Using electronic health records to provide timely evidence for routine clinical decisions for people living with Alzheimer's Disease or Alzheimer's Related Disorders

by
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Dedication

To grandma and grandad,

lots of love & olive oil.

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"Our ultimate goal, after all, is not a good death but a good life to the very end."

-Atul Gawande, *Being Mortal: Medicine and What Matters in the End*

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Abstract

Growing emphasis on the early diagnosis of cognitive impairment and Alzheimer's disease and related dementias (ADRD) increases the demand for providers to make informed care decisions. Most of the care for people recently diagnosed with cognitive impairment or ADRD falls on primary care physicians (PCPs), as frontline providers for older adults. Many of the clinical decisions PCPs face when caring for patients with cognitive impairment are not currently supported by robust evidence. Given the heterogeneity of cognitive impairments and dementias and the expense of randomized controlled trials (RCTs), we cannot rely exclusively on RCTs to provide evidence for clinical decisions across the range of conditions and unique patient or family considerations. Unclear guidelines on treatment strategies lead to large inconsistencies in how patients are treated, potentially causing harm and exacerbating health inequities. There is a large and growing need for evidence on best practices in early dementia care using accessible, timely data, and rigorous methods.

Centering causal inference, this dissertation rigorously evaluates three important clinical decisions commonly encountered by PCPs caring for patients experiencing cognitive decline. Additionally, this dissertation leverages electronic health records from the University of California, San Francisco (UCSF) or health systems within the larger University of California (UC) system. Chapter 1 uses both traditional observational and econometric methods to explore

whether referral to specialty memory care at first diagnosis of impairment improves patient outcomes. Chapter 2 applies an emulated target trial design to investigate whether prescriptions for antidementia medications (memantine or acetylcholinesterase inhibitors) are associated with patient outcomes. Finally, many conditions, including urinary tract infections (UTIs), though not specific to patients with cognitive impairment, are more common among this population. Among people with cognitive impairment, inappropriate UTI management, specifically discordant antibiotics, may be especially harmful. Chapter 3 evaluates the performance of LASSO models predicting discordant antibiotic treatment among older adults with suspected UTIs. This dissertation demonstrates how to leverage EHRs to evaluate the efficacy of current and future innovations in dementia clinical care across diverse patients. Additionally, this work includes in-depth discussion of the limitations of causal inference methods and EHRs in this applied setting.

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List of Abbreviations

AChEIs: acetylcholinesterase inhibitors

AD: Alzheimer's disease

ADRD: Alzheimer's disease and related dementias

AUROC: Area under the Receiver Operating Characteristic Curve

CCI: Charlson Comorbidity Index

CI: Confidence interval

ED: Emergency department

EHRs: Electronic health records

HR: Hazard ratio

ICD: International Classification of Diseases

IPTW: Inverse probability of treatment weights

ITT: Intent-to-treat

IV: Instrumental variable

LASSO: Least absolute shrinkage and selection operator

MCI: Mild cognitive impairment

NPV: Negative predictive value

OR: Odds ratio

PCP: Primary care provider

PPV: Positive predictive value

PS: Propensity score

RCT: Randomized controlled trial

Rx: Prescription

SD: Standard deviation

SNOMED: Systematized Nomenclature of Medicine

UC: University of California

UCSF: University of California, San Francisco

UTI: Urinary tract infection

VaD: Vascular dementia

Chapter 1 - Referral to Specialty Memory Care for Patients with Cognitive Impairment

INTRODUCTION

Primary care providers (PCPs) care for the majority of patients experiencing cognitive impairment and make about 65% of diagnoses of mild cognitive impairment (MCI) and Alzheimer's disease and related dementias (ADRD) in the United States.[1] Despite our health system's reliance on PCPs to deliver first-line dementia care, many PCPs feel unprepared to provide it beyond starting a diagnostic evaluation.[2,3] The lack of empirical evidence surrounding care recommendations may contribute to this apprehension.

Memory specialists may be able to improve the quality-of-care for individuals with dementia and their caregivers, by connecting patients to specialized resources or clinical trials and providing expert recommendations for mitigating modifiable risk factors.[4–10] However, there is minimal evidence for whether specialty memory care improves quality-of-care or specificity of the dementia diagnosis, with only one small randomized controlled trial (RCT) finding limited effects of memory clinics on caregiver-rated quality of life.[7] Given the trend toward worse access to memory specialists,[2,11] which has rapidly deteriorated with demand for new anti-amyloid monoclonal antibody treatments,[12] it is important to identify the extent to which memory clinics improve these patient-centered outcomes.

Because this evidence is intended to inform clinical practice and resource allocation, identification of a causal effect—rather than simply a statistical association—should be a priority. RCTs of such access are not feasible. Traditional covariate-control methods are limited

by unmeasured confounding, a bias that may be magnified in electronic health records (EHR) with minimal ability to adjust for important social determinants of heath.[13–16] To provide robust empirical evidence, modern causal inference approaches, such as instrumental variables (IV) analyses, can triangulate across all available imperfect evidence.[17–19] For example, so-called physician preference IVs have been used to mitigate confounding by indication and identify a causal effect of a treatment on an outcome.[20–23] Wide variation in referral patterns among PCPs—with some clinicians routinely referring to specialist care and other PCPs typically managing care themselves—allows for application of preference IVs to identify the causal effect of referral to specialty memory care on patient-centered outcomes (Figure 1.1).

We evaluated the relationship of referral to specialty memory care with 13 quality-of-care outcomes and diagnosis specificity among a population of older adults diagnosed with cognitive impairment by their PCPs at a large health system in the San Francisco Bay Area with longitudinal follow-up in EHR. We demonstrated how covariate-control and preference-based IV models can be used together to triangulate the best possible empirical evidence regarding treatment for individuals experiencing cognitive impairment.

METHODS

Study Population

Our cohort was comprised of older adults (aged 55 and older) first diagnosed with cognitive impairment by a PCP within the University of California, San Francisco (UCSF) medical system from 2005 to 2023. We defined baseline as the first ICD-defined diagnosis of mild cognitive impairment, memory loss, Alzheimer's disease, vascular dementia, or nonspecific dementia

(Supplementary File 1.1) made by a PCP. PCPs included providers in one of 24 non-pediatric primary care departments spanning the following department specialties: internal medicine, family medicine, geriatric medicine (including home-based primary care), women's health, and executive health. Geriatric medicine was included in this primary care definition as we conceptualized that the type of clinical care geriatricians offer is more like PCPs than the care provided by specialists included in this study (neurologists and specialty memory care).

Of 10,067 individuals diagnosed with cognitive impairment in primary care, we excluded 905 (9.0%) who were diagnosed before 2005 and 1,408 (14.0%) who were younger than 55 years at diagnosis. We excluded 1,129 (11.2%) individuals who were the first or only patient seen by a provider and 1 individual with a recorded death date prior to cognitive impairment diagnosis (0.01%), for a final sample size of 6,624 patients treated by 469 clinicians. We followed this cohort for up to 5 years after baseline using a de-identified EHR database updated through August 19, 2024.[24] For de-identification and patient privacy, all dates in this dataset were date-shifted by up to 365 days. All date-shifting was consistent within an individual, allowing for accurate calculations of ages and time of events relative to baseline. The analysis was exempted by the Institutional Review Board at UCSF (IRB#23-40363). Patient informed consent was waived because analyses were conducted on preexisting data.

Referral to Specialty Care

Our primary exposure was referral to a department that provides specialized memory care, including relevant neurology departments, the Memory and Aging Center at UCSF, and geriatric psychiatry (Supplementary File 1.1). For example, general neurology was included in this

definition, but neuro-oncology and neuro-spine departments were excluded. To account for any small delays in providers registering a referral in the EHR system, referrals were included if they were recorded within 5 days after first cognitive impairment diagnosis.

Physician Preference Instrument

Our instrumental variable approach leverages variation in physician preferences as a predictor of observed referral status. Preference instruments rely on the premise that when presented with multiple treatment options with similar or unknown benefit, the provider will decide based on their preference.[20,25,26] Given large variation in primary care referral patterns and vague clinical guidelines, the benefits of specialty memory care are unclear.[1,27,28]

Physician preference was defined at a provider and patient level, as the percent of all prior patients with cognitive decline who the provider referred to specialty care. As defined, preference ranges from 0% to 100% and was allowed to vary across successive patients seen by the same provider. As preference was defined by prior patients, we expected preference to be independent of any patient-level confounders of observed referral and our outcomes, thereby satisfying a key IV assumption (Figure 1.1).

Quality-of-Care Outcomes

Based on prior literature, we identified 13 outcomes associated with quality-of-care,[29–31] defined in the EHR from 1) prescription orders, 2) healthcare utilization, or 3) ICD-defined geriatric outcomes. We used prescription orders to identify incident prescriptions for antipsychotics, benzodiazepines, and potentially inappropriate medications in older adults with cognitive

impairment (anticholinergics, antipsychotics, benzodiazepines, and "Z-drugs").[32] Clinical encounters were used to define whether an emergency department (ED) visit, hospitalization, or preventable hospitalization occurred during follow-up. Preventable hospitalizations were defined as a hospital admission for an acute and chronic ambulatory care-sensitive condition, using primary diagnoses matching ICD codes recommended by the Centers for Medicare & Medicaid Services.[33] Finally, we used ICD-9/10 codes to identify incident delirium, depression, falls, fecal incontinence, hip fractures, urinary incontinence, and weight loss (Supplementary File 1.1).

Diagnosis Specificity Outcome

We included a secondary outcome of diagnosis specificity, as prior work has hypothesized that memory clinics may provide a more specific dementia diagnosis (e.g., Alzheimer's disease [AD] instead of non-specific dementias).[4,9,10] Among individuals without a specific diagnosis from primary care at baseline (i.e., not AD or vascular dementia [VaD]), we identified the earliest date of a specific dementia diagnosis from ICD-9 and ICD-10 codes, such as AD, VaD, frontotemporal dementia, or dementia with Lewy bodies (Supplementary File 1.1).

Patient- and Provider-level Covariates

We adjusted our models for patient- and provider- level confounders measured at baseline. Patient-level covariates included age (years), sex (female or male), self-reported race (Asian, Black, Other, or White), self-reported Hispanic identity (Hispanic, not Hispanic, or unknown), insurance used for baseline visit (private, public, or self-pay), categorical indicator for year of diagnosis (2005-2010, 2011-2015, 2016 and after), and diagnosed cognitive condition (ADRD, MCI or memory loss). Provider-level covariates included medical degree (MD/DO or other),

medical specialty (family medicine, geriatrics, internal medicine, or other), and provider's case complexity. For each patient, we defined their provider's case complexity as the percentage of patients their provider treated with a chronic comorbidity in the year of their cognitive impairment diagnosis (see Supplementary File 1.1 for list of conditions and corresponding ICD codes). Although there is no consensus on the best measure of case complexity, this definition is consistent with prior studies adjusting for case-mix.[34]

To better characterize this cohort of patients, we also used the following characteristics descriptively: marital status (married, single, widowed, other), smoking status (current, former, never, unknown), years since first UCSF clinical encounter, average number of encounters in the year prior to baseline, and history of comorbidities at baseline (diabetes, depression, hypertension, congestive heart failure, chronic kidney disease, and stroke). We additionally described providers using the following characteristics: sex (male, female), average number of patients seen per year, and average number of patients experiencing cognitive impairment per year. When describing provider characteristics, one outlier was removed for having seen an average of 33,782 patients annually, an erroneous number likely due to an unresolvable error within the EHR database.

Observational Model

Our primary model fit Aalen additive hazards models of time to each of 14 outcomes from observed referral status, with adjustment for age, sex, race, Hispanic identity, insurance status, year of diagnosis, cognitive condition, provider degree, provider specialty, and patient complexity. The Aalen additive hazards model measures the absolute difference in the hazard

comparing patients who were referred to those who were not. Participants were censored 100 days after their last encounter recorded in the EHR database (selected based on the distribution of time between visits in this cohort, Supplementary File 1.2), death, or end of study period (5 years after baseline). Deaths were identified from EHR linkage to California death records. For incident outcomes (i.e. medication or diagnostic-based outcomes), participants with prevalent prescriptions or diagnoses of interest were removed from the cohort.

Secondary observational models fit two probit regressions at 1-, 2-, and 5-years post-baseline including models 1) for the primary outcome among survivors and 2) for a composite outcome of the outcome of interest, death, or censoring among the whole cohort. These regressions included the same adjustment set and removal of prevalent outcomes when appropriate.

All these models produced an intent-to-treat estimate of the association between referral and quality-of-care outcomes. We measured referrals to rather than actual encounters with specialty memory care because actual use of specialty care is confounded by numerous unmeasured patient, family, and system level factors. We evaluated the amount of cross-over (the percent of the unreferred who nonetheless completed a visit with a specialty memory care clinic) and referral take-up (the percent of those referred who completed a visit with specialty memory care over follow-up).

Instrumental Variable Model

To investigate causal relationships between referral to specialty memory care and quality-of-care, we compared observational models to an IV model using physician preference as an

instrument. Four main conditions must be met for an IV to be valid.[35,36] First, the relevance condition entails that the instrument strongly predicts the exposure. We confirmed the strength of our physician preference instrument using a traditional F-statistic from a linear model and presented the magnitude of the association using an odds ratio from an unadjusted logistic regression. Second, the independence assumption requires no unmeasured confounders of the instrument and outcome. This assumption cannot be proven to be true, but plausibility can be assessed based on measured confounders. As provider case-mix is considered the largest confounder of preference IVs,[25] we included adjustment for provider characteristics and provider's patient complexity. Third, the exclusion restriction assumption requires that the only effect of preference on our outcome operates through referral to specialty care. While this assumption is not verifiable, we explored one of the few plausible violations, i.e., that providers who frequently refer to specialty memory care also refer to other departments. Finally, we adopt the monotonicity assumption, in which the effect of the IV only generalizes to "compliers". In the context of preference instruments, compliers are patients, who when treated by different providers, would only ever receive the provider's preferred treatment.[25,37] We provided detailed characterizations of the patients and providers included in this cohort to define who these compliers may be, with further discussion of the limitations of monotonicity.

We used Aalen additive hazard models using a control-function approach: first calculating the residual for the instrument from a linear regression of referral on preference and confounders, and second, modeling time to our outcome of interest from observed referral status, the residual from the first equation, and confounders.[38] IV models were adjusted for the same covariates as

observational models, with censoring occurring 100 days after their last encounter, death, or end of study period, and had confidence intervals calculated from bootstrapped standard errors.

Secondary IV models used a bivariate probit approach, which assume underlying, latent normally-distributed exposure and outcome variables.[39] Fully adjusted bivariate models were fit for primary outcomes at 1-, 2-, and 5-years after baseline among survivors. To account for censoring and death, we also fitted fully adjusted bivariate models for a composite outcome of the outcome of interest or death at each time point among the whole cohort.

Bivariate probit models were conducted using StataMP 18. All other analyses were conducted in R (version 4.1.3; 2022-03-10).

Sensitivity Analyses

We included 3 sensitivity analyses. First, as we anticipated ICD-defined diagnoses to be subject to measurement error, we included a sensitivity analysis using direct measurements for weight, the only diagnosis with a frequently measured correlate. Specifically, we repeated analyses using the most recent measurements of weight at baseline, 1-, 2-, and 5-years after baseline. We excluded 34 weight measurements (0.01%) with values greater than 625 pounds due to potential measurement error. Linear regressions for weight (in lbs.) were fit at 1, 2, and 5 years from observed referral status among survivors, adjusted for baseline weight and the same set of covariates. IV models used a two-stage least squares approach to estimate the association between referral status and weight, also additionally adjusted for baseline weight.

Second, given varying opinions of whether geriatrics falls under primary or specialty care,[40] we excluded diagnoses made by geriatricians (n excluded=578) and repeated our primary analyses Aalen additive hazard models.

Third, we repeated our primary analysis with an extended measurement window for referral to account for referrals that occur after initial diagnosis. For this analysis, we restricted to individuals who lived and were not lost to censoring by two years after cognitive impairment diagnosis (n=3,164). We defined referral in the two years after diagnosis, with follow-up starting at two years after diagnosis.

RESULTS

Patient and Provider Characteristics

Our final analytic sample included 6,624 individuals diagnosed with ADRD (25.9%), MCI (12.4%), or memory loss (61.7%) by a PCP (mean [SD] age at diagnosis, 74.7 years [8.2], 61.8% female, 52.8% White; Table 1.1). Of this group, 1,019 (15.4%) were referred to specialty memory care at the time of diagnosis. Those who were referred were more likely to have a diagnosis of memory loss (74% versus 60%) and had more clinical encounters with UCSF in the year prior to this diagnosis (34 encounters vs. 28).

These diagnoses were made by 469 unique clinicians, consisting of 21% family medicine clinicians, 5% geriatricians, 31% internists, and 43% with another primary specialty (Supplementary File 1.1). On average, the providers who referred more frequently saw fewer

patients with cognitive impairment per year (14.1% of patients vs. 18.4%). Geriatricians also referred less frequently compared to other primary care specialties.

Observational Analyses of Referral with Outcomes

At 5 years after diagnosis, prescription for potentially inappropriate medications was the most common outcome (55.7% of the cohort), and hip fracture the least common outcome (4% of the cohort; Supplementary File 1.1). Death and loss to follow-up were common: 41% of the cohort was lost to follow-up (Supplementary File 1.1) and 22% were deceased (Supplementary File 1.1) within 5 years of diagnosis. Censoring was differential by referral group. At most endpoints (1, 2, and 5-years), individuals who were referred were less likely to have died or been lost to follow-up compared to individuals who were not referred.

Referral was not significantly associated with 5-year cumulative hazard of any quality-of-care outcomes except for depression (hazard difference: 0.093, 95% CI: 0.008-0.179), though the estimate for antipsychotics (0.06, 95% CI: -0.013, 0.133; Table 1.2) was increasing and consistent with clinically meaningful effects. Referral was also associated with increased average instantaneous hazard of depression (Supplementary File 1.1). Plots of time-varying trends indicate that referral may be associated with increased short-term hazard of healthcare utilization (i.e. emergency room visits and hospitalizations), but confidence intervals were wide (Figure 1.2). Referral to memory care was also strongly associated with increased 5-year cumulative hazard of receiving a more specific dementia diagnosis (0.094, 95% CI: 0.037, 0.150; Table 1.2), and time-varying trends show association was present within the first year after diagnosis (Figure 1.2).

In secondary models using bivariate probit models, referral was associated with increased risk of diagnostic specificity among survivors throughout the first 5 years after diagnosis (Supplementary File 1.3). Referral was associated with increased risk of hospitalization and ED visits at years 1 and 2.

Some patients who were not referred to memory care at baseline received specialty care during follow-up: 1,833 (32.7%) of those not referred to specialist care at their initial diagnosis had a confirmed visit with specialty memory care within 5 years of diagnosis (Supplementary File 1.1).

Preference IV Analysis

Physician preference for referral was strongly predictive of actual referral (F-statistic = 637); a 10-percentage point increase in prior patients referred was associated with 1.33 times the odds of observed referral (95% CI: 1.30-1.37). In IV analyses, referral to specialty memory care was only associated with decreased 5-year cumulative hazard of weight loss (hazard difference = -0.348, 95% CI: -0.601, -0.094). Referral was not associated with other quality-of-care outcomes or diagnosis specificity (Table 1.2), though estimates were consistent with potentially meaningful effect sizes and confidence intervals were wide. Most point estimates hovered close to the null over time, for example delirium and fecal incontinence, or were consistent in direction with covariate-control models, like weight loss and hospitalizations (Figure 1.3). Additionally, some IV estimates were large in magnitude, like urinary incontinence with a 5-year cumulative hazard of 0.147, but with confidence intervals too wide to detect an effect. In IV estimated models, referral was not associated with diagnosis specificity (Figure 1.3).

In secondary IV analyses using bivariate probit models, referral was associated with decreased risk of weight loss at year 1 after diagnosis among survivors (Supplementary File 1.3).

We also evaluated a potential violation of the exclusion restriction assumption, in which physician preference for referral to specialty memory care could also be predictive of referral to other clinical services. Individuals who were referred at baseline were more likely at every timepoint to have been referred to other services than individuals who were not referred (Supplementary File 1.1). Among the referred group, the most common of these other referrals were to radiology (n=229), physical therapy (n=199), and gastroenterology (n=127) out of 2,406 total referrals.

Sensitivity Analyses

In covariate-control and IV models, referral to specialty memory care was not associated with directly measured weight at 1-, 2-, or 5-years after baseline (Supplementary File 1.1). All IV estimates were consistent with increased weight loss, whereas models using ICD-defined weight loss indicated referral was associated with decreased risk of weight loss. Finally, traditional observational models produced point estimates closer to the null than IV models. For example, referral to specialty care was associated with a modest -0.033-pound weight difference at year 5 in an observational model (95% CI: -2.396-2.329), whereas IV models estimated this difference to be –3.838 (95% CI: -13.676-6.000).

Results were similar when excluding diagnoses made by geriatricians, and the magnitude of the association with weight loss was larger (IV hazard difference: -0.419, 95% CI: -0.645, -0.192; Supplementary File 1.1). There was no association between referral and quality-of-care in either observational or IV models when using an extended two-year measurement window of referral (Supplementary File 1.1), though estimates were less precise due to smaller sample sizes.

DISCUSSION

We evaluated the intent-to-treat relationships between referral from primary care to specialty memory care and quality-of-care outcomes among patients with cognitive impairment. Referral was associated with increased cumulative hazard of diagnosis specificity and depression diagnosis use in covariate-control models, though these relationships were not present in IV models. IV models suggested decreased cumulative hazard of hip fracture and delirium, and increased hazard of antipsychotics prescriptions, prescriptions for potentially inappropriate medications, hospitalizations, and urinary incontinence. Despite the clinically meaningful effect sizes, these IV models were not sufficiently powered to provide precise estimates. While referral was associated with decreased risk of weight loss in IV models, the opposite relationship was observed when using directly measured weight. The qualitative difference between these models demonstrates the need for causal models and evidence triangulation in the context of work with EHRs.[41,42] Taken together, we found that referral to memory care was observationally associated with more diagnosis specificity and increased depression risk, but otherwise conflicting evidence for the role of memory care in improving patient quality-of-care.

While we show some evidence for an association between referral and worsened QoC, like increased prescriptions for potentially inappropriate medications, this may be due to increased healthcare utilization. For example, loss to follow-up and death was differential by treatment group. Referral to more clinical care logically leads to more healthcare utilization, including more diagnoses and prescriptions.[43] Further work is needed to identify whether any effect of referral on these outcomes is due to detection bias.

This work is inconsistent with prior literature hypothesizing a minimal effect of specialty memory care on patient quality-of-care outcomes.[1,44,45] Covariate-control models suggested increased risk of depression, while IV models suggested harmful to beneficial effects of specialty memory care. Given the range of the plausible estimates in this work, future studies in larger samples are needed to further triangulate a causal effect.[17–19] As access to specialty memory care is currently limited and wait lists are likely to be exacerbated by the approval of anti-amyloid medications,[12] this research question is especially timely. Notably, we have not considered other important outcomes with mixed evidence for benefit or harm, such as changes in cognition,[46,47] self-reported quality of life,[48,49] and caregiver wellbeing.[50,51] Where possible, future work should also consider the effect of specialty memory care on these outcomes.

The validity of our IV analyses relies on four assumptions.[25,35,36] First, we confirmed a strong association between physician preference and referral to specialty memory care. Second, although we cannot confirm the independence assumption is met, we adjusted for the most common confounder of preference IV analyses, case mix.[25] Third, we found a potential violation of the exclusion restriction assumption, in which providers with a preference for referral to

specialty memory care also refer to other clinical departments. This pleiotropy is a limitation of the present analysis to the extent that these referrals (primarily to radiology, physical therapy, and gastroenterology) influenced quality-of-care, and this is a priority for future work. Lastly, we must assume this effect only generalizes to "compliers", i.e., those individuals whose physician's preferences determined whether they were referred. Our estimates do not apply to individuals who would always be referred to specialty care or never referred to care, given their own preferences and characteristics. This assumption is challenging to interpret in the context of preference instruments, and deterministic monotonicity is thought to rarely hold.[25,37] As we were unable to quantify this bias, we aimed to describe our providers and patients in this cohort as thoroughly as possible to attempt to classify this subpopulation of compliers.

Our work has some notable limitations, in addition to the limitations of IV outlined above. The most important limitation is the imprecision of the IV estimates, without which causal interpretation of the associations are subject to caveats. We also cannot rule out the presence of residual confounding, such as by patient education. Further, even in the covariate-controlled models, we lacked the power to stratify by racial and ethnic identity. As there are large racial disparities in access to primary care and specialist dementia care,[1,11] this is an important future direction for researchers with access to larger clinical datasets. This work was done within a specific healthcare context. We limited our analyses to primary care providers, though we recognize that emergency departments also play an important role in providing dementia care to vulnerable older adults.[52] Additionally, these results may not be generalizable to healthcare systems that do not require referrals to receive specialty care or [53] to primary care departments with integrated memory care services.[4,54] The present analysis also does not consider any

heterogeneity in care received within specialty memory care, when there may be meaningful difference by specialist seen. Finally, the intent-to-treat estimates produced by this work may have been biased towards the null, as there was some group crossover present.

This project also has notable strengths. Minimal observational work has investigated the associations between specialty memory care and patient-centered outcomes. By centering triangulation in our approach, we identified conflicting evidence across these two methods. Our results suggest that traditional covariate-control approaches overestimate point estimates, so augmenting these methods with IV or similar approaches is important. Additionally, we have demonstrated another application of physician preference analysis, which we believe has potential to address other clinical questions of dementia care.

In conclusion, we found that referral to specialty memory care was consistent with increased hazard of diagnosis specificity and depression in both observational models. While IV models were underpowered, they also suggested referral may reduce risk of delirium and hip fracture in addition to increases in healthcare utilization. Future work should further evaluate these causal relationships with more statistical power as our best estimates represented clinically meaningful effect sizes. Collaborations across multiple health care systems or analyses within very large systems will be necessary to complete this goal. This work would be needed to help identify any benefits of specialty care, which would help identify which patients would benefit from this care and define future clinical guidelines and recommendations.

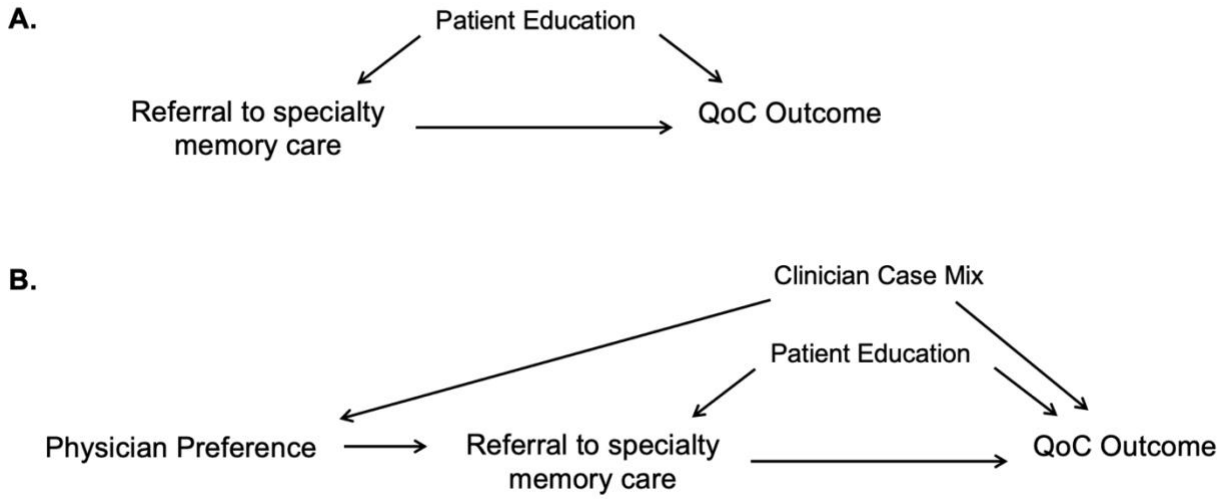

Figure 1.1: Directed acyclic graphs for observational and instrumental variable models. Using a covariate-control approach, the relationship between referral and quality-of-care is confounded by unmeasured confounders, such as patient education which is not defined in electronic health records (Panel A). Preference for referral is independent of these patient-level confounders, allowing for a less-biased estimate for the association between referral and quality-of-care (Panel B). The main confounder of this IV is clinical case mix, which can be defined using available EHR data.

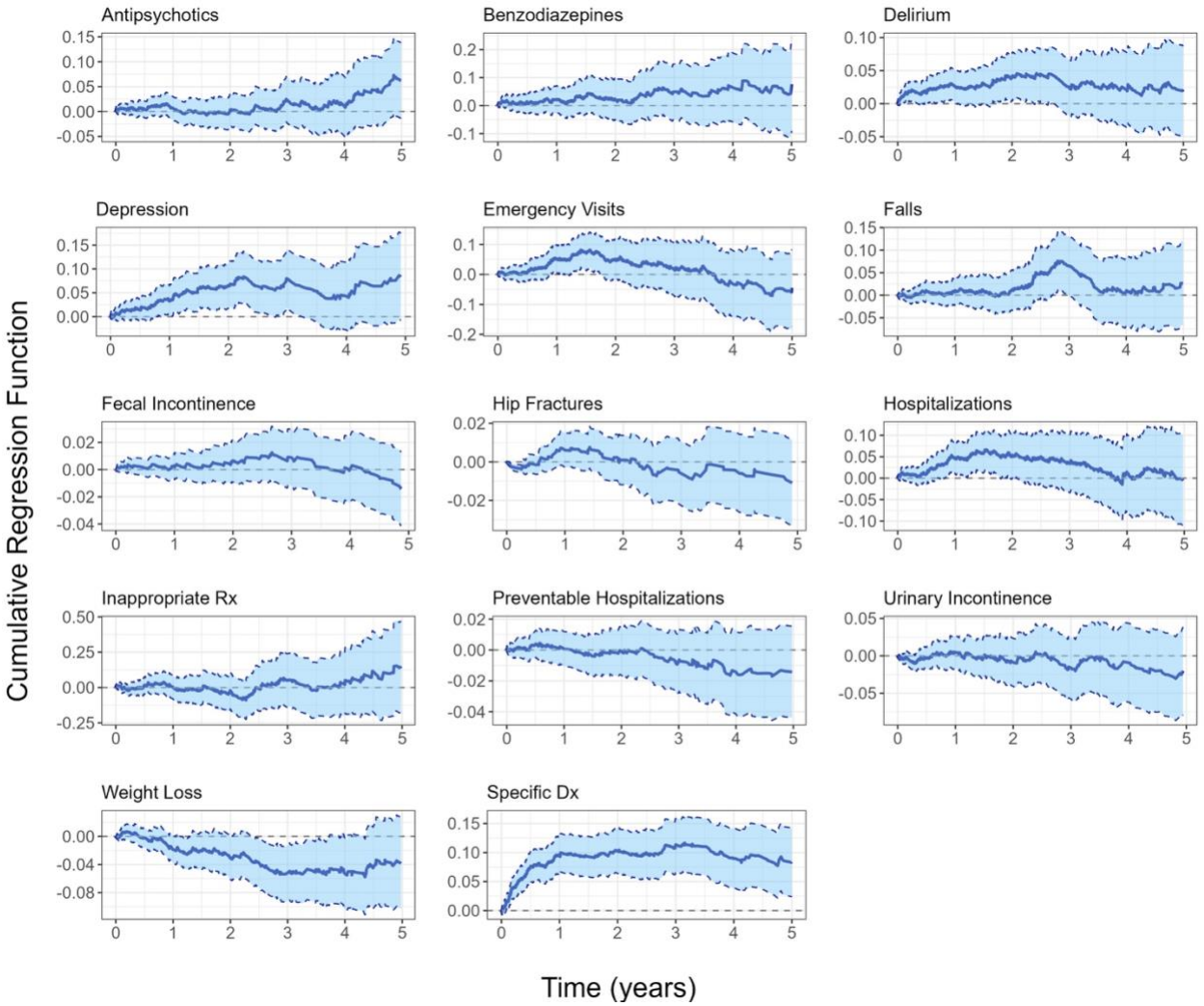

Figure 1.2: Time-varying coefficients for referral to specialty memory care from observational models.

Coefficients from Aalen additive hazards models using covariate control for 13 quality-of-care outcomes and diagnosis specificity. Dotted lines represent the 95% confidence intervals for estimates. Models were adjusted for age, sex, self-reported race, self-reported Hispanic identity, insurance type, categorical indicator for year of diagnosis, diagnosed cognitive condition, provider medical degree, provider medical specialty, and provider's case complexity.

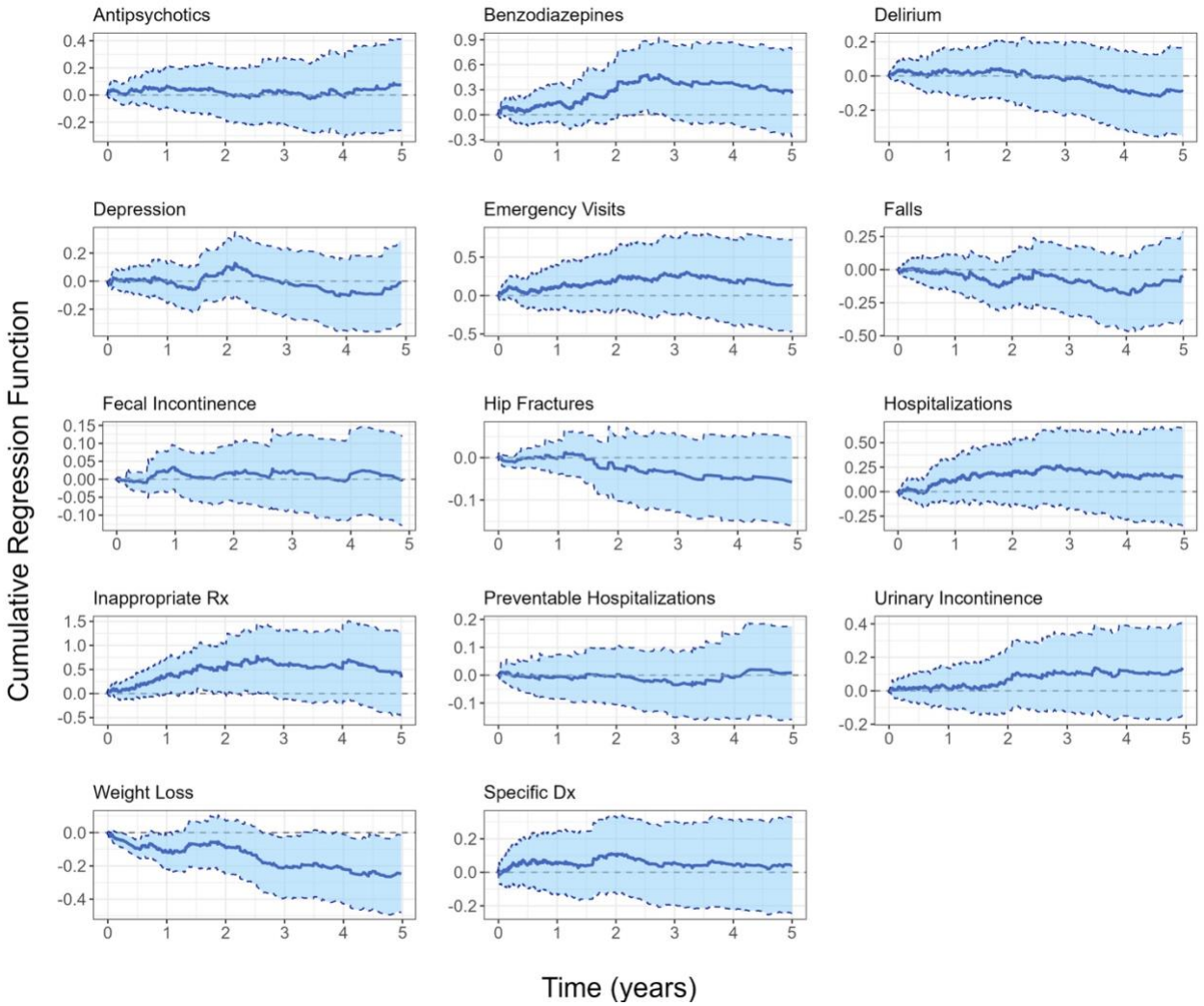

Figure 1.3: Time-varying coefficients for referral to specialty memory care from instrumental variable models.

Coefficients from instrumental variable models (Aalen additive hazards) for 13 quality-of-care outcomes and diagnosis specificity. Dotted lines represent the 95% confidence intervals for estimates from bootstrapped standard errors. Models were adjusted for age, sex, self-reported race, self-reported Hispanic identity, insurance type, categorical indicator for year of diagnosis, diagnosed cognitive condition, provider medical degree, provider medical specialty, and provider's case complexity.

Table 1.1: Descriptive characteristics of analytic cohort.
Characteristics measured at time of ADRD, MCI, or memory loss diagnosis by a UCSF primary care clinician. Values are n(%) or mean(sd).

Characteristic		**Referred at diagnosis (n=1,019)**	**Not referred at diagnosis (n=5,605)**	**Total analytic cohort (n=6,624)**
Model covariates				
Age (years)		73.7 (8.27)	74.9 (8.21)	74.7 (8.23)
Female		586 (57.7)	3,510 (62.6)	4,096 (61.8)
Racial Identity				
	Asian	255 (25.0)	1,452 (25.9)	1,707 (25.8)
	Black	80 (7.9)	441 (7.9)	521 (7.9)
	Other	133 (13.1)	767 (13.7)	900 (13.6)
	White	551 (54.1)	2,945 (52.5)	3,496 (52.8)
Hispanic ethnicity				
	Yes	74 (7.3)	471 (8.4)	545 (8.2)
	No	911 (89.4)	4,948 (88.3)	5,859 (88.5)
	Unknown	34 (3.3)	186 (3.3)	220 (3.3)
Insurance Type				
	Private	134 (13.2)	531 (9.5)	665 (10.0)
	Public	753 (73.9)	3,669 (65.5)	4,422 (66.8)
	Self-Pay	132 (13.0)	1,405 (25.1)	1,537 (23.2)
Cognitive Condition				
	ADRD	152 (14.9)	1,565 (27.9)	1,717 (25.9)
	MCI	116 (11.4)	704 (12.6)	820 (12.4)
	Memory Loss	751 (73.7)	3,336 (59.5)	4,087 (61.7)
Additional descriptive covariates				
Marital Status				
	Single	182 (17.9)	996 (17.8)	1,178 (17.8)
	Married	455 (44.7)	2,331 (41.6)	2,786 (42.1)
	Widowed	219 (21.5)	1,525 (27.2)	1,744 (26.3)
	Other	163 (16.0)	753 (13.4)	916 (13.8)
Smoking Status				
	Never	583 (57.2)	3,145 (56.1)	3,728 (56.3)
	Former	400 (39.3)	1,954 (34.9)	2,354 (35.5)
	Current	34 (3.3)	165 (2.9)	199 (3.0)
	Unknown	2 (0.2)	341 (6.1)	343 (5.2)
Years as patient at UCSF		16.0 (11.0)	15.3 (11.3)	15.4 (11.2)
Average number of encounters in year before baseline		34.2 (30.4)	27.8 (28.3)	28.8 (28.7)
History of diabetes		341 (33.5)	1,854 (33.1)	2,195 (33.1)
History of depression		404 (39.6)	1,961 (35.0)	2,365 (35.7)
History of hypertension		728 (71.4)	4,055 (72.3)	4,783 (72.2)
History of congestive heart failure		150 (14.7)	848 (15.1)	998 (15.1)

Characteristic	Referred at diagnosis (n=1,019)	Not referred at diagnosis (n=5,605)	Total analytic cohort (n=6,624)
History of chronic kidney disease	127 (12.5)	662 (11.8)	789 (11.9)
History of stroke	138 (13.5)	762 (13.6)	900 (13.6)

Table 1.2: Cumulative coefficients from Aalen additive hazard models.
The coefficient for referral to specialty memory care represents cumulative excess risk over 5 years of follow-up. Confidence intervals for the instrumental variable model were calculated from bootstrapped standard errors. Models were adjusted for age, sex, self-reported race, self-reported Hispanic identity, insurance type, categorical indicator for year of diagnosis, diagnosed cognitive condition, provider medical degree, provider medical specialty, and provider's case complexity.

Outcome	**Sample Size**	**Cumulative coefficient for referral (95% CI)**	
		Observed Model	**Instrumental Variable Model**
Antipsychotics Rx	5,960	0.06 (-0.013, 0.133)	0.111 (-0.265, 0.486)
Benzodiazepine Rx	4,352	0.065 (-0.076, 0.207)	-0.058 (-0.564, 0.448)
Delirium	5,665	0.017 (-0.047, 0.082)	-0.182 (-0.404, 0.04)
Depression	4,259	0.093 (0.008, 0.179)	-0.07 (-0.359, 0.219)
Emergency department visit	6,624	-0.025 (-0.143, 0.094)	-0.069 (-0.644, 0.505)
Falls	4,658	0.042 (-0.046, 0.13)	-0.008 (-0.375, 0.359)
Fecal Incontinence	6,303	-0.009 (-0.034, 0.017)	-0.021 (-0.153, 0.111)
Hip Fracture	6,313	-0.009 (-0.03, 0.012)	-0.078 (-0.175, 0.019)
Hospitalization	6,624	0.001 (-0.098, 0.101)	0.07 (-0.399, 0.539)
Potentially Inappropriate Rx	3,438	0.146 (-0.162, 0.454)	0.527 (-0.384, 1.437)
Preventable Hospitalization	6,624	-0.013 (-0.041, 0.014)	0.02 (-0.144, 0.184)
Urinary Incontinence	4,885	-0.002 (-0.059, 0.056)	0.147 (-0.138, 0.431)
Weight Loss	5,117	-0.033 (-0.094, 0.027)	-0.348 (-0.601, -0.094)
Diagnosis Specificity	5,870	0.094 (0.037, 0.15)	0.027 (-0.235, 0.29)

Chapter 2 - Memantine, Acetylcholinesterase Inhibitors, and Quality-of-Care Outcomes Among Patients with Cognitive Impairment

INTRODUCTION

Primary care providers (PCPs) are a crucial source of dementia care in the United States, as they make 65% of all diagnoses of cognitive impairment and prescribe the majority of anti-dementia medications.[1,55] Until very recently, PCPs only had the option of prescribing one or both of two FDA-approved drug classes: acetylcholinesterase inhibitors (AChEIs) and/or memantine. Despite providing modest gains in cognition,[56,57] these medications remain common, with between 30-60% of individuals with cognitive impairment receiving a prescription at some point.[55,58] Because of their regular use, it is also necessary to evaluate whether they have other effects on patients.

Randomized control trials (RCTs) assessed how AChEIs and memantine affect patient quality-of-life as a secondary outcome. There is minimal evidence that AChEIs improve quality-of-life when used alone, though some RCTs showed small benefits in functional status[59–62] and others found evidence for negative psychiatric events.[63] There is additionally minimal evidence for improvements in quality-of-life or functional status on memantine monotherapy.[64] However, when used together, dual therapy can modestly improve quality-of-life.[65,66] These trials have limited generalizability given that structured RCTs don't reflect real-world use of medications and often underrepresent racial and ethnic groups who are disproportionately burdened by dementia.[67–69] Observational studies can address these key limitations of RCTs, but they are susceptible to more biases. A recent review found that 57% of studies evaluating medication effectiveness using claims-based data had immortal time bias and 44% had prevalent user bias.[70]

Careful consideration of these biases is warranted when evaluating the efficacy of anti-dementia medications in observational data.

Emulating target trials can minimize immortal time and prevalent user biases.[71,72] By designing an observational study to mimic a hypothetical RCT for the same research question, observational data can come close to estimating an intent-to-treat (ITT) analysis from an RCT, though it cannot rule out unmeasured confounding. To our knowledge, no observational study has applied this framework to evaluate anti-dementia medications. Given the recent approval of new classes of anti-amyloid biologics, it is important to demonstrate how emulated target trials can be applied to evaluate these medications in the future.[73]

By emulating target trials for each anti-dementia medication, we estimated the intent-to-treat effect of memantine or AChEIs on quality-of-care outcomes using electronic health records (EHRs) from a large network of healthcare providers in California. Given the potential gaps in measured covariates in the EHR data, we additionally evaluated the likelihood of residual confounding in a sample of All of Us Research Program participants with more comprehensive survey and clinical data.

METHODS

Study Population

Our cohort was comprised of adults aged 55 and older diagnosed with cognitive impairment by a PCP within the University of California medical system from 2012 to 2024. EHRs were available from the University of California Data Warehouse, which included diagnoses, medications, and

encounters from six University of California health systems.[74] We defined primary care departments as departments that were both: 1) mapped as an outpatient department in the EHR system and 2) included a term indicative of primary care in the department name (ex. "General Health", "Family Medicine", etc.). This definition included 471 departments and spanned the following specialties: internal medicine, family medicine, geriatric medicine (including home-based primary care), and executive health.

Of 61,539 individuals diagnosed with cognitive impairment in primary care, we excluded 7,543 (12.3%) who were younger than 55 years at diagnosis. Additionally, to ensure appropriate matching with non-initiators, we excluded individuals who were initially prescribed memantine (n=4,430, 7.2%) or AChEIs (n=7,993, 13.0%) prior to first cognitive impairment diagnosis. These exclusions resulted in an analytic sample of 49,566 for memantine and 46,003 for AChEIs. Additionally, only birth year was available in this de-identified dataset. Ages were calculated assuming a birthdate in the middle of the year (July 2nd). The current analysis was confirmed exempt by the Institutional Review Board at the University of California, San Francisco (IRB#23-40363). The requirement for patient informed consent was waived since analyses were conducted on preexisting data.

Target Trial Emulation

To address common biases in pharmacoepidemiology, specifically prevalent user and immortal time biases, we used an emulated target trial framework to motivate our study design and analytic plan.[71,75] We first identified important design components of two theoretical RCTs for anti-dementia medications (memantine, AChEIs) and quality-of-life. For example, this

theoretical RCT for AChEIs would randomize older adults with cognitive impairment to either receive AChEIs or placebo, start follow-up time at point of initiation, and prioritize an intent-to-treat model for the primary analysis. Second, we used these components to guide the analysis of our observational data, with care to closely align the eligible sample and statistical analysis (Table 2.1). While observational data does not have randomization or placebo control groups, we were able to closely align our definition of the exposure (initiation versus non-initiation), baseline (matched initiation date), and the selection of a statistical model (ITT). We created separate trials for memantine and AChEI initiation.

Quality-of-Care Outcomes

Given limitations of claims-based data, we identified a panel of 11 outcomes associated with quality-of-life and mortality,[29–31] defined in the EHR from either 1) incident prescription orders, 2) healthcare utilization, 3) SNOMED CT-defined (Systematized Nomenclature of Medicine Clinical Terms) incident geriatric outcomes, or 4) death. We used prescription orders to identify incident antipsychotic and benzodiazepine use. Clinical encounters were used to define whether an emergency department (ED) visit or hospitalization occurred during follow-up. We used SNOMED codes to identify incident delirium, depression, falls, hip fractures, fecal incontinence, and urinary incontinence. (Supplementary File 2.1). Finally, we identified date of death from EHRs, which included updated linkage to California death records.

Initiation of Anti-Dementia Medications and Creation of Cohorts

From our eligible sample of UC patients, we created trials separately for anti-dementia medication type and outcome. We identified first-time initiators of memantine or AChEIs

(donepezil, rivastigmine, and galantamine) during the study period from prescription orders. Using incidence density sampling, we matched each initiator with up to 5 individuals who had not yet initiated the anti-dementia medication of interest and who were an active patient in the UC system at the time of initiator's initiation. We matched these participants on birth year (distance matched, with a maximum 5-year difference), most recent cognitive impairment diagnosis (memory loss, mild cognitive impairment [MCI], Alzheimer's disease and related dementias [ADRD]), and time (i.e. non-initiators were active patients in the UC system at time of initiator's first prescription). For trials of incident outcomes (prescriptions and geriatric outcomes), we removed participants with prevalent prescription use or diagnoses from the eligible sample of initiators and non-initiators. Non-initiators could be matches for multiple initiators (on different initiation dates), and initiators could serve as controls prior to their first initiation of an anti-dementia medication. Follow-up time began for both initiators and non-initiators at the matched initiation date (defined from here as baseline). The matching process created 20 unique cohorts for each medication and outcome, as models for prevalent outcomes (ED visits, hospitalizations) and death were evaluated in the same cohort.

Covariates

We identified 8 pre-baseline covariates from EHR, including race (Asian, Black, other, unknown, White), ethnicity (Hispanic or Latino, not Hispanic or Latino, unknown), sex (male or female), other anti-dementia medication use (i.e. for a memantine trial, whether or not they had previously or currently used an AChEI), UC site (UCD, UCI, UCLA, UCR, UCSD, and UCSF), count of encounters in the year prior to baseline, count of prescription orders in the year prior to baseline, indicator for having a visit with a neurologist in the year prior to baseline, history of

sensory impairments (Supplementary File 2.1), history of mobility problems,[76] and Charlson Comorbidity Index (CCI). CCI was calculated using the comorbidity package in R (version 1.1.0), using adapted and validated SNOMED codes.[77]

Inverse Probability of Treatment Weights

For each cohort, we modeled the probability of anti-dementia medication initiation (memantine or AChEI) in a logistic regression from pre-baseline covariates, excluding matched factors (age, cognitive impairment diagnosis, and year of trial) because by design these variables were not associated with medication initiation in the analytic data. For initiators, stabilized weights were calculated as the proportion of initiators in the cohort divided by their predicted probability of initiation given covariates (i.e. their propensity score). For non-initiators, stabilized weights were calculated as the proportion of non-initiators in the cohort divided by one minus their propensity score (1-PS). Analyses were restricted to individuals with propensity scores from the 1st and 99th percentile. If an initiator was dropped, all their matched non-initiators were also dropped. Final models additionally adjusted for decile of propensity score.

Statistical Analysis

For each combination of anti-dementia medication and outcome (i.e. 22 trials), we evaluated intent-to-treat Cox proportional hazard models for our quality-of-care outcome, censored at death, a lapse in healthcare utilization of half a year (including visits and prescription orders), or end of study period (12-13-2024). In addition to the IPTW-stabilized weights, all models were adjusted for covariates, matched factors (age [years], cognitive impairment diagnosis [memory

loss, MCI, and ADRD], and trial year [continuous]), and deciles of propensity score. To account for any clustering, robust standard errors were used.

We considered four secondary analyses. First, we considered changes in treatment assignment in a per protocol analysis. These models included additional censoring for changes in anti-dementia medication use. Initiators were censored at first 60-day lapse in their medication use, defined as 60 days after the end date on their medication order. Non-initiators were censored when they initiated the anti-dementia drug of interest. Second, we stratified primary ITT and per protocol models by cognitive impairment diagnosis (memory loss, MCI, and ADRD). Third, we limited the eligible sample to patients with a diagnosis of Alzheimer's disease, the primary indication for both medications.[78,79] We created new matched samples and reran models for this population. Fourth, we evaluated the potential for effect modification by concurrent use of the other anti-dementia medication. For example, when evaluating memantine initiation, we investigated the potential of interaction by concurrent acetylcholinesterase inhibitor use.

Bias Analysis

As EHRs are susceptible to residual confounding as there are few social history variables available,[13,15,16] we assessed the extent to which our results could be biased by residual confounding. First, we calculated e-values for each statistically significant ITT estimate in the whole sample. The e-value is a convenient way to summarize vulnerability to unmeasured confounding bias. It is defined as the magnitude of an effect an unmeasured confounder would need to have on anti-dementia medication initiation and the outcome to fully account for the observed association. E-values assume the strength of association of the confounder with the

exposure is identical to the association with the outcome, although unmeasured confounding may still fully account for the observed HR if the association of the confounder with the exposure is weaker but the association with the outcome is stronger (or vice versa).[80] E-values were calculated using the 'EValue' package in R (version 4.1.3).

Second, we identified predictors of memantine or AChEI initiation in a sample of 5,247 All of Us participants with cognitive impairment. The All of Us research program, which enrolls individuals living in the US through over 340 sites, includes a sociodemographic and health behavior survey at enrollment. As most participants also agree to link their EHR data, we were able to look at a larger range of predictors of medication initiation in this sample than EHRs alone. We fit logistic regressions for ever receiving a prescription of memantine or AChEIs from predictors of interest. We split up predictors into two groups. Our primary model included 8 predictors not available in UC EHRs, in addition to age (years, defined as date of first prescription for initiators and date of survey for non-initiators), sex (male, female, other/unknown), and race (non-Hispanic Asian, non-Hispanic Black, Hispanic, non-Hispanic White, other, missing): education (less than high school, high school, some college, college or above, missing), smoking status (smoker, non-smoker, missing), alcohol use (yes, no, missing), income (less than 10k, 10-25k, 25-35k, 35-75k, more than 75k, missing), marital status (married, living with partner, divorced, separated, widowed, never married, missing), general health (excellent, very good, good, fair, poor, missing), birth country (outside US, US, missing), health insurance coverage (yes, no, missing). Our secondary model included all predictors from the primary model, plus 13 overlapping covariates with UC EHR: healthcare utilization and self-reported indicators for history of comorbidities at survey (cancer, hypertension, asthma, coronary

heart disease, chronic kidney disease, dementia, heart failure, stroke, congestive heart failure, heart attack, diabetes, obesity). Additionally, we ran both models with and without adjustment for ever use of the other anti-dementia medication. By comparing the strength of these predictors to our calculated e-values, we were able to identify whether any of the variables measured in All of Us would be likely to have meaningfully confounded our emulated trial estimates. All analyses were conducted in R (versions 4.3.2 and 4.1.3).

RESULTS

Sample characteristics

From eligible samples of 49,566 for memantine and 46,003 for AChEIs, there were 6,061 initiators of memantine (8.2%) and 9,784 initiators of AChEIs (21.3%) from which we created our matched cohorts. Propensity score distributions for memantine and AChEI initiators substantially overlapped with those for matched non-initiators (Supplementary File 2.2). After dropping extreme propensity scores, matched pairs differed in birth year by a maximum of 0.006 years (Supplementary File 2.1).

Initiators of memantine had fewer prescription orders (24.9 vs 33.6) and encounters (25.6 vs 35.9) in the prior year to baseline compared to matched non-initiators (Table 2.2). Additionally, memantine initiators were much more likely to also be taking AChEIs at or before the time of memantine initiation compared to controls (69.6% vs 38.6%). Initiators of AChEIs had similar patterns, with fewer prescriptions and encounters in the year prior to baseline compared to non-initiators (Table 2.3). After weighting, covariate balance improved for both memantine (Supplementary File 2.1) and AChEI cohorts (Supplementary File 2.1).

Falls were the least common outcome, with an incidence rate of 7.35 per 1,000 person-years in the memantine cohort and 7.08 per 1,000 person-years in the AChEI cohort. In the memantine cohort, death was the most common outcome (110.67 deaths per 1,000 person-years), while emergency visits were the most common outcome in the AChEI cohort (111.85 cases per 1,000 person-years; Supplementary File 2.1)

Memantine Initiation and Quality-of-Care

Memantine initiation was associated with increased hazard of all outcomes except death and falls (Figure 2.1), including hazard of receiving an antipsychotic prescription (HR = 1.60, 95% CI: 1.45-1.75), emergency room visits (HR = 1.19, 95% CI: 1.08-1.30), and depression (HR = 1.44, 95% CI: 1.26-1.64). Point estimates were largely consistent when stratified by most recent cognitive impairment diagnosis, except memantine initiation was associated with decreased hazard of death among those with ADRD (HR = 0.94, 95% CI: 0.87-1.01) but increased hazard of death among those with memory loss (HR = 1.39, 95% CI: 1.17-1.66; Supplementary File 2.1). Estimates for memantine initiation were similar in rematched samples restricted to patients with AD (Supplementary File 2.2).

There was qualitative interaction by concurrent AChEI use for the association between memantine initiation and death. Among individuals concurrently or previously using an AChEI, memantine initiation was associated with decreased risk of death (HR = 0.84, 95% CI: 0.78-0.91). For individuals without prior or concurrent AChEI use, memantine initiation was associated with increased risk of death (HR=1.13, 95% CI: 1.02-1.26; Supplementary File 2.2).

By the end of study follow-up, 11.1% of non-initiators had initiated memantine (Supplementary File 2.1). In per protocol models accounting for this initiation, memantine was still associated with increased hazard of QoC outcomes, except for death (Supplementary File 2.2). Memantine initiation was strongly associated with decreased hazard of death when accounting for deviations from assigned treatment group (HR = 0.69, 95% CI: 0.60-0.78).

AChEI Initiation and Quality-of-Care

AChEI initiation was associated with increased hazard of antipsychotic initiation (HR = 1.67, 95% CI: 1.51-1.84), emergency visits (HR = 1.23, 95% CI: 1.14-1.34), and depression (HR = 1.86, 95% CI: 1.67-2.06; Figure 2.1). AChEIs were not associated with death overall (HR = 0.99, 95% CI: 0.92-1.05), but were associated with decreased mortality in the ADRD population (HR = 0.87, 95% CI: 0.79-0.95) and increased mortality in the memory loss population (HR = 1.37, 95% CI: 1.24-1.51; Supplementary File 2.1). Memantine initiation was also associated with decreased risk of death in a cohort restricted to patients with AD (HR = 0.79, 95% CI: 0.66-0.94; Supplementary File 2.2). There was not meaningful effect modification by concurrent memantine use (Supplementary File 2.2).

By the end of follow-up, 15.6% of non-initiators had received a prescription for an AChEI (Supplementary File 2.1). In per protocol models, the magnitude of the associations between AChEI initiation, falls (HR = 2.13, 95% CI: 1.42-3.21), and depression (HR = 2.43, 95% CI: 2.15-2.76) were notably larger than ITT models. Additionally, AChEI initiation was associated with reductions in mortality (HR = 0.58, 95% CI: 0.51-0.66).

Bias Analysis

E-values for intent-to-treat estimates for memantine ranged from 1.45 to 2.11, and e-values for AChEIs ranged from 1.40-2.44 (Supplementary File 2.1). The largest e-value for AChEIs corresponded to falls, while the largest e-value for memantine corresponded with antipsychotics. The smallest e-value for both anti-dementia medications corresponded with hospitalizations.

Among 5,247 patients with cognitive impairment in the All of Us cohort, there were 371 (7.1%) ever initiators of memantine and 858 (16.4%) ever initiators of AChEIs. Among covariates not included in EHRs, marital status was predictive of memantine and AChEIs, with odds ratios larger than 1.4 or less than 0.71 (the inverse of 1.4). For example, divorced individuals had 0.55 times the odds of memantine use (95% CI: 0.39-0.77) and 0.65 times the odds of AChEI use (95% CI: 0.0.52-0.82; Table 2.4) compared to married individuals. The range of coefficients for living with a partner, separated, widowed, and never married ranged from 0.15-0.74 for memantine use and 0.52-0.72 for AChEI use.

Education was also predictive of memantine initiation, specifically college attainment (OR = 0.68, 95% CI: 0.45-1.02), some college (OR = 0.69, 95% CI: 0.46-1.05), and high school (OR = = 0.72, 95% CI: 0.47-1.09) compared to less than high school attainment. Categories for missing variables (marital status, general health, health insurance) were also strongly predictive of initiation of both medications, although such missingness categories are difficult to interpret. The magnitude of the associations for marital status and education was similar when additionally including clinical covariates (Supplementary File 2.1).

DISCUSSION

In these emulated target trials estimating the intent-to-treat effect of initiation of memantine or AChEIs on quality-of-care outcomes and mortality, initiation of either medication was associated with increased hazard of all outcomes except for death. Initiation of either medication was most associated in magnitude with prescriptions for antipsychotics or benzodiazepines, emergency room visits, depression, and delirium. Concurrent AChEI use qualitatively modified the relationship between memantine initiation and mortality. Though we adjusted for many clinical confounders, we were unable to adjust for sociodemographic factors due to limitations within EHRs. Our bias analysis using data from All of Us found that marital status and education were strong predictors of anti-dementia medication use, even when adjusting for clinical factors. Residual confounding may account for the weaker association with hospitalizations. However, it is unlikely that residual confounding by these factors would fully account for other associations stronger in magnitude. In summary, we found that the initiation of memantine or AChEIs were associated with many negative geriatric outcomes, despite being unable to adjust for marital status or education.

Our work is largely inconsistent with prior work showing no effect or small benefits of memantine[64] or AChEIs[59–62] on quality-of-life and functional status. As this prior work has been based on RCTs, differences in eligibility criteria, real-world medication use, or confounding may explain differences between the present study and prior literature. However, our work is consistent with a meta-analysis of RCTs finding that AChEIs are associated with increased risk of psychiatric adverse events, including depression.[63] Additionally, our results are consistent with a two observational studies which have evaluated the association between anti-dementia

medications and geriatric outcomes. One prior study found that anti-dementia medication use was associated with reductions in hip fracture, though this study evaluated ever versus never use of medications.[81] Another study found that initiators of AChEIs were more likely to experience syncope and related-outcomes, including hospitalizations and hip fracture due to falls.[82] Our work improves upon these prior studies by incorporating an emulated target trial design less prone to bias and investigating other patient-centered outcomes. These estimates are also consistent with documented, rare adverse events identified in RCTs and post-approval studies: dizziness, suicidal ideation, and urinary incontinence for memantine[78,83] and urinary incontinence, gastrointestinal issues, hallucinations, and depression for AChEIs.[79,84] Some of these rare events were more common in our cohort. For example, urinary continence had an incidence rate of about 46 cases per 1,000 person-years.

Receiving a prescription for an anti-dementia medication may prompt individuals to receive more healthcare. For example, receiving a prescription may prompt follow-up visits to adjust dose, discuss side effects, and prescribe refills. By spending more time with providers than individuals without active prescriptions, patients are more likely to have other, unrelated conditions recognized and treated. This is a detection bias, representing an indirect effect of memantine or AChEIs on the outcomes we selected.[85] As RCTs and cohorts with regularly scheduled follow-up are less susceptible to this bias by following up with both treatment groups equally, it is plausible that this bias could have increased the magnitude of our estimates, accounting for some of the difference between our estimates and prior work.

Our bias analysis in the All of Us cohort indicated that residual confounding by sociodemographic factors unavailable in EHRs is unlikely to fully explain our primary results. This was not a comprehensive quantitative bias analysis, and it is important to note that the influence of the confounder also depends on its prevalence in the cohort and its association with the outcome of interest.[86] Additionally, this simple bias analysis did not consider the direction of the confounding or joint effect of confounders, such as the presence of confounding by both education and marital status. While the combined effect of these confounders is not additive (i.e. the full effect of confounding by education and marital status would not be the simple sum of their effects on anti-dementia medication use), it is likely larger than the effect of either confounder alone. As such, the results from this bias analysis should be interpreted as an indication of the plausibility of confounding rather than conclusive estimates of the confounding. We believe this was important to include, given that sociodemographic factors often strongly predict medication use. It is likely that confounding by marital status and education exists in our models using EHRs and it explains estimates closer to the null, such as the estimate for hospitalization. It is less likely that confounding by either of these factors fully explains stronger associations, such as the relationship between anti-dementia medication use and antipsychotics, but we cannot exclude that possibility.

Our study has some notable strengths. First, to our knowledge, this is the first application of the emulated target trial design to anti-dementia medications. By using this framework, we were able to better account for immortal time and prevalent user biases than previous studies of ever versus never medication use.[71,75] Second, we were able to address an important data limitation of EHRs by augmenting the EHR analyses with evidence sociodemographic predictors of anti-dementia

medication use in the All of Us cohort. Lastly, we utilized EHRs from a UC system with patients spanning northern and southern California. In addition to being a large sample, it was generally more racially and ethnically diverse than other studies on dementia care (29-30% non-White, 10% Hispanic).

This study also has limitations. First, we excluded individuals with prescriptions prior to cognitive impairment diagnosis (7-13% of the sample). It would be challenging to identify a good match for those initiators, as non-initiators without a cognitive impairment diagnosis would otherwise have no indicator of cognitive decline within EHRs. While we excluded these individuals to ensure better matches, we recognize that individuals sometimes receive anti-dementia prescriptions prior to initial diagnosis and that our results would not generalize to this population with better baseline cognitive function. Second, we may have missed important predictors of prescription use in our bias analysis, specifically caregiver support and social isolation. The direction of the association for some predictors in the bias analysis was also opposite the expected direction, which may indicate some selection bias in that sample. For example, while higher education has been found to be associated with increased use of memantine,[87,88] we found that receiving a college education was associated with decreased odds of receiving memantine compared to individuals with less than high school attainment. Third, despite our bias analysis, we cannot eliminate the possibility of residual confounding by factors we did not assess. Our intent-to-treat estimates do not necessarily represent causal effects.

In conclusion, we found that memantine and AChEIs were associated with increased risk of negative geriatric outcomes, especially prescriptions for antipsychotics or benzodiazepines, both

measures of healthcare utilization, depression, and delirium. For memantine, these associations were modified by concurrent AChEI use. A bias analysis found that while education and marital status predict prescriptions for anti-dementia medications, they are likely not strong enough to account for associations between anti-dementia medications and antipsychotics, benzodiazepines, delirium, and depression. Future work should investigate heterogeneity in these relationships by important clinical or demographic factors, which may help to identify subgroups at higher risk of these adverse outcomes. Clinicians may want to weigh risk of these adverse outcomes against the potential for cognitive benefit when prescribing memantine or AChEIs. Finally, we hope the emulated target trial framework is additionally utilized for real-world evaluation of anti-amyloid medications, such as lecanemab, if access to these medications expands.

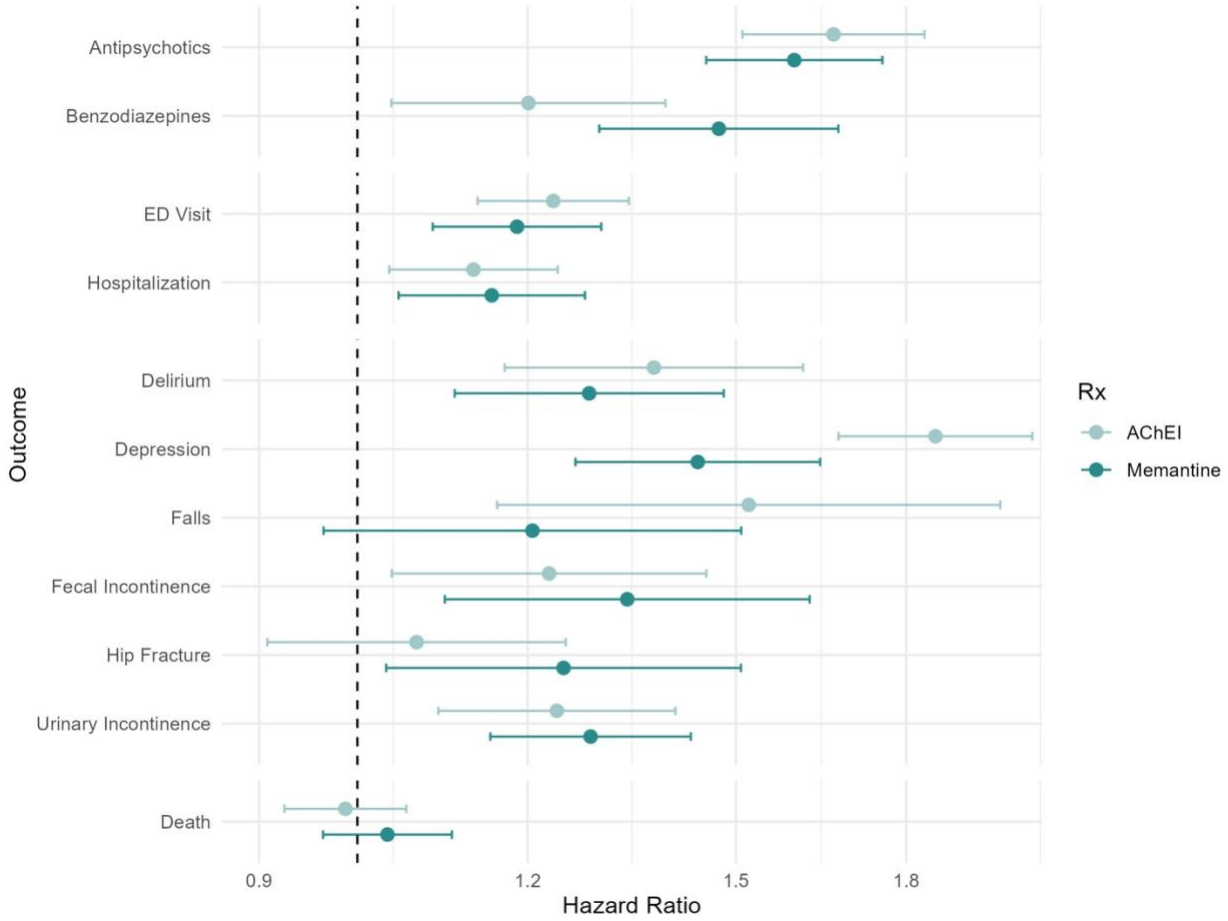

Figure 2.1: Intent-to-treat hazard ratios for AChEI or memantine initiation.
Models used IPTW-stabilized weights with trimming of extreme propensity scores, and were adjusted for race, ethnicity, sex, other anti-dementia medication use, UC site, count of encounters in the year prior to baseline, count of prescriptions in the year prior to baseline, Charlson Comorbidity Index (CCI), prior neurology visit, history of sensory impairment, history of mobility problems, age, most recent cognitive impairment diagnosis, trial year, and deciles of propensity score.

Table 2.1: Components of a theoretical randomized trial and their observational analogues. We conceptualized that trials would occur separately for memantine and AChEI initiation, though features of these trials would be otherwise identical. For simplicity, we have denoted "anti-dementia medication" to mean either memantine or AChEIs.

Protocol Component	Theoretical RCT	Emulated Trial in Observational Data
Treatment Groups	• Anti-dementia medication (memantine or AChEI) versus placebo	• Initiation of anti-dementia medication versus no initiation • Cohort created using matching, where non-initiators can be matches more than once • Initiators can be used as a non-initiator match prior to initiation
Eligibility Criteria	• Never before users of anti-dementia medication • Aged 55 or older with baseline ADRD, memory loss, or mild cognitive impairment diagnosed by a primary care provider • No history of quality-of-care outcomes	• No prior documented prescriptions for anti-dementia medication in EHRs • Aged 55 or older with baseline ADRD, memory loss, or mild cognitive impairment diagnosed by a primary care provider • Current users of medical system (range of use defined by first and last documented encounters) • For diagnostic and prescription outcomes: no prior history of outcome in EHRs
Treatment Assignment	• Randomized at study baseline	• Prescription initiation date determined from EHRs
Follow-up Period	• Starts at randomization • Ends at the earliest of outcome, death, or end of study period	• Starts at first date of anti-dementia medication prescription (for initiators) or matched initiator's first date of anti-dementia medication prescription (for non-initiators) • Ends at the earliest of outcome, death, administrative end of follow-up (12-13-2024), or loss to follow-up (lapse in healthcare utilization of 183 days).
Outcome	• Panel of quality-of-care and geriatric outcomes assessed by study team	• Panel of 11 quality-of-care and geriatric outcomes in EHRs selected to approximate quality-of-life

Protocol Component	Theoretical RCT	Emulated Trial in Observational Data
		• Outcomes span: 1) diagnoses, 2) prescriptions, 3) healthcare utilization
Primary Causal Contrast of Interest	• Intent-to-treat effect of anti-dementia medications compared to placebo on quality-of-care	• Intent-to-treat effect of anti-dementia medication initiation compared to no initiation on 11 QoC outcomes, controlling for baseline covariates
Primary Analysis Plan	• Cox models modeling time to quality-of-care outcome, interpret coefficient for treatment	• Cox models modeling time to quality-of-care outcome, with weighting and adjustment for baseline covariates • Interpret coefficient for initiation
Secondary Analysis Plan	• Per protocol analysis including additional censoring when individuals in the treatment arm stop taking treatment and when individuals in the placebo arm start taking treatment.	• Per protocol analysis including additional censoring when: 1) initiators have prescriptions that lapse (greater or equal to 60 day gap in prescriptions) and 2) at date of first anti-dementia medication for non-initiators

Table 2.2: Descriptive characteristics of memantine cohort.
Characteristics of largest analytic cohort for memantine initiators and matched non-initiators after dropping extreme propensity scores. Values are n(%) or mean(sd).

Characteristic		**Initiators (n=5,757)**	**Matched non-initiators (n=28,345)**	**Total (n=34,102)**
Male		2,181 (37.88)	9,984 (35.22)	12,165 (35.67)
Racial Identity				
	Asian	702 (12.19)	4,133 (14.58)	4,835 (14.18)
	Black	337 (5.85)	2,124 (7.49)	2,461 (7.22)
	Other	465 (8.08)	2,515 (8.87)	2,980 (8.74)
	Unknown	493 (8.56)	2,284 (8.06)	2,777 (8.14)
	White	3,760 (65.31)	17,289 (60.99)	21,049 (61.72)
Hispanic Identity				
	Yes	560 (9.73)	3,080 (10.87)	3,640 (10.67)
	No	4,818 (83.69)	23,495 (82.89)	28,313 (83.02)
	Unknown	379 (6.58)	1,770 (6.24)	2,149 (6.3)
UC-Site				
	Irvine	907 (15.75)	3,527 (12.44)	4,434 (13)
	Davis	1,409 (24.47)	7,355 (25.95)	8,764 (25.7)
	Los Angeles	2,285 (39.69)	9,179 (32.38)	11,464 (33.62)
	Riverside	5 (0.09)	39 (0.14)	44 (0.13)
	San Diego	798 (13.86)	3,976 (14.03)	4,774 (14)
	San Francisco	353 (6.13)	4,269 (15.06)	4,622 (13.55)
AChEI Use at Trial		4,005 (69.57)	10,936 (38.58)	14,941 (43.81)
Number of prescriptions in prior year		24.88 (24.27)	33.62 (32.92)	32.15 (31.8)
Number of healthcare encounters in prior year		25.58 (26.01)	35.86 (35)	34.13 (33.87)
Charlson Comorbidity Index		1.75 (1.46)	1.76 (1.54)	1.76 (1.53)
Prior neurology visit		2,414 (41.93)	6,445 (22.74)	8,859 (25.98)
History of sensory impairment		1,327 (23.05)	6,717 (23.7)	8,044 (23.59)
History of mobility problems		568 (9.87)	3,378 (11.92)	3,946 (11.57)

Table 2.3: Descriptive characteristics of AChEI cohort.
Characteristics of largest analytic cohort for AChEI initiators and matched non-initiators after dropping extreme propensity scores. Values are n(%) or mean(sd).

Characteristic		**Initiators (n=9,326)**	**Matched non-initiators (n=45,900)**	**Total (n=55,226)**
Male		3,531 (37.86)	16,219 (35.34)	19,750 (35.76)
Racial Identity				
	Asian	1,272 (13.64)	6,143 (13.38)	7,415 (13.43)
	Black	535 (5.74)	3,381 (7.37)	3,916 (7.09)
	Other	720 (7.72)	4,102 (8.94)	4,822 (8.73)
	Unknown	725 (7.77)	3,692 (8.04)	4,417 (8.0)
	White	6,074 (65.13)	28,582 (62.27)	34,656 (62.75)
Hispanic Identity				
	Yes	852 (9.14)	4,912 (10.7)	5,764 (10.44)
	No	7,949 (85.23)	38,480 (83.83)	46,429 (84.07)
	Unknown	525 (5.63)	2,508 (5.46)	3,033 (5.49)
UC-Site				
	Irvine	1,323 (14.19)	6,024 (13.12)	7,347 (13.3)
	Davis	2,522 (27.04)	12,788 (27.86)	15,310 (27.72)
	Los Angeles	3,035 (32.54)	13,957 (30.41)	16,992 (30.77)
	Riverside	16 (0.17)	48 (0.1)	64 (0.12)
	San Diego	1,399 (15.0)	6,332 (13.8)	7,731 (14.0)
	San Francisco	1,031 (11.06)	6,751 (14.71)	7,782 (14.09)
Memantine Use at Trial		1,045 (11.21)	4,167 (9.08)	5,212 (9.44)
Number of prescriptions in prior year		24.33 (25.16)	38.51 (36.04)	36.12 (34.85)
Number of healthcare encounters in prior year		25.09 (26.94)	43.93 (44.1)	40.75 (42.3)
Charlson Comorbidity Index		1.54 (1.44)	1.59 (1.51)	1.58 (1.49)
Prior neurology visit		3,750 (40.21)	8,097 (17.64)	11,847 (21.45)
History of sensory impairment		1,995 (21.39)	11,267 (24.55)	13,262 (24.01)
History of mobility problems		716 (7.68)	5,181 (11.29)	5,897 (10.68)

Table 2.4: Predictors of memantine and AChEI use.
Predictors (odds ratios) of ever use of memantine and AChEIs in the All of Us cohort from sociodemographic and health behavior variables. Model 1 is an unadjusted model. Model 2 includes adjustment for all predictors and age, sex, and racial identity. Model 3 adds adjustment for ever use of the other anti-dementia medication.

Predictor	**Ever memantine use; OR (95% CI)**			**Ever AChEI use; OR (95% CI)**		
	Model 1	**Model 2**	**Model 3**	**Model 1**	**Model 2**	**Model 3**
Education (ref: Less than HS)						
High School	0.71 (0.47-1.06)	0.72 (0.47-1.09)	0.73 (0.46-1.16)	0.86 (0.64-1.16)	0.88 (0.65-1.2)	0.98 (0.7-1.37)
Some college	0.69 (0.47-1.01)	0.69 (0.46-1.05)	0.74 (0.47-1.16)	0.75 (0.56-1.01)	0.78 (0.57-1.06)	0.86 (0.61-1.19)
College or above	0.66 (0.45-0.96)	0.68 (0.45-1.02)	0.67 (0.42-1.06)	0.84 (0.63-1.11)	0.88 (0.65-1.2)	1 (0.72-1.4)
Missing	0.9 (0.44-1.83)	0.91 (0.42-1.97)	1 (0.42-2.4)	0.76 (0.44-1.32)	0.79 (0.44-1.44)	0.78 (0.41-1.49)
Smoking Status (ref: Non-smoker)						
Smoker	1.01 (0.81-1.26)	1.06 (0.84-1.34)	1.13 (0.88-1.44)	0.9 (0.77-1.06)	0.96 (0.81-1.13)	0.93 (0.78-1.11)
Missing	1.01 (0.53-1.91)	1.13 (0.56-2.25)	1.22 (0.57-2.62)	1.04 (0.66-1.62)	0.94 (0.57-1.55)	0.9 (0.53-1.54)
Alcohol use (ref: no)						
Yes	0.85 (0.61-1.18)	0.9 (0.64-1.27)	1.02 (0.7-1.49)	0.74 (0.59-0.94)	0.78 (0.61-1)	0.77 (0.59-1)
Missing	0.61 (0.25-1.47)	0.53 (0.2-1.38)	0.51 (0.18-1.46)	0.97 (0.57-1.65)	0.88 (0.49-1.59)	1 (0.54-1.87)
Income (ref: 35-75k)						
Less than 10k	0.92 (0.6-1.4)	0.98 (0.62-1.56)	0.99 (0.6-1.62)	0.84 (0.61-1.14)	0.89 (0.64-1.25)	0.9 (0.63-1.29)
10-25k	0.81 (0.55-1.19)	0.91 (0.61-1.35)	0.81 (0.52-1.24)	1 (0.77-1.29)	1.1 (0.84-1.45)	1.17 (0.87-1.56)
25-35k	0.81 (0.5-1.31)	0.86 (0.53-1.4)	0.79 (0.47-1.34)	0.91 (0.65-1.27)	0.95 (0.68-1.33)	0.99 (0.69-1.41)

Predictor		Ever memantine use; OR (95% CI)			Ever AChEI use; OR (95% CI)		
		Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Income (ref: 35-75k)							
	More than 75k	0.83 (0.58-1.17)	0.75 (0.52-1.07)	0.81 (0.55-1.19)	0.87 (0.68-1.11)	0.76 (0.59-0.98)	0.8 (0.61-1.05)
	Missing	1.11 (0.81-1.52)	1.09 (0.79-1.52)	1.07 (0.75-1.53)	1.04 (0.83-1.31)	1.02 (0.81-1.3)	1.01 (0.78-1.3)
Marital Status (ref: Married)							
	Living with partner	0.16 (0.04-0.64)	0.15 (0.04-0.63)	0.15 (0.04-0.64)	0.7 (0.42-1.18)	0.69 (0.41-1.16)	0.9 (0.53-1.54)
	Divorced	0.59 (0.43-0.81)	0.55 (0.39-0.77)	0.65 (0.46-0.94)	0.7 (0.56-0.87)	0.65 (0.52-0.82)	0.74 (0.58-0.94)
	Separated	0.82 (0.44-1.52)	0.74 (0.39-1.38)	0.79 (0.39-1.58)	0.77 (0.48-1.23)	0.72 (0.45-1.16)	0.77 (0.46-1.28)
	Widowed	0.71 (0.51-0.98)	0.66 (0.47-0.93)	0.79 (0.55-1.15)	0.76 (0.6-0.96)	0.71 (0.56-0.91)	0.76 (0.59-0.99)
	Never married	0.56 (0.38-0.84)	0.53 (0.35-0.8)	0.64 (0.41-0.99)	0.55 (0.41-0.74)	0.52 (0.39-0.7)	0.56 (0.41-0.77)
	Missing	0.61 (0.28-1.31)	0.39 (0.16-0.98)	0.48 (0.17-1.34)	0.61 (0.35-1.07)	0.48 (0.26-0.9)	0.6 (0.32-1.14)
Birth Country (ref: US)							
	Outside US	1.29 (0.89-1.86)	1.14 (0.78-1.68)	1.01 (0.66-1.54)	1.38 (1.05-1.81)	1.25 (0.95-1.66)	1.24 (0.91-1.68)
	Missing	1.29 (0.89-1.86)	1.49 (0.65-3.45)	1.3 (0.48-3.52)	1.61 (0.9-2.89)	1.7 (0.92-3.13)	1.61 (0.84-3.12)
General health (ref: Excellent)							
	Very good	1.34 (0.8-2.26)	1.34 (0.8-2.27)	1.31 (0.75-2.31)	1.17 (0.82-1.67)	1.17 (0.82-1.68)	1.11 (0.75-1.63)
	Good	1.15 (0.7-1.92)	1.11 (0.66-1.85)	1.13 (0.65-1.95)	1.07 (0.76-1.51)	1.05 (0.74-1.48)	1.04 (0.72-1.51)
	Fair	1.29 (0.77-2.16)	1.21 (0.72-2.03)	1.26 (0.72-2.21)	1.09 (0.77-1.55)	1.05 (0.74-1.5)	1.02 (0.7-1.49)
	Poor	1.16 (0.63-2.12)	1.07 (0.58-1.97)	1.08 (0.56-2.09)	1.08 (0.71-1.63)	1.05 (0.69-1.6)	1.07 (0.68-1.68)

Predictor	Ever memantine use; OR (95% CI)			Ever AChEI use; OR (95% CI)		
	Model 1	**Model 2**	**Model 3**	**Model 1**	**Model 2**	**Model 3**
General health (ref: Excellent)						
Missing	1.91 (0.86-4.25)	2.04 (0.89-4.68)	1.66 (0.66-4.15)	2.03 (1.15-3.56)	1.98 (1.1-3.58)	1.79 (0.94-3.39)
Health insurance (ref: no)						
Yes	1.22 (0.49-3.06)	1.17 (0.46-2.96)	1.18 (0.44-3.16)	1.13 (0.6-2.13)	1.11 (0.59-2.1)	1.07 (0.55-2.07)
Missing	1.87 (0.62-5.59)	1.66 (0.54-5.15)	1.58 (0.46-5.5)	1.35 (0.61-2.96)	1.26 (0.56-2.85)	1.09 (0.46-2.61)
Ever use of other anti-dementia medication	--	--	13.09 (10.14-16.89)	--	--	12.95 (10.09-16.61)

Chapter 3 - Clinical and Sociodemographic Predictors of Antibiotic Discordance Among Older Adults with Suspected Urinary Tract Infections

INTRODUCTION

Urinary tract infections (UTIs) are one of the most common bacterial infections found in older adults.[89] UTIs are especially important to diagnose correctly and treat in patients with age-related risk factors and comorbidities, as UTIs can lead to delirium, decreased mobility, and hospitalization.[90–93] However, treatment for UTIs is complicated by antimicrobial resistance. Older adults are differentially burdened by antimicrobial resistant infections compared to younger age groups,[94,95] and importantly the prevalence of resistant UTIs in older adults is increasing.[96]

While most older adults with a suspected UTI receive a prescription for an empiric antibiotic,[89] antibiotic discordance, when the organism causing the infection is resistant to the antibiotic prescribed, is common. Prior studies have found that 9-14% of UTIs are treated with discordant antibiotics.[97,98] While in younger populations discordant UTI treatment may not impact outcomes substantially,[98,99] discordant treatment in older adults is associated with serious outcomes, such as hospitalization.[97,100,101]

Prior studies have used prediction models to identify patterns of antibiotic susceptibility in UTIs.[102–105] To our knowledge, no models have predicted antibiotic discordance, even though antibiotic discordance is the key clinical outcome we aim to avoid. As the presence of a resistant organism does not always lead to discordant antibiotic therapy, predicting individuals at higher risk of discordant antibiotic therapy may be of more clinical importance. Reliably identifying

individuals at higher risk of discordant or concordant antibiotic therapy could help allocate resources to higher risk patients, guide prescribing decisions, and determine which patients require extended clinical follow-up.

We used logistic regressions with a LASSO penalty to predict antibiotic discordance among a large population of older adults with suspected UTI presenting in both outpatient and inpatient settings. Our models pulled from 42 variables commonly measured at time of UTI diagnosis measured in electronic health records (EHRs). We additionally implemented and evaluated models stratified by important clinical subgroups, such as place of care (healthcare-associated versus community-associated infections).

METHODS

Study Population

We identified routine urine cultures for older adults (aged 55 years and older) from the University of California, San Francisco medical system EHRs from January 1, 2014 to August 15, 2023. As we were primarily interested in appropriate antibiotic prescribing, we only included cultures which grew an organism and those where non-topical antibiotics were prescribed from 48 hours before to 24 hours after the time of culture. We allowed for repeated cultures per individual over time.

Of 126,219 patients with completed urine cultures during the study period who were prescribed antibiotics, we excluded 59,946 patients who were younger than 55 years at time of culture (47.5%), 24,861 patients whose culture did not grow an organism (19.7%), 177 patients with missing data (0.1%), and 46 patients with other/unknown sex due to small sample size (0.04%,

Supplementary File 3.1). After these exclusions, our final sample included 41,189 cultures representative of 24,430 unique individuals. We additionally considered a subpopulation of cultures with any antibiotic resistance (n=16,242, 10,996 unique individuals). This analysis was approved by the Institutional Review Board at UCSF (IRB# 19-27233). Patient informed consent was waived because analyses were conducted on preexisting data.

Susceptibility and Antibiotic Discordance

We extracted results from antimicrobial susceptibility testing from EHRs. If susceptibility was not tested or if susceptibility to a particular antibiotic was not tested, we assumed the organism was susceptible. Results that indicated intermediate resistance were considered resistant. We defined antibiotic discordance as the prescribing of an antibiotic that the cultured organism demonstrated resistance to. If multiple antibiotics were prescribed from 48 hours before to 24 hours after the time of culture, any discordance between antibiotics and organism were considered discordant treatment, even if the organism was susceptible to one of the antibiotics.

Covariates

We considered 36 covariates as possible predictors of antibiotic discordance, including 31 clinical and 5 sociodemographic variables. Categorical variables were entered as binary indicators and were not required to be selected together. There were a total of 42 features to be selected from when including each level of a categorical variable separately. We only considered observable covariates at time of culture, so we did not include organism or class of antibiotic resistance as predictors.

Sociodemographic covariates included: age (years), sex (female, male), race (Asian, Black, Latinx, White, Other), preferred language (Chinese, English, Spanish, Other), and insurance used at culture visit (private, public, other). Clinical covariates included: place of care (defined as healthcare-associated if a hospitalization occurred in the 90 days before culture, otherwise defined as a community-associated infection), history of the prescribing provider following local prescribing guidelines, history of a prior urinary tract infection in the year prior to culture, history of recurrent urinary tract infections (3 or more ICD-defined diagnoses of UTI in the past year, 3 or more urine cultures in the past year, or 2 or more ICD-defined diagnoses of UTI in the past 6 months, or 2 or more urine cultures in the past 6 months), 6 indicators for presence of conditions in the 5 days before culture (renal disease, urinary tract infection, pyelonephritis, delirium, sepsis, and bacteremia), and 21 indicators for ICD-defined comorbidities in the year prior to culture (alcohol use disorder, asthma, cancer, cardiovascular disease, chronic obstructive pulmonary disease, cognitive complaints, congestive heart failure, dementia, depression, human immunodeficiency virus, hypertension, interpersonal violence, kidney stones, liver disease, obesity, pelvic organ prolapse, post-traumatic stress disorder, renal disease, tobacco use disorder, urinary abnormalities, urinary incontinence). ICD-9/10 codes used to identify covariates are listed in Supplementary File 3.2. Provider history of prescribing with guidelines was defined as the percent of prior patients with suspected UTI who were prescribed trimethoprim-sulfamethoxazole or nitrofurantoin (following national guidelines for empirical antibiotics by the Infectious Disease Society of America[106]) and ranged from 0% to 100%.

Statistical Analysis

We fit prediction models for antibiotic resistance among 1) all cultures and 2) cultures with resistant organisms. For both populations (all cultures and cultures with resistance), we first

randomly sampled 70% of the analytic sample for training the model and set aside the remaining 30% to evaluate its predictive performance. Next, we fit models for antibiotic discordance in the training sample using logistic regressions with a LASSO (Least Absolute Shrinkage and Selection Operator) penalty for regularization. These LASSO models selected covariates from candidate predictors by adding a penalty, lambda, that penalizes model complexity and prevents overfitting.[107] We determined the best lambda value for each model using 10-fold cross-validation. In the test sample, we evaluated the predictive performance of this model by calculating the area under the receiver operating characteristic (AUROC) curve and sensitivity, specificity, and negative and positive predictive values at Youden's index, the cutoff of predictive values that maximizes sensitivity and specificity.[108]

In secondary analyses, we refit and evaluated prediction models within important strata identified a priori: age (65 years and older; younger than 65), place of care (healthcare acquired infection; community-associated infection), provider history of prescribing with guidelines (median or above [better history]; below median [worse history]), and the most predictive factor identified from main models with large enough strata (>200 individuals, bacteremia at time of culture for both populations).

RESULTS

Cohort Characteristics

The 4,636 cases of discordant (11.3% of all urine cultures and 28.5% of resistant cultures; Supplementary File 3.2) were more likely to have a prior UTI (31.5% versus 26.5%), more likely to have a healthcare-associated infection (83.6% versus 74.7%), and less likely to be female

(39.2% versus 65.7%; Table 3.1) than cases receiving concordant treatment. *E. coli* was the most common place of care both for individuals with discordant (47.7%) and concordant treatment (29.2%; Supplementary File 3.2). Finally, 33.4% of patients with discordant treatment were treated with fluoroquinolone compared to 20.4% of those with concordant treatment (Supplementary File 3.2).

Prediction of Antibiotic Discordance

LASSO models selected 37 features for the population of all cultures and 31 features for the population of resistant cultures (Table 3.2). Bacteremia within 5 days of urine culture was one of the strongest predictors of antibiotic discordance among all cultures (OR = 1.73) and resistant cultures (OR = 1.64). These models both achieved an AUROC of 0.60 (Figure 3.1). At Youden's Index, the negative predictive value was higher among all cultures (0.91) than in resistant cultures (0.78), but the positive predictive value was low in both populations. Model sensitivity (0.66) was also higher than specificity, which was no better than random chance (0.48-0.51, Table 3.3).

Stratified Prediction Models

Predictors selected by refitted LASSO models among stratified populations are found in Supplementary File 3.2. Among all cultures, the model with the highest AUROC was in patients without bacteremia at culture (0.61; Supplementary File 3.1). When restricting to resistant cultures, the model with the highest AUROC was in patients with bacteremia at culture (0.63, Supplementary File 3.1). Five stratified models had the same or larger negative predictive values compared to the full sample of cultures (Table 3.3), with the best performance in community-

associated infections and providers with better history of following guidelines. Among resistant cultures, four stratified models had the same or larger negative predictive values compared to the overall model, with the best performance in community-associated infections. There were no large gains in positive predictive value, except for in the population of resistant cultures with bacteremia at culture (0.53 versus 0.37 when using all resistant cultures). Finally, in resistant cultures, models in community-associated infections had high sensitivity (0.92), but models in community-associated infections had high specificity in all cultures (0.84).

DISCUSSION

We created prediction models for antibiotic discordance from urine cultures and a subpopulation of resistant cultures from a large healthcare system in California. While overall performance measured by AUROC was poor, negative predictive values were high (>0.90 among all cultures). Overall, our models had worse overall predictive power compared to published models for antibiotic susceptibility. Our models had similar overall performance compared to Kanjilal et al.[103] (AUROC 0.56-0.64) and Corbin et al.[105] (0.61-0.73), but notably worse performance compared to Yelin et al.[104] (0.70-0.83) and Lee at al.[102] (0.93-0.94). It is expected that performance of models for antibiotic discordance would be worse than those for antibiotic susceptibility, as the former is modeling both susceptibility and provider prescribing patterns. However, our models often had better negative predictive values compared to Lee et al. (0.78-0.83),[102] indicating that it may be more reliable to predict concordant (appropriate) treatment than susceptibility. Future research should consider whether clinical decision tools could incorporate prediction models for antibiotic susceptibility and models for antibiotic discordance, and whether these models outperform either model alone.

We additionally were able to identify whether predictors of antibiotic discordance differed by clinically relevant subpopulations. For example, delirium at culture was a strong predictor of antibiotic discordance in overall models, but stratified LASSO models indicated delirium at time of culture was only important among patients 65 years and older. This is consistent with prior work showing that delirium can accompany the clinical presentation of a UTI among older adults.[91,109] As predictors of discordant treatment differ by clinical subpopulation, machine learning models that can account for these interactions, such as tree-based methods, may be more successful.[110]

Our study has some notable strengths. Importantly, we modeled antibiotic discordance instead of antibiotic susceptibility, as this is a state that is intervenable and potentially more clinically relevant. Individuals at high risk of discordance may need closer follow-up, or for some patients, protocols of care may need to be altered. We also included a large and diverse sample of patients with urine cultures. While some prior prediction models limited to inpatient[102,105] or outpatient[103] encounters, we included both. Finally, we refit models among clinically relevant strata, demonstrating that there are important interactions that should be considered when creating a clinical decision tool for antibiotic discordance (e.g. place of care).

There are also limitations to our work. We did not include laboratory measurements, features from urinalysis, or presenting symptoms as predictors in our models. Future work should consider incorporating these factors, as they may be associated with UTI severity and complications.[111,112] Additionally, in this data, susceptibility testing was not conducted by

microbiology laboratory nor were all possible antibiotics always tested. We assumed that if susceptibility testing was not performed, that the organism was susceptible. As a result, there is likely unavoidable measurement error in our definition of antibiotic discordance. Though we validated our model in a subsample of patients, we were unable to assess the performance of this model in an independent population. Future research should prioritize developing models in datasets with multiple healthcare centers to better assess real-world performance of the prediction model. Finally, as we did not use clinical contes, we did not capture all the clinical context made when making these clinical decisions.

In this study developing prediction models for antibiotic discordance, we found that using common clinical features produced a model that could reliably identify patients with concordant treatment (i.e. high negative predictive value). Clinically, a model with high negative predictive value would help clinicians allocate resources and identify patients without need for extensive follow-up. We also found that predictors of antibiotic discordance differed by strata, suggesting that future research should use tree-based methods to account for these interactions. Future work should investigate whether a model for antibiotic discordance could be used independently or in conjunction with models for antibiotic susceptibility in a clinical decision tool for antibiotic prescribing for UTIs.

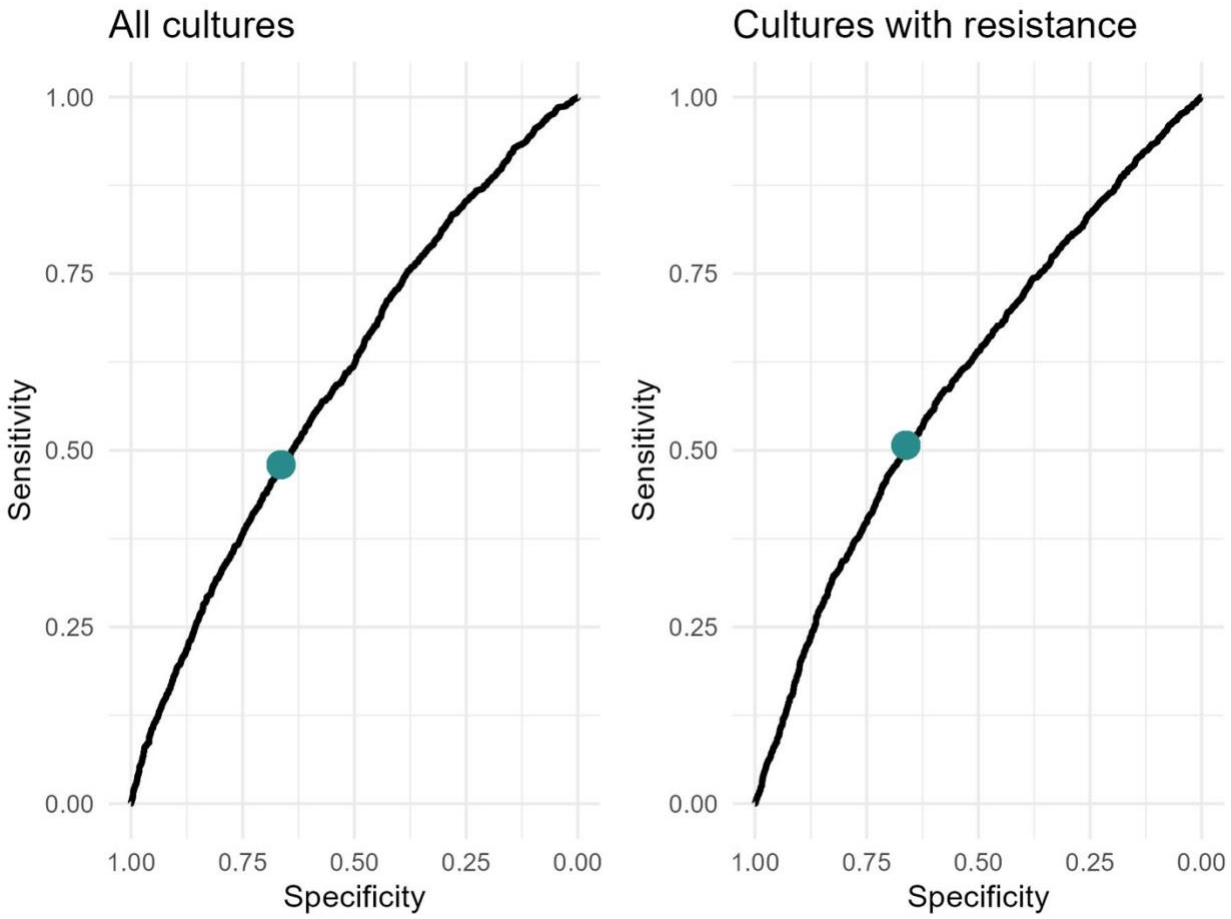

Figure 3.1: ROC curves for models predicting antibiotic discordance.
ROC curves from LASSO models for antibiotic discordance among all cultures (left) and cultures with resistance (right). Youden's index is indicated on the curve with a blue dot.

Table 3.1: Descriptive characteristics of the full sample of urine cultures.
Values are n (%) or mean (sd).

Characteristic		**Discordant antibiotic treatment (n=4,636)**	**Concordant treatment (n=36,553)**	**Total analytic cohort (n=41,189)**
Age (years)		72.9 (10.8)	72.5 (10.8)	72.5 (10.8)
Female		1,816 (39.2)	24,017 (65.7)	26,837 (65.2)
Racial identity				
	Asian	1,005 (21.7)	6,791 (18.6)	7,796 (18.9)
	Black	390 (8.4)	2,773 (7.6)	3,163 (7.7)
	Latinx	572 (12.3)	4,068 (11.1)	4,640 (11.3)
	White	2,379 (51.3)	20,664 (56.5)	23,043 (55.9)
	Other/Unknown	290 (6.3)	2,257 (6.2)	2,547 (6.2)
Insurance Type				
	Private	446 (9.6)	4,120 (11.3)	4,566 (11.1)
	Public	3,449 (74.4)	25,146 (68.8)	28,595 (69.4)
	Other/Unknown	741 (16.0)	7,287 (19.9)	8,028 (19.5)
Preferred language				
	Chinese	372 (8.0)	2,421 (6.6)	2,793 (6.8)
	English	3,648 (78.7)	30,305 (82.9)	33,953 (8.4)
	Spanish	275 (5.9)	1,667 (4.6)	1,942 (4.7)
	Other/Unknown	341 (7.4)	2,160 (5.9)	2,501 (6.1)
Prior UTI		1,461 (31.5)	9,682 (26.5)	11,143 (27.1)
Healthcare-associated infection		3,874 (83.6)	27,308 (74.7)	31,182 (75.7)
Bacteremia at culture		136 (2.9)	466 (1.3)	602 (1.5)
Sepsis at culture		1,595 (34.4)	9,776 (26.7)	11,371 (27.6)
History of cardiovascular disease		940 (20.3)	6,681 (18.3)	7,621 (18.5)
History of dementia		207 (4.5)	1,627 (4.5)	1,834 (4.5)
Year of culture				
	2014-2019	2,204 (47.5)	19,448 (53.2)	21,652 (52.6)
	2020-2023	2,432 (52.5)	17,105 (46.8)	19,537 (47.4)

Table 3.2: Features selected by LASSO models for antibiotic discordance.
Selected predictors of antibiotic discordance from logistic regressions with a LASSO penalty and their odds ratio, among all urine cultures (n=41,189) and a subsample of cultures with resistant organisms (n=16,242).

Predictor	**Odds ratio**	
	All urine cultures	**Urine cultures with resistance**
Bacteremia at culture	1.73	1.64
Pyelonephritis at culture	1.52	1.09
Healthcare acquired infection	1.44	1.29
Sepsis at culture	1.42	1.38
Delirium at culture	1.36	1.06
Language: Spanish	1.30	1.07
History of urinary abnormalities	1.27	1.19
History of kidney stones	1.18	1.18
History of renal disease	1.16	1.18
Prior UTI	1.16	--
Race: Black	1.14	--
Race: Other	1.12	--
Race: Asian	1.11	1.02
History of liver disease	1.09	1.16
Language: Other	1.08	1.10
Recurrent UTI	1.07	1.08
History of congestive heart failure	1.07	--
Insurance: Other	1.05	1.12
History of cardiovascular disease	1.04	0.95
Insurance: Public	1.04	--
History of tobacco use disorder	1.03	1.03
Race: Latinx	1.03	--
Language: Chinese	1.01	1.01
Age (per year increase)	1.00	1.00
History of depression	0.96	0.95
History of cognitive complaints	0.95	1.00
Provider prescribing history	0.95	0.92
History of COPD	0.94	0.99
History of cancer	0.94	--
Sex: Female	0.93	1.00
History of obesity	0.92	--
History of pelvic organ prolapse	0.89	0.91
History of hypertension	0.89	0.88
UTI at culture	0.88	0.73
History of dementia	0.85	0.87
Renal disease at culture	0.78	--

Predictor	Odds ratio	
	All urine cultures	Urine cultures with resistance
History of interpersonal violence	0.66	--
History of alcohol use disorder	--	1.22
History of urinary incontinence	--	0.95
History of asthma	--	0.87
History of PTSD	--	0.59

Table 3.3: Evaluation metrics of LASSO prediction models of antibiotic discordance. AUROC, negative predictive value, positive predictive value, sensitivity, and specificity of LASSO prediction models in the overall samples and refitted within clinically relevant strata.

Sample	Training sample size	Test sample size	AUROC	Sensitivity	Specificity	Negative predictive value	Positive predictive value
1. All urine cultures							
Full sample	28,832	12,357	0.60	0.48	0.66	0.91	0.16
Age stratified							
>= 65 years	20,478	8,777	0.60	0.38	0.78	0.91	0.18
< 65 years	8,354	3,580	0.60	0.37	0.78	0.92	0.15
Place of care							
Healthcare-associated	21,827	9,355	0.60	0.55	0.60	0.90	0.16
Community-associated	7,005	3,002	0.53	0.24	0.84	0.93	0.11
Provider prescribing history							
Better history of following guidelines	14,417	6,179	0.60	0.58	0.58	0.93	0.12
Worse history of following guidelines	14,415	6,178	0.60	0.49	0.65	0.90	0.17
Bacteremia at culture							
Yes	421	181	0.51	0.49	0.58	0.81	0.24
No	28,411	12,176	0.61	0.46	0.69	0.91	0.16
2. Urine cultures with any antibiotic resistance							
Full sample	11,369	4,873	0.60	0.51	0.66	0.78	0.37
Age stratified							
>= 65 years	8,415	3,606	0.59	0.57	0.58	0.78	0.34
< 65 years	2,955	1,266	0.59	0.57	0.60	0.78	0.36
Place of care							
Healthcare-associated	8,835	3,786	0.60	0.54	0.62	0.76	0.38
Community-associated	2,535	1,086	0.51	0.92	0.13	0.86	0.21
Provider prescribing history							
Better history of following guidelines	5,685	2,437	0.59	0.67	0.48	0.81	0.31

Sample	Training sample size	Test sample size	AUROC	Sensitivity	Specificity	Negative predictive value	Positive predictive value
Provider prescribing history							
Worse history of following guidelines	5,684	2,436	0.58	0.58	0.55	0.72	0.39
Bacteremia at culture							
Yes	224	96	0.63	0.49	0.73	0.69	0.53
No	11,145	4,777	0.59	0.53	0.61	0.77	0.34

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