (from class 120) | Added by Investigator |
| 54A | cardiac vasopressor agents | Added by Investigator |
| 54B | asthma vasopressor agents | Added by Investigator |
| 54C | hypotenison, chock, and anesthesia vasopressor agents | Added by Investigator |
| 930 | leukotrien asthma agents (from class 129) | Added by Investigator |
| 931 | cystic fibrosis alpha agents (from class 129) | Added by Investigator |
| 932 | sodium chloride (from class 129) | Added by Investigator |
| 933 | surfactant agents (from class 129) | Added by Investigator |
| 998 | protein lysates | Added by Investigator |
| 999 | medical and diagnostic supplies and nutritional supplements | Added by Investigator |
| | | |

| | |
|---|---|
| (1) : | * If the source indicates "Expanded by Multum" it means that the class is not used anymore but that |
| | Multum decided to expand into further subsets, e.g., cephalosporins (class 9) were divided into four |

| | | |
|---|---|---|
| | | New classes between first, second, third, and fourth generations (classes 159 to 162). |
| | | * If the source indicates "Expanded by Investigator" it means that the class is not used anymore but that the investigator decided to divide it further. |
| | | * If the source indicates "Added by Investigator" then a new class was created either from a previous Multum class (99A, 99B) or from a non-existing Multum class (e.g., classes 0, 998, and 999). |
| | | * All other classes (unmarked in the source column) represent original Multum classes. |

# APPENDIX D

## SAS PROGRAM FOR LOGISTIC MODELS ON DEVELOPMENT SAMPLE

SAS MACRO for validation of mortality comorbidity index controlling for shrinkage with bootstrap technique. The initial macro was developed by Schemper (Mittlbock M, Schemper M. Explained variation for logistic regression. Statistics in Medicine 1996; 15(19):1987-97). It was modified by JF Ricci to include shrunk c-statistic estimates with bootstrapped 95% confidence interval, to use a stepwise selection procedure, and to tally the number of times each covariate will be significant in each of the stepwise logistic model.

The list of variables in this example (age, age square, sex, ischemic, hemorrhagic stroke, Charlson, black) does not reflect the list that will be used during the build-up of the real models. It was only used to verify that the macro does what it is expected to do. For reasons of efficacy, only 500 observations were included and three bootstraps requested in this example at the debugging stage.

```
************************** PROGRAM START ****************************;

Quit;
OPTIONS NOCENTER NONOTES SOURCE;

*****************************************************************;
****  COMPUTATION OF EXPLAINED VARIATION MEASURES       ********;
****                 SUMS-OF SQUARES R-SQUARE           ********;
****                 SUMS-OF SQUARES R-SQUARE ADJUSTED  ********;
****                 ENTROPY R-SQUARE                   ********;
****                 ENTROPY R-SQUARE ADJUSTED          ********;
****                 ENTROPY R-SQUARE SHRINKED          ********;
****  AND                                               ********;
****                 C-STATISTIC DISCRIMINATION INDEX   ********;
****                 CONTROLLED FOR SHRINKAGE           ********;
****                                                    ********;
****  FOR LOGISTIC REGRESSION WITH BOOTSTRAP            ********;
****                                                    ********;
*****************************************************************;

*************** BEGINN MACRO ********************************;

%MACRO EVL_SHR (INITIAL=, DATA=, DEP= , TITLE=' ', VAR= , BOOT=0,
OUT=);

*count the number of variables list in the dep = statement;
%LET COUNT=1;
%LET WORD=%NRBQUOTE(%SCAN(&VAR,&COUNT,%STR( )));
%DO %WHILE(&WORD^=);
  %let vari&count=&word;
  %LET COUNT=%EVAL(&COUNT+1);
  %LET WORD=%NRBQUOTE(%SCAN(&VAR,&COUNT,%STR( )));
%END;
%LET COUNT=%EVAL(&COUNT-1);

*************** BEGIN BOOTSTRAP *******************************;


data _obsdata; set &data;
  %do i=1 %to &count;
    if &&vari&i=. then delete;
  %end;
  if &dep=. then delete;
run;
data _obsdata; set _obsdata end=last;
```

```
  n=_n_;
  if last then call symput('nobs',_n_);
run;

%IF &BOOT>0 %THEN
   %let bootnr=%eval(&boot+1);
%else
   %let bootnr=1;

%DO i=1 %TO &bootnr;
  %if &i>1 %then %do;
    DATA _data;
      SEED=0;
      %DO J=1 %TO &NOBS;
        CALL RANUNI(SEED,Z);
        N=INT(Z*&NOBS+1);
        OUTPUT;
      %END;
      keep n;
    RUN;
    proc sort data=_data; by n;
    data _data; merge _data(in=d) _obsdata; by n;
      if d;
    run;
  %end;
  %else %do;
    data _data; set _obsdata; run;
  %end;

**************************************************************************
The Proc logistic run the first time for the full model using no
bootstrap on original sample) and using no stepwise procedure
**************************************************************************;

  TITLE "&TITLE";
  PROC LOGISTIC DATA=_DATA DESCENDING OUTEST=_TEST
       %if &i>1 %then noprint; ;
    MODEL &DEP = &VAR / RL MAXITER=500 RSQ
       %if &i>1 %then selection=stepwise sle=0.15 sls=0.05 include=1; ;
    OUTPUT OUT=_D1 P=P_I XBETA=SCORE;
  RUN;

**************************************************************************
* Include =1 option, because if age square is significant then most
*
* of the times age is not, so then age (main effect is forced into the
*
* model).  And if age square is not significant (depending on the
*
* bootstrap sample), then age is always.  Then, in that case the
*
* include = 1 has no consequences for the stepwise model
*
**************************************************************************;

  DATA _TEST; SET _TEST; MM=1;
    KEEP INTERCEP MM;
```

```
  RUN;

  PROC SORT DATA=_D1; BY &DEP;
  DATA _D1; SET _D1; BY &DEP; MM=1;
    IF P_I=. OR &DEP=. THEN DELETE;
    KEEP &DEP P_I MM SCORE;
  RUN;

  PROC FREQ DATA=_D1 NOPRINT; TABLES &DEP / OUT=_F;
  DATA _F; SET _F; MM=1;
    P_ROH=PERCENT/100;
    IF _N_=2;
    KEEP MM P_ROH;
  RUN;

  DATA _D1; MERGE _D1 _F _TEST; BY MM;
  RUN;
  DATA _D1; SET _D1;
    n=_n_;
    ERR_E=(&DEP-P_I)**2;
    SSE+ERR_E;
    ERR_T=(&DEP-P_ROH)**2;
    SST+ERR_T;
    RESP+&DEP;
    if p_i=1 then p_i=0.999999;
    if p_i=0 then p_i=0.000001;
    ENTR_E=(&DEP*LOG(P_I) + (1-&DEP)*LOG(1-P_I));
    SS_ENE+ENTR_E;
    ENTR_T=(&DEP*LOG(P_ROH) + (1-&DEP)*LOG(1-P_ROH));
    SS_ENT+ENTR_T;
  RUN;


************* Get the C statistic from the logistic model ******;
*proc printto allows to route the procedure to an output file -
 the print = option routes the output procedure to given file;

filename printo 'c:/temp/printo.sas';
proc printto print=printo new;

PROC LOGISTIC DATA=_DATA DESCENDING OUTEST=_TEST2;
    MODEL &DEP = &VAR / MAXITER=500
     %if &i>1 %then selection=stepwise sle=0.15 sls=0.05 include=1; ;
RUN;

*stop routing the output to an external file;
proc printto;

*infile the logistic output and read the value of c statistic;
data _d2;
 infile printo;
input @30 word1 $11. @;
if word1 = 'c         =' then
    do;
        keep c;
        input c ;
        output;
```

```
   end;

data _d2;
 set _d2;
mm =1;
keep mm c;

* OUTPUT THE C STATISTIC OF THE BOOTSRAPED MODELS TO A DATA SET;
%if &i>1 %then %do;
data _d3;
  set _d2 (rename=(c=c_boot));
%end;

* OUTPUT THE C STATISTIC OF THE NON BOOTSRAPED MODEL TO A DATA SET;
%if &i=1 %then %do;
data _d0;
 set _d2 (rename=(c=c_app));
%end;


/*********** Get the variables that loaded on the model**************
* re-route the output data set so that the external file can be freed
* and read a second time.  Need to redirect the output back to its
* default location. *
* To redirect the output back to the default location simply issue the
following:*
*  proc printto
*******************************************************************
*****/

proc printto;

*******************************************************************
* Reading all variables in the model and their p value - READ ALL
* POTENTIAL VARIABLES THAT REMAINED AFTER THE STEPWISE PROCEDURE -
* THIS STEP WILL COUNT THE NUMBER OF TIMES EACH VARIABLE WAS FOUND
* SIGNIFICANT AT 0.05 AFTER THE STEPWISE SELECTION FOR EACH BOOTSTRAP
* The list given in the if variable statement below has to be edited
* every time a new input data set is used do that it contains all
* potential predictors
*******************************************************************;

data _c;
  infile printo;
input @1 variable $13. @;
if variable in ('AGE        1' 'CHARLSON   1' 'HEMORAGE   1' 'SEX
1'
             'ISCHEMIC   1'    'BLACK      1' 'AGE_SQ     1')
   then do;
        input param se wald proba;
        keep variable proba;
        output;
   end;

data _c (keep = variable in&i);
 length variable $8.;
 set _c;
```

```
if proba le 0.05 then in&i = 1;
        else in&i=0;
proc sort; by variable;

*merge the p-values score with the existing data set;
data all;
 merge _c all;
 by variable;


/*********************************************************************
* Get all the variables that loaded on the bootstrap stepwise sample
* and submit these variables to the original non-bootstrapped sample to
* obtain the c original
*********************************************************************/

data _test2; set _test2;
drop _link_ _type_ _name_ intercep _lnlike_;

proc transpose data=_test2 name=variable
               out=test2 (keep=variable col1);

* Exports the data set so that variables can be read in later for logit
model;
filename printoA 'c:/temp/variable.sas';
proc printto print=printoA new;
 data test2; set test2;
  if col1 = . then delete; drop col1;
  proc print noobs;
proc printto;

/*********************************************************************
* Count how many variables remained after the stepwise and output the
number * * to a global macro variable - the difference with the data
set _d3 is that
* the AGE will be included even though it might not be significant when
age * square loaded in the model
*********************************************************************/

data _null_;
 set test2 end=end;
 n = _n_;
 if end then call symput('nvar',left(put(n,2.)));
run;

%macro list1(j);
data _test3;
 infile printoA n=%eval(&j+1);
input @1 dummy $8.;
 if dummy = 'VARIABLE' then do;
 do i = 1 to %eval(&j);
 array all{%eval(&j)} $8. ;
 input  #(i+3) all{i} $8.;
 end;
end;
else delete;
drop i dummy;
```

```
proc print;
%mend list1;

%list1(&nvar);

filename printoB 'c:/temp/list.sas';
proc printto print=printoB new;
proc print noobs data= _test3;
proc printto;

data _null_;
 infile printoB;
 input @1 dummy $4. @;
 if dummy = 'ALL1' then do;
 input #3 @1 list $200.;
 call symput('listvar',left(list));
 end;
run;

%macro dum(i,j);
%put **** all &j covariates remaining after stepwise are ****;
%put **** &i ****;
%mend dum;
%dum(&listvar,&nvar);

* rerun the variable list into a logistic model with original sample *
* and output the c origin and c boot to a single set to get optimism ;

%if &i>1 %then %do;

filename printoC 'c:/temp/printoC.sas';
proc printto print=printoC new;
PROC LOGISTIC DATA=&INITIAL DESCENDING ;
    MODEL &DEP = &listvar / MAXITER=500;
RUN;
proc printto;

**** infile the logistic output and read the value of c statistic ****;
data _test4;
 infile printoC;
input @30 word1 $11. @;
if word1 = 'c         =' then
    do;
        keep c_orig;
        input c_orig;
        output;
   end;

data _d4;
  set _test4;
mm = 1;

*merge the c on bootsrap sample and on original sample;
data _d4;
 merge _d4 _d3;
 by mm;
optimism  = c_boot - c_orig;
```

```
%end;

*****************************************************************;

DATA _D1; MERGE _D1 _D2; BY MM;

data _d1;
    LABEL N='NR OF OBSERVATIONS'
          K='NR OF COVARIATES WITHOUT INTERCEPT'
          R2_SS='SUMS OF SQUARES R2'
          R2_SS_AD='ADJUSTED SUMS OF SQUARES R2'
          CHI='MODEL CHI-SQUARE'
          SHR='SHRINKAGE COEFFICIENT'
          R2_SS_SH='SHRINKED SUMS OF SQUARES R2'
          SSE='ERROR SUMS OF SQUARES'
          SST='TOTAL SUMS OF SQUARES'
          MSE='MEAN SQUARE ERROR'
          MST='MEAN SQUARE TOTAL'
          MSe_shr='SHRINKED MSE'
          MST_shr='MST FOR SHRINKAGE'
          stde_shr='SQUARE ROOT OF SHRINKED MSE'
          stdt_shr='SQUARE ROOT OF MST FOR SHRINKAGE'
          evl_shr='Explained Mean Standard Deviation'
          c = 'Concordance C-Statistic';

 SET _D1; BY MM;
    IF LAST.MM;
    R2_SS=1-SSE/SST;
    K=&COUNT;
    R2_SS_AD=1 - (SSE/(N-K-1))/(SST/(N-1));
    MSE=SSE/(N-K-1);
    MST=SST/(N-1);
    CHI=-2*(SS_ENT-SS_ENE);
    SHR=(CHI-K)/CHI;
    R2_SS_SH=R2_SS*SHR;
    mse_shr=(sst*(1-shr)+sse*shr)/n;
    mst_shr=sst/n;
    stdt_shr=sqrt(mst_shr);
    stde_shr=sqrt(mse_shr);
    evl_shr=1- stde_shr/stdt_shr;
  RUN;


  %if &i=1 %then %do;
    data _loop_1; set _d1; drop mm; run;
  %end;
  %else %do;
    data _d1; merge _d1 _d4; by mm;
      keep n k r2_ss r2_ss_ad r2_ss_sh shr c c_orig c_boot optimism;
      label     optimism = 'Optimism on original c'
                c_orig   = 'C on origin sample'
                c_boot   = 'C on bootstrap sample';
  run;
    proc append base=boot_r2 new=_d1; run;
  %end;
```

```
%end;  /****** end of bootstrap procedure - loop ********/

%if &boot>0 %then %do;
 proc means n mean std min max maxdec=3;
   var c_boot c_orig optimism;
   title2 'detailed analysis of c on bootstrap samples';
%end;

%if &boot>0 %then %do;
  proc univariate data=boot_r2 plot normal noprint;
     var r2_ss_ad r2_ss_sh c optimism;
     output out=_ci pctlpre=adj_ shr_ c_ opt_ pctlpts=2.5 50.0 97.5;
  run;
  data _ci;
    label adj_2_5 ='lower 95% CI'
          adj_97_5='upper 95% CI'
          shr_2_5 ='lower 95% CI'
          shr_97_5='upper 95% CI'
          c_2_5   ='lower 95% CI'
          c_97_5  ='upper 95% CI'
          opt_2_5 ='lower 95% CI'
          opt_50  ='Median Value'
          opt_97_5='upper 95% CI';
     set _ci;
  run;

  data _loop_1;
    merge _loop_1 _ci;
  run;
%end;

* Export the data set with all summary info from the bootstrap to a
   data set outside the macro environment;
DATA &OUT;
  SET _loop_1;

PROC PRINT LABEL NOOBS data=_loop_1;
  title2 'R2 UNADJUSTED (EXPLAINED VARIANCE OF OUTCOME)';
  VAR N K R2_SS sse sst;
run;

PROC PRINT LABEL NOOBS data=_loop_1;
  title2 'R2 ADJUSTED BY DEGREES OF FREEDOM (EXPLAINED VARIANCE OF
OUTCOME)';
  VAR R2_SS_AD
      %if &boot>0 %then %do; adj_2_5 adj_97_5 %end; mse mst ;
run;

PROC PRINT LABEL NOOBS data=_loop_1;
  title2 'R2 ADJUSTED BY SHRINKAGE (EXPLAINED VARIANCE OF OUTCOME)';
  VAR shr R2_SS_SH
      %if &boot>0 %then %do; shr_2_5 shr_97_5 %end; mse_shr mst_shr ;
RUN;

PROC PRINT LABEL NOOBS data=_loop_1;
  title2 'C Statistic (DISCRIMINATOIN INDEX)';
  VAR c
```

```
      %if &boot>0 %then %do; c_2_5 c_97_5 %end; ;
RUN;

PROC PRINT LABEL NOOBS data=_loop_1;
  title2 'Optimism on C Statistic (DISCRIMINATOIN INDEX)';
  VAR
      %if &boot>0 %then %do; opt_2_5 opt_50 opt_97_5 %end; ;
RUN;

PROC PRINT LABEL NOOBS data=_loop_1;
  title2 'R2 ADJUSTED BY SHRINKAGE (EXPLAINED STANDARD DEVIATION OF
OUTCOME)';
  VAR EVL_shr STDE_SHR STDT_SHR;
RUN;
title2;

*count how many times each variable was significant for each of the
bootstrap
*where the total number of bootstrap is &bootnr - 1;

data all;
 set all;
array in {*} in2-in&bootnr;
firstrun = in1;
cases = 0;
max= &boot;
format per_cent 4.1;
do i = 1 to max;
if in{i} = . then in{i} = 0;
if in{i} = 1 then cases = cases+1;
per_cent = cases *100 / max;
end;

Proc print;
var firstrun cases max per_cent;
id variable;
title 'all significant variables at 0.05 after each bootstrap';
title2 "A total of &boot bootstraps were performed";

proc datasets nolist;
  delete _d1 _test _test2 _test3 _f _obsdata _data _c _d2
         %if &boot>0 %then %do; _ci boot_r2 _d3; %end; ;
run;

%MEND;
*************** END MACRO *********************************;


libname new 'c:/jfr/stroke/data/comorbidity';

*first create a data set with all possible independent variables ;
* variables have to be created in ascending alphabetical order;
data all;
input variable $8. in0;
variable = upcase(variable);
cards;
age      1
```

```
sex      1
age_sq   1
black    1
charlson 1
hemorage 1
ischemic 1
;
proc sort; by variable;
proc print;
title 'ALL INITITIAL VARAIBLES ENTERED IN THE N MODEL - THIS IS A
CHECK';


data indexes;
 set new.trash (obs=500);
if white = 0 and black = 0 then delete;
age_sq = age * age;

%EVL_SHR (DATA=indexes,
          INITIAL=indexes,
          TITLE=Charlson Score and Stroke ,
          DEP=CENSOR ,
          VAR=age age_sq sex ischemic hemorage charlson black,
          BOOT=3,
          OUT=bootout
          );

* BE CAREFUL TO PLACE AGE AS THE FIRST VARIABLE INTO THE LIST SO THAT
WHEN THE iNCLUDE=1 SATEMENT IS USED IN THE LOGISTIC REGRESSION -
STEPWISE - IT REFERS TO THE AGE VARIABLE;


**********************************************************************;
**                                                                  **;
**  DATA       NAME OF THE DATA SET TO BE BOOTSTRAPED               **;
**  INITIAL    NAME OF THE DATA SET ** NOT ** TO BE BOOTSTRAPED     **;
**  TITLE                                                           **;
**  DEP        NAME OF THE DEPENDENT VARIABLE (SHOULD BE CODED      **;
**                  ALWAYS WITH 0/1 - 1 being the death event       **;
**  VAR        NAME OF INDEPENDENT VARIABLES SEPARATED BY A BLANK   **;
**  BOOT       nr of bootstrap samples    (DEFAULT: BOOT=0)         **;
**                   0 if no bootstrap CI should be calculated      **;
**                1000 is recommended for calculating bootstrap CI  **;
**                (WARNING: the bootstrap-calculations may          **;
**                          need a longer time for calculations     **;
**                                                                  **;
**********************************************************************;

quit;

proc print data = bootout; title 'all bootstrap statistics';

run;

****************************** PROGRAM END ***********************************;
```

# APPENDIX E

## EXTERNAL VALIDATION SAS PROGRAM FOR LOGISTIC MODELS

```
/* program that gets the Georgia model coefficients and c-statistics
   and applies the coefficients to the North Carolina population and
   get:
1) the c-statistic on North Carolina:  2 * c - 1 = Somer-s D  OR
   c = (Somer-s D + 1) / 2
2) the r-squre of the adjusted shrunk r-square  on the NC sample
3) Hosmer-Lemeshow test (p-value)                                    */


quit;
libname outga 'c:/dissertation/data/dementia/georgia/dissertation';
libname outnc 'c:/dissertation/data/dementia/north
carolina/dissertation';

title 'Testing of Dementia 6-month mortality - Drug based index on NC
       sample';

data GA;
  set outga.allvar;
sample = 'GA';
keep censor06   sample
     age       sex      black    hospital  n_homes   rxcancer
     rxcardi2  rxcardi3 rxcardi4 rxopiate
     rxrespi1  rxrespi2 rxrespi3 rxulcer;

data NC;
 set outnc.sample1;
sample = 'NC';

* create a copy of censoring variable and set original one to missing;
censor_t  = censor06;
censor06 = .;

keep censor06    censor_t sample
     age       sex      black    hospital  n_homes   rxcancer
     rxcardi2  rxcardi3 rxcardi4 rxopiate
     rxrespi1  rxrespi2 rxrespi3 rxulcer;


*******************************************************************
 Get the Somer-s D and c statisitc on the NC sample
*******************************************************************;

data together;
 set ga nc;

proc logistic descending outest = coeff noprint;
 model censor06 = age       sex      black    hospital  n_homes
                  rxcancer  rxcardi2  rxcardi3 rxcardi4 rxopiate
                  rxrespi1  rxrespi2 rxrespi3 rxulcer
              / rsquare rl lackfit;
output out=out p=pred xbeta=score;

data p2;
 set out;
if censor06 ne .;
pred2 = floor(500*pred);

PROC FREQ;
 TABLES censor06 * pred2 / noprint MEASURES;
title2 'Somer-s D for original sample on GA data';
title3 '2 * c - 1 = Somer-s D or c = (Somer-s D + 1) / 2';
```

```
* testing index on North Carolina population;
data p3;
 set out;
if censor_t ne .;

pred2 = floor(500*pred);
PROC FREQ;
 TABLES censor_t * pred2 / MEASURES noprint;
title2 'Somer-s D for predicted sample on NC data';
title3 '2 * c - 1 = Somer-s D or c = (Somer-s D + 1) / 2';


*****************************************************************
 graph predicted and observed values in 10 groups on the NC sample
*****************************************************************;

* testing index on North Carolina population;
data graph;
 set out;
if censor_t ne .;
proc sort;
 by pred;

data graph;
 set graph;
if _n_ < 501 then group = '01';
else if 501  le _n_ < 1001 then group = '02';
else if 1001 le _n_ < 1501 then group = '03';
else if 1501 le _n_ < 2001 then group = '04';
else if 2001 le _n_ < 2501 then group = '05';
else if 2501 le _n_ < 3001 then group = '06';
else if 3001 le _n_ < 3501 then group = '07';
else if 3501 le _n_ < 4001 then group = '08';
else if 4001 le _n_ < 4501 then group = '09';
else group = '10';

proc sort;
 by group;

proc means n mean sum noprint;
 var censor_t pred;
by group;
output out=graph2 sum=sum_obs sum_pred;

proc plot;
 plot sum_obs * group = 'o' sum_pred * group = 'p' / overlay;
 title3 'observed and predicted mortality by decile';


*************************************************************************
Compute the r-square of the adjusted shrunk r-square on the NC sample
*************************************************************************;

PROC SORT DATA=out; BY censor_t;
DATA out2; SET out; BY censor_t; MM=1;
 IF pred=. OR censor_t=. THEN DELETE;
KEEP censor_t pred MM SCORE;

PROC FREQ DATA=out2 NOPRINT; TABLES censor_t / OUT=_F;
DATA _F; SET _F; MM=1;
 P_ROH=PERCENT/100;
 IF _N_=2;
 KEEP MM P_ROH;
```

```
DATA out2; MERGE out2 _F ; BY MM;

DATA out2; SET out2;
    n=_n_;
    ERR_E=(censor_t-pred)**2;
    SSE+ERR_E;
    ERR_T=(censor_t-P_ROH)**2;
    SST+ERR_T;
    RESP+censor_t;
    if pred=1 then pred=0.999999;
    if pred=0 then pred=0.000001;
    ENTR_E=(censor_t*LOG(pred) + (1-censor_t)*LOG(1-pred));
    SS_ENE+ENTR_E;
    ENTR_T=(censor_t*LOG(P_ROH) + (1-censor_t)*LOG(1-P_ROH));
    SS_ENT+ENTR_T;

data out2;
    LABEL N='Number of observations'
          K='Covariates in initial model'
          R2_SS='SUMS OF SQUARES R2'
          R2_SS_AD='ADJUSTED SUMS OF SQUARES R2'
          CHI='MODEL CHI-SQUARE'
          SHR='SHRINKAGE COEFFICIENT'
          R2_SS_SH='SHRINKED SUMS OF SQUARES R2'
          SSE='ERROR SUMS OF SQUARES'
          SST='TOTAL SUMS OF SQUARES'
          MSE='MEAN SQUARE ERROR'
          MST='MEAN SQUARE TOTAL'
          MSe_shr='SHRINKED MSE'
          MST_shr='MST FOR SHRINKAGE'
          stde_shr='SQUARE ROOT OF SHRINKED MSE'
          stdt_shr='SQUARE ROOT OF MST FOR SHRINKAGE'
          evl_shr='Explained Mean Standard Deviation';

 SET out2; by mm;
    if last.mm;
    R2_SS=1-SSE/SST;
    K=34;
    R2_SS_AD=1 - (SSE/(N-K-1))/(SST/(N-1));
    MSE=SSE/(N-K-1);
    MST=SST/(N-1);
    CHI=-2*(SS_ENT-SS_ENE);
    SHR=(CHI-K)/CHI;
    R2_SS_SH=R2_SS*SHR;
    mse_shr=(sst*(1-shr)+sse*shr)/n;
    mst_shr=sst/n;
    stdt_shr=sqrt(mst_shr);
    stde_shr=sqrt(mse_shr);
    evl_shr=1- stde_shr/stdt_shr;

proc print label;
 var N K R2_SS R2_SS_AD R2_SS_SH SSE evl_shr;
title3 'R-square sum of square on NC sample';

run;


/* Note: The Somer's D statistic reported in the LOGISTIC procedure's
printed output treats the response variable as the independent variable
(usually denoted D(X|Y)).
To obtain Somer's D(Y|X) for binary response cases with single trial
syntax, create a variable of predicted probabilities using the OUTPUT
statement. LOGISTIC categorizes predicted probabilities into intervals
```

```
of length 0.002 before computing Somer's D. You can categorize your
predicted values in a DATA step with a statement like this:
      pred2 = floor(500*pred);
Then, assuming your response variable is called Y, submit the following
statements:
 PROC FREQ;  TABLES Y*PRED2 / MEASURES;  RUN;
Note that the value of Somer's D(C|R) matches (except possibly for
sign) the value given by LOGISTIC. Somer's D(Y|X) is reported as
Somer's D(R|C) except that the sign should be changed if you are not
using a descending response variable ordering.
Laslty,
remember that 2 * c - 1 = Somer's D or c = (Somer's D + 1) / 2   */


*********************************************************************
/*** Hosmer-Lemeshow tests.  This is file: H_L.INC                ***/
/*** Macros designed to test goodness of fit of                   ***/
/*** the logistic regression                                      ***/
*********************************************************************;

%macro last(list);
/* Last element from the LIST is extracted and is stored in LAST_IND */
%let i=0;
%do %while(%scan(&list,&i+1) ne );
%let i=%eval(&i+1);
%end;
%let last_ind=%scan(&list,&i);
%mend;

%macro rank2a(cutpoins);
/* This macro is used in the macro RANK2 */
/* Variable RANK2 is created on the basis of CUTPOINS */

%let i=0;
%do %while(%scan(&cutpoins,&i+1,' ')  ne  );
%let i=%eval(&i+1);
%let cut=%scan(&cutpoins,&i,' ');
if &pred > &cut then rank2=&i;
%end;
%mend;

%macro rank2(indpndnt,dpndnt,pred,cutpoins);

data temp1;
   set &data_out(keep=&pred &dpndnt &indpndnt _level_);

/* Observations with missing values for the dependent variable or any
   independent variables are omitted */
   if &pred ne . ;
   if &dpndnt ne .;

/* Ranks for Method 2 (fixed values of the estimated probability)
   are computed */

%if &cutpoins ne  %then %rank2a(&cutpoins);

run;
%mend;


%macro rank1(n_tiles);

/* Ranks for Method 1 are computed. */
```

```
proc rank data=temp1    /* TIES=HIGH or TIES=LOW */
          out=temp2 ties=high groups=&n_tiles;
var &pred;
ranks rank1;
run;
%mend;

%macro sort(pred,indpndnt,method);
proc sort data=temp2;
by rank&method &indpndnt;
run;


%mend;

%macro datastep(last_ind,indpndnt,method);
data temp3(keep=lcutpnt ucutpnt
                    nobs ncov_pat obs1 exp1 obs0 exp0 pi_k c_hat
rank&method)
     temp4(keep=c_hat df prob);

   set temp2 end=eof;
   by rank&method &indpndnt;
   retain df -2;
/* LCUTPNT  - stands for the lowest predicted probability
   UCUTPNT  - stands for the highest predicted probability
   PI_K     - stands for PI sub K
   NCOV_PAT - number of covariate patterns
   OBS0     - number of observed events
   OBS1     - number of observed NO events
   EXP0     - number of expected events
   EXP1     - number of NO expected events
*/

   retain lcutpnt 1 ucutpnt 0;

   mj+1;   *Counts nonmissing observations within covariance pattern;

   pi_k+&pred;
   if mj>0 and last.&last_ind then do;mj=0; ncov_pat+1;end;
   nobs+1;
   exp0+&pred;
   obs0+(&dpndnt=_level_);
   lcutpnt=min(&pred,lcutpnt);
   ucutpnt=max(&pred,ucutpnt);

   if last.rank&method then do;
   rank&method=rank&method+1;
   obs1=nobs-obs0;
   exp1=nobs-exp0;
   pi_k=pi_k/nobs;
   c_hat=(obs0-exp0)*(obs0-exp0);
   c_hat=c_hat/(nobs*pi_k*(1-pi_k));
   sm_c_hat+c_hat;
   df+1;
   output temp3;

   lcutpnt=1;
   ncov_pat=0;
   nobs=0;
   exp0=0;
   obs0=0;
   pi_k=0;
   end;
```

```
   if eof then do;
   c_hat=sm_c_hat;
   prob=1-probchi(c_hat,df);
   output temp4;
   end;
run;

%mend;

%macro printm(method);

proc print data=temp3 split='*' noobs;
var  lcutpnt ucutpnt nobs ncov_pat obs0 exp0 obs1 exp1 c_hat;
id rank&method;
label rank&method="GRP";
label lcutpnt='Lowest*predicted*probab.*';
label ucutpnt='Highest*predicted*probab.*';
label nobs='# of* obs.';
label ncov_pat='# of*cov.*patt.';
label obs1=' OBS *count*NO*EVENT';
label obs0=' OBS *count*  *EVENT';
label exp1=' EXP *count*NO*EVENT';
label exp0=' EXP *count*  *EVENT';
label c_hat='Hosmer *Lemesh.*stat.*';
sum  nobs ncov_pat obs1 exp1 obs0 exp0 c_hat;
run;

proc print data=temp4 split='*' noobs;
label df='Degrees of freedom';
label c_hat='Hosmer-Lemeshow statistics';
run;
%mend;

%macro printm1;
title2
"The H-L Test. Collapse based on percentiles of the estimated
probabilities.";
title3 "Logistic regression output file: &data_out.. Dependent var:
&dpndnt..";
%printm(1);
%mend;

%macro printm2;
title2
"The H-L Test. Collapse based on fixed values of the estimated
probabilities.";
title3 "Logistic regression output file: &data_out.. Dependent var:
&dpndnt..";
%printm(2);
%mend;


%macro mhl1(data_out,indpndnt,pred,n_tiles,cutpoins,last_ind);

%rank2(&indpndnt,&dpndnt,&pred,&cutpoins);
%rank1(&n_tiles);

/*  Collapse based on percentiles of the estimated probabilities.*/
%sort(&pred,&indpndnt,1);
%datastep(&last_ind,&indpndnt,1);
%printm1;
```

```
/* Collapse based on fixed values of the estimated probabilities */
%if &cutpoins ne  %then %do;
%sort(&pred,&indpndnt,2);
%datastep(&last_ind,&indpndnt,2);
%printm2;
%end;
%mend;

%macro H_L(data_out=_LAST_,
           indpndnt=,
           dpndnt=,
           pred=,
           g1=10,
           g2=0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9
);

%if (&g1= ) %then

%put Error: Macro variable 'G1' is blank. It should be a number.;

%if (&g1 ne  ) %then %do;

/* The last independent variable on the list is extracted from
   the list of independent variables. */
%let last_ind=;
%last(&indpndnt);

%mhl1(&data_out,&indpndnt,&pred,&g1,&g2,&last_ind);
%end;
%mend;


/* This file name is: H_L.SAS */
/********** Invocation of H_L macro ****************************/
* %inc 'h_l.inc';

%H_L(data_out=out,
     dpndnt=censor_t,
     indpndnt= age       sex      black    hospital  n_homes   rxcancer
               rxcardi2  rxcardi3 rxcardi4 rxopiate
               rxrespi1  rxrespi2 rxrespi3 rxulcer,
     pred=pred,
     g2=
);

run;
```

# APPENDIX F

## EXTERNAL VALIDATION STATA PROGRAM FOR LEAST SQUARED MODELS

```
version 6.0
clear
set mem 50000
display "date: $S_DATE; time: $S_TIME"

/* program that gets Huber-White estimate of the cost model for GA
   DEMENTIA - drug-based only
   Number of months the patients lived first year post-AD/D was
   applied as a weight and costs were annualized for each patient on
   the GA sample and perform validation test on NC dementia patients */

use “C:\Dissertation\Data\dementia\georgia\dissertation\allvar.dta”,
clear
set mat 100

* create a cost variable that is annualized;
generate cost = mdc_di * 12 / timecost

* create a weight variable proportional to number of months patient was
  alive first year post-AD/D so that the variance is larger for obs
  where the number of months of survival is smaller generate
  weight  = timecost / 12

#delimit;
* delete outlier that was found in drug and ICD-9-CM GA models;
drop if base_id == “SASWTISHAI”;

reg cost age age_2 hospital n_homes
             rxcardi2 rxcardi4 rxdiab2 rxepilep rxinsul rxopiate
             rxpvd  rxrespi1 rxrespi2 rxrespi3  rxulcer
            [aweight = weight], robust;
#delimit cr

* start the validation process and import out of sample NC data set

use “C:\Dissertation\Data\Dementia\North Carolina\Dissertation\
sample1.dta”, clear

generate cost = mdc_di * 12 / timecost

predict resid, residuals
predict yhat
summarize resid mdc_di cost yhat, detail

tabulate tumor malignan, row col chi2

pwcorr yhat cost, star(0.05)

summarize resid
display "mean errors = " r(mean)
generate sef = (resid  - r(mean)) * (resid  - r(mean))

summarize sef
display "sum of squared errors  = " r(sum)
generate ssef = r(sum)

summarize cost
```

```
display "mean cost = " r(mean)
generate sto = (cost - r(mean)) * (cost - r(mean))

summarize sto
display "sum of squared totals  = " r(sum)
generate ssto = r(sum)

*compute the out-of-sample r-square
generate r2_pred = 1 - (ssef / ssto)

keep ssef ssto r2_pred
list in 5000
```

* Note: Make sure that you use the number of observations that is the exact sample size in the validation sample, i.e., 5,000 patients in that example.

# APPENDIX G

## EXTERNAL VALIDATION STATA PROGRAM FOR COX PROPORTIONAL HAZARD MODELS

This is a two-part program. The first half runs the GA ambulatory Cox model for drugs and predicts proportional hazards for the NC sample. The second half calls for a STATA macro to compute the c-statistic (next page) which was provided by a STATA employee.

**PART 1:**

```
version 5.0
clear
set mem 200000
display "date: $S_DATE; time: $S_TIME"

/* program that gets survival for GA ambulatory - drug-based only
   and get c-statistic on NC sampe                                  */

use "C:\Dissertation\Data\Ambulatory\Georgia\Ph.D\gasurv.dta", clear
set mat 200

#delimit;

stcox age      age_2    gender            medicare program
      rxcancer rxdepres rxepilep rxgout   rxhta1   rxhta2   rxinsul
      rxlipid  rxopiate rxpvd    rxrheuma rxschizo rxtuberc
      rxulcer  rxrespi1 rxrespi2 rxrespi3 rxcardi1 rxcardi2
      rxcardi3 rxcardi4 rxviral;

use "C:\Dissertation\Data\Ambulatory\North Carolina\Ph.D\
        survivnc1.dta", clear;
* Selects a 50% random sample to limit obs to 60,000

sample 50;

predict hr;

summarize hr;

* Calls for the STCSTAT macro – saved in ado/personal directory
stcstat;

#delimit cr
```

Note: When setting the data set to a survival data set with command STSET, it must be done in STATA version 5.0 as the STCSTAT macro was written with version 5.0.

## **PART 2:** STCSTAT MACRO

```
*! version 1.0.0  6feb1997
program define stcstat /* [if exp] [in range] */
        version 5.0
        st_is

        local if "opt"
        local in "opt"
        local options "noSHow"
        parse "`*'"

        if "$S_E_cmd2" != "stcox" {
                error 301               /* last estimates not found
*/
        }

        st_show `show'
        di

        local wt : char _dta[st_w]
        if "`wt'" != "" {
                di in red "stcstat may not be used with weighted data"
                exit 498
        }

        local t0 : char _dta[st_t0]
        if "`t0'" != "" {
                di in red /*
        */ "stcstat may not be used with late entry or time-varing
data"
                exit 498
        }

        local t : char _dta[st_t]
        local d : char _dta[st_d]

        tempvar h Dv touse
        quietly {
                predict `h' `if' `in'
                mark `touse' `if' `in'
                markout `touse' `h'

                sort `touse' `h'
                count if `touse'
                local obs = _result(1)
                if $S_E_subj != _result(1) {
                        noi di in blu "note:  " in ye "$S_E_subj" in
blu /*
                        */ " obs used in estimating Cox model, whereas"
_n /*
                        */ _col(8) in ye _result(1) in blu /*
                        */ " obs used to calculate c statistic"
                        noi di
                }
```

```
                local D 0
                local N 0
                local T 0
                local i = _N - `obs' + 1
                while `i' < _N {
                        local j = `i' + 1

                        gen `Dv' = `d'[`i'] & `d' in `j'/l
                        replace `Dv' = 2 /*
                        */ if (!`Dv') & `d'[`i'] & `t'[`i']<=`t' in
`j'/l
                        replace `Dv' = 3 /*
                        */ if (!`Dv') & `d' & `t'[`i']>=`t' in `j'/l

                        count if `Dv' in `j'/l
                        local D = `D' + _result(1)

                        count if `Dv' & `h'[`i']==`h' in `j'/l
                        local T = `T' + _result(1)

                        count if `Dv'==1 & `h'[`i']!=`h' & `t'[`i']>`t'
/*
                        */ in `j'/l
                        local N = `N' + _result(1)

                        count if `Dv'==3 & `h'[`i']!=`h' &
`t'[`i']>=`t' /*
                        */ in `j'/l
                        local N = `N' + _result(1)

                        drop `Dv'
                        local i = `i' + 1
                }
        }

        di in gr "Number of subjects:" _col(37) "S = " in ye /*
                */ %16.0g `obs'
        di in gr "Number of comparisons:" _col(37) "D = " in ye /*
                */ %16.0g `D'
        di in gr "Number of orderings as expected:" _col(37) "N = "in
ye /*
                */ %16.0g `N'
        di in gr "Number of tied predictions:" _col(37) "T = " in ye /*
                */ %16.0g `T'
        di
        global S_5 = (`N'+`T'/2)/`D'
        di in gr _col(25) "(N + T/2) / D =" /*
                */ _col(50) in ye %7.5f $S_5
        global S_1 `obs'
        global S_2 `D'
        global S_3 `N'
        global S_4 `T'
end
exit
```