Development of a machine learning model to predict mild cognitive impairment using natural language processing in the absence of screening

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Abstract

Background: Patients and their loved ones often report symptoms or complaints of cognitive decline that clinicians note in free clinical text, but no structured screening or diagnostic data are recorded. These symptoms/complaints may be signals that predict who will go on to be diagnosed with mild cognitive impairment (MCI) and ultimately develop Alzheimer's Disease or related dementias. Our objective was to develop a natural language processing system and prediction model for identification of MCI from clinical text in the absence of screening or other structured diagnostic information.

Methods: There were two populations of patients: 1794 participants in the Adult Changes in Thought (ACT) study and 2391 patients in the general population of Kaiser Permanente Washington. All individuals had standardized cognitive assessment scores. We excluded patients with a diagnosis of Alzheimer's Disease, Dementia or use of donepezil. We manually annotated 10,391 clinic notes to train the NLP model. Standard Python code was used to extract phrases from notes and map each phrase to a cognitive functioning concept. Concepts derived from the NLP system were used to predict future MCI. The prediction model was trained on the ACT cohort and 60% of the general population cohort with 40% withheld for validation. We used a least absolute shrinkage and selection operator logistic regression approach (LASSO) to fit a prediction model with MCI as the prediction target. Using the predicted case status from the LASSO model and known MCI from standardized scores, we constructed receiver operating curves to measure model performance.

Results: Chart abstraction identified 42 MCI concepts. Prediction model performance in the validation data set was modest with an area under the curve of 0.67. Setting the cutoff for correct classification at 0.60, the classifier yielded sensitivity of 1.7%, specificity of 99.7%, PPV of 70% and NPV of 70.5% in the validation cohort.

Discussion and conclusion: Although the sensitivity of the machine learning model was poor, negative predictive value was high, an important characteristic of models used for population-based screening. While an AUC of 0.67...
Background
The U.S. population is aging and age-related diseases like Alzheimer’s Disease and related dementias (ADRD) are becoming more prevalent [1, 2]. ADRD are brain disorders that cause problems with memory, thinking and behavior [3]. Symptoms usually develop slowly and get worse over time and there is no known cure [3]. “Mild cognitive impairment” (MCI) is defined as cognitive decline greater than expected for an individual’s age and educational attainment [4]. MCI is often diagnosed during the symptomatic predementia phase of ADRD [4]. Subsequent to patient- and family-reported symptoms (e.g., memory deficits), primary care clinicians sometimes administer a standardized screening instrument such as the Mini Mental State Exam (MMSE) [5] or Montreal Cognitive Assessment (MoCA) [6] to identify MCI. However, there is currently insufficient evidence to support universal screening with these instruments [7]. Thus, screening is not performed routinely and as much as half of cognitive impairment goes unrecognized and undiagnosed in primary care [8]. Thus, routine use of machine learning methods applied to clinical notes could speed the time to identification and case management of MCI—thereby enabling earlier psychosocial intervention and reduction in the disease burden [9, 10] and reducing the delay of skills training for home-based care providers (spouses and adult children) who often need training on better coping strategies [11]. Early intervention can also be cost effective [10].

A variety of approaches have been explored to better detect cognitive impairment including identifying patterns of health care utilization prior to diagnosis [12], use of audio recordings to complement neurocognitive testing [13], and analysis of transcript data to identify changes in cognition over time [14]. Ford and coauthors provide a nice review of how structured and unstructured data from primary care electronic health records can be used to predict dementia [15]. Most research into predicting changes in cognition has focused on the use of structured data such as medication utilization [16–22], diagnoses [23–29], procedures [30], and social determinants of health [31–36] that are associated with developing full-blown Alzheimer’s Disease or related dementias (ADRD) [15, 37–43]. We are not aware of any published studies that have tested models predicting development of mild cognitive impairment (MCI) or data abstracted from clinical notes using natural language processing to predict MCI or ADRD, though, Sanghavi and Noderer are conducting work in this area [44]. Berisha et al. [14] discovered declines in language complexity with the progression of Alzheimer’s Disease using transcript data. Kharrazi and colleagues have also reported that the prevalence of geriatric syndromes is significantly underestimated using structured data alone and that many geriatric syndromes are likely to be missed if unstructured data (i.e., clinical text) are not analyzed [45]. Dementia was one characteristic more highly correlated with descriptions of “frailty” in the research on geriatric syndromes [46].

The purpose of this study was to develop and evaluate a machine learning model employing predictors derived from a natural language processing (NLP) system for
identifying patients with MCI from routinely collected clinical notes in patients’ electronic health record.

Methods
Overview
There were 4 main steps in our approach to developing the prediction model: (1) developing and applying the NLP system; (2) training a classifier in a gold standard population using the output from the NLP system; (3) refinement of training the classifier in a general population of individuals; and (4) validation of the prediction model in a withheld sample of general population individuals.

This study involved two groups of patients: participants in the Adult Changes in Thought study [47] and a general population cohort of patients receiving care at Kaiser Permanente Washington (KPWA) with Mini-mental State Exam (MMSE) scores or Montreal Cognitive Assessment (MoCA) scores. The study period is January 1, 2004 through September 30, 2015.

We first trained an NLP system on the routine clinic notes of 100% of the ACT cohort participants (n = 1473) and 60% (n = 1435) of the general population cohort to classify patients as positive or negative for symptoms and complaints associated with MCI. We subsequently trained a classifier to predict MCI as independently measured by the MMSE or MoCA score. We used a threshold score of 26 for both the MMSE and MoCA to identify a positive test [48–50].

Prior to developing the NLP system and training machine learning models we selected a 40% (n = 956) random sample of the general population cohort individuals to withhold for model validation. We validated the classifier using clinical text and scores in this 40% withheld general population sample.

Population
General population cohort
Our general population cohort included individuals aged ≥ 65 years with an MMSE or MoCA assessment and who were continuously enrolled for two years prior to administration of the assessment. During the study period, 9.7% (n = 15,396/158,937) of individuals in the general population meeting inclusion for the study had MMSE or MOCAs administered due to concerns about memory (and not part of a screening program).

Subjects from the general population were excluded if there was evidence of a diagnosis of mild cognitive impairment, Alzheimer’s Disease or related dementia, Parkinson’s Disease, or psychotic disorder, and/or use of a medication to treat Alzheimer’s Disease (e.g., donepezil) in the clinical record in the 2 years prior to the MMSE or MoCA assessment.

ACT cohort
The Adult Changes in Thought (ACT) study [47] includes randomly selected, cognitively intact KPWA members. Participants were required to be 65 years of age or older at the time of enrollment, which occurred from 1994 through 1996. A similar group of participants was enrolled between 2000 and 2002. Participants were invited to return at 2-year intervals to identify incident cases of dementia [47].

ACT study participants were assessed for dementia at baseline and every 2 years thereafter by the Cognitive Abilities Screening Instrument (CASI), with scores ranging from 0 to 100 where higher scores indicate better cognitive functioning [51–53]. We translated CASI scores to MMSE scores using a validated crosswalk previously developed in ACT [47]. Dementia-free participants continue with scheduled follow-up visits. The index date for dementia is recorded as the midpoint between the study visit when dementia was first diagnosed and the previous study visit [47, 53].

We selected a subset of ACT participants who were continuously enrolled in KPWA for 2 years prior to their index date so they would have, in addition to ACT study-specific data, electronic encounter notes from routine care required for the NLP system. The index date for individuals in the ACT cohort was defined by the first positive CASI score (score ≤ 85, indicating mild cognitive impairment).

Data
Adult changes in thought (ACT) data
Data on ACT participants (diagnoses, CASI test scores, dates of exams) were obtained from the ACT data repository maintained at the Kaiser Permanente Washington Health Research Institute.

Health system data and virtual data warehouse
Information on enrollment and health care utilization including diagnoses, procedures, and pharmacy dispensings, are recorded and maintained at KPWA in a virtual data warehouse (VDW) [54].

Developing and applying the NLP system
Developing and applying our NLP system involved: (1) assembling clinical notes for processing, (2) identifying MCI-related concepts, (3) annotating clinical notes, and (4) extracting relevant information from clinical notes to include in the prediction model.
Assembling clinical notes for processing

Clarity® is the relational database for data extracted from the Epic® EHR. It contains structured EHR data and free-text clinical “notes”. A “note” is the free text section of documentation for a clinical encounter recorded in an electronic health record. Clinicians may enter information about socio-demographic context, impressions of the patient, patient history, or supporting information for a diagnosis (e.g., symptoms/complaints). Notes vary in length between a few characters and several hundred words and may contain information copied and pasted from elsewhere in a patient’s EHR. In addition to the presence of characteristics/features, clinicians may also document the absence of these characteristics/features (e.g., “patient denies problems with sleep”). The notes used in this study are the routinely collected notes in the Kaiser Permanente Washington health system and are broadly representative of documentation found across Kaiser Permanente systems and other health care organizations.

For NLP system training and analyses we used all Family Practice (Primary Care) and Behavioral Health encounter notes during the two years preceding a patient’s index date if that date occurred between January 1, 2004 and September 30, 2015. We chose the study period start date based on availability of encounter notes for ACT enrollees. We limited our corpus of notes to those from the departments of Family Practice and Behavioral Health because these are the settings in which patients are most likely to report cognitive issues to their physician. We excluded Neurology and Speech and Language Pathology notes because they are settings where known cognitive deficits are likely to be referred for follow-up. We were interested in identifying patients that had similar complaints or deficits but did not appear to have appropriate follow-up. Separate corpora were constructed for ACT patients and general population patients.

We defined an index date as the first occurrence of a structured diagnosis for MCI in a patient’s electronic health record. Patients who never received a diagnosis of MCI were matched 1:1 by age, sex, race/ethnicity, and occurrence of a health care visit during the same 3-month calendar period to those who did receive an MCI diagnosis. That is, control cases inherit their index date from their matched MCI cases. The corpora included all notes in the 730 days preceding the index date.

The goal of the NLP investigation was to identify people with evidence of MCI noted in free text that was not recorded/documentated in structured diagnosis or pharmacy data in the 2 years prior to the index date. We classified people as positive or negative for evidence of MCI and used this information as an input to predict future MCI status as independently measured by MMSE or MoCA scores in the medical record (i.e., structured data) on the index date.

Identifying MCI-related concepts and annotation

The first step in building an NLP system was to identify relevant terms and phrases which might indicate MCI. We manually reviewed notes from the ACT cohort to identify an initial set of terms and phrases. These were expanded through further manual review of notes sampled from the general population corpus and loaded into a chart abstraction interface called brat [55].

The abstractors (TD, AG, RP) reviewed 10,391 notes and highlighted sections of text which might indicate MCI. These results were reviewed, and the most significant terms and phrases were grouped semantically into 42 unique concepts (CUIs) which are presented along with a brief description in Table 1. Linguistically equivalent word form variations were added (“call” → “called”, “calling”, “calls”). The complete list of terms and phrases used along with the associated CUIs is included as an Additional file 1: Appendix. The rules for identifying text are also included as an Additional file 2: Appendix.

Extracting relevant information from clinical notes

Using a locally developed Python program called pyTAKES [56–58] we extracted terms and phrases from notes corresponding to each concept (Table 1) in both the ACT cohort and general population cohort. pyTAKES identifies the terms and phrases from the list by first isolating sentences from the input note and tokenizing each sentence. pyTAKES then examines the tokenized input to determine if the target term matches any token. When searching for a phrase (e.g., the CUI “DECLINE” is associated with the phrase “loss cognitive ability”), pyTAKES looks for each word in succession, allowing for up to two intervening words. For example, “loss cognitive ability” will match “loss of cognitive ability”. The immediate contexts of each term (i.e., the 180 characters immediately before and after) are also retained allowing for a subsequent step to remove boilerplate (i.e., template language). Boilerplate was eliminated by identifying terms that shared either the same previous 180 characters or subsequent 180 characters with other patients.

All of the identified concepts were then supplied as features to the predictive model as binary features: coded 1 if any CUI was present in the patient’s notes, and 0 otherwise.
Table 1  Concepts associated with mild cognitive impairment

| Variable   | Description                                                                 | ACT count | Gen. Pop. Pop. count |
|------------|------------------------------------------------------------------------------|-----------|----------------------|
| S_EXCL     | References to stroke (used to exclude patients from analysis)               | 351,995   | 21,423               |
| WITHX      | Patient accompanied by family member                                        | 212,669   | 14,603               |
| RESPONS    | Responsibility being assumed by family member                               | 123,834   | 19,895               |
| NEGATE     | Atenolol, hypercalcemia, statins, and "remember to take" boilerplate language | 122,559   | 8703                 |
| HALLUC     | Hallucination issues                                                          | 75,042    | 6515                 |
| HEADACHE   | Headache/concern for stroke or brain injury                                  | 67,955    | 5550                 |
| W_EXCL     | Traumatic brain injury, dehydration, etc. (used to exclude patients from analysis) | 49,853    | 3091                 |
| DECLINE    | Declining memory/cognitive abilities                                         | 49,522    | 13,559               |
| WANDER     | Wandering, getting lost, or unable to recognize                             | 42,677    | 1821                 |
| CALLED     | Reference to communication going through family member                       | 36,073    | 3140                 |
| FORGET     | Forget/can't remember                                                        | 28,412    | 3310                 |
| DONEPEZIL  | Donepezil, Aricept discussed (e.g., regarding what the medications can do) | 18,910    | 821                  |
| CONCERN    | Family showing concern for patient                                           | 15,576    | 3568                 |
| FORGETFL   | Forgetful                                                                    | 11,146    | 1372                 |
| EXAM       | Cognitive evaluation                                                         | 10,828    | 6027                 |
| OTHER_SA   | Communication goes through family members                                    | 5474      | 562                  |
| S_HALLUC   | Strong hallucination concern                                                 | 4791      | 294                  |
| ICD_EXCL   | Dementia ICD diagnosis code appearing in text                               | 3622      | 60                   |
| DEMENTIA   | Severe dementia noted                                                        | 2426      | 85                   |
| REFERAL    | Referral for cognitive assessment                                            | 1653      | 659                  |
| COMPREHE   | Poor understanding/comprehension                                              | 1606      | 184                  |
| W_DECLIN   | Decline in word finding, vocabulary, explaining, etc                         | 1548      | 148                  |
| CONCENTR   | Difficulty concentrating                                                     | 1363      | 545                  |
| EARLY      | Early dementia                                                               | 1204      | 344                  |
| DECLINE_   | Communication/call concerning memory decline                                 | 1127      | 87                   |
| FORGETX    | Forget [something] e.g., keys                                                | 978       | 115                  |
| S_CONCER   | Worsening or strong concern for dementia                                     | 861       | 237                  |
| PLAN       | Related care plan to family member                                           | 829       | 47                   |
| HAL_EXCL   | Hallucination issues resolved                                                | 742       | 79                   |
| BOI_INCL   | Boilerplate text describing memory problems not necessarily specific to the patient | 559    | 141                  |
| OTH_EXCL   | Headache/memory complaint relating to non-patient                            | 409       | 22                   |
| RISK       | Risk of dementia                                                             | 379       | 139                  |
| W_CONCER   | Concern for word finding, vocabulary, explaining, etc                        | 377       | 26                   |
| ICD_INCL   | MCI ICD diagnosis code appearing in text but not in structured data          | 255       | 82                   |
| DENIAL     | Patient denies problem with memory or functioning                            | 204       | 6                    |
| EXM_EXCL   | Normal cognitive exam                                                        | 137       | 203                  |
| STIMULANT  | Stimulant medications (modafinil, Provigil, etc.)                            | 113       | 37                   |
| SENILE     | Not thinking well/not lucid                                                  | 73        | 0                    |
| BURDEN     | Burden on family member                                                      | 58        | 15                   |
| BOOK       | Names of relevant books, including 36-h Day, Dignified Life, and Ageless Outings | 41       | 1                    |
| EXCLUDE    | Words referencing forgetfulness excluded because of ambiguity concerns       | 3         | 7                    |
| WELLNESS   | Wellness check                                                               | 0         | 0                    |

**Machine learning model inputs**

The NLP system described above identified people with documentation of symptoms and complaints of MCI but who did not have a diagnosis or treatment for MCI or dementia at the time the clinical note was entered. The next step in building the predictive model was to expand our pool of potential predictors available to our prediction model. We included imputed household income and imputed education from census data based on where patients lived, as well as patient demographic
information in the form of age, sex, and race/ethnicity. Additionally, based on clinical judgement, we specified three aggregate predictors from the concepts in Table 1. There was one aggregate predictor for symptoms, one for behaviors, and one for forgetfulness. We calculated each as the sum of occurrences of relevant CUIs in a patient's notes as follows: Symptom Sum = (WANDER + FORGET + FORGETFL + CONCENTR + DECLINE + W DECLIN + COMPREHE + S_HALLUC + RISK); Behavior Sum = (CONCERN + CALLED + WITHX + S CONCER + W_CONCER + REFERAL + PLAN); and Forgetful Sum = (FORGET + FORGETFUL + FORGETX). Thus, the Symptom Sum varies between 0 and 9, the Behavior Sum varies between 0 and 7, and the Forgetful Sum varies between 0 and 3). Please refer to Table 1 for the definitions of the concepts [59–62].

Machine learning statistical approach
We used a least absolute shrinkage and selection operator (LASSO) logistic regression approach [63] to construct a prediction model on our general population training dataset using the NLP-derived concepts and demographic variables. The LASSO approach retains the subset of predictors with the strongest effects by shrinking some coefficients to zero and thereby improves model interpretability [64]. We used tenfold cross-validation to estimate the tuning parameter. The optimal amount of shrinkage was established using ten-fold cross-validation.

Our prediction target was a binary indicator of MCI present/absent based on a MoCA or MMSE score ≥ 26 or ≤ 26 on the index date. Predictor variables included patient age, sex, and race, presence or absence of each of the concepts we identified, and each of the three symptom scores. Using the concepts identified from the NLP system and known MCI from MMSE or MoCA scores, we constructed receiver operating curves (ROC) to measure the performance of the LASSO model in correctly predicting MCI status. We specified a range of cut-off points and performance characteristics (sensitivity, specificity, PPV, NPV) were evaluated on both training and validation datasets.

Table 2  Corpora descriptive statistics for characters, words, and tokens

| Corpus            | Num. chars Mean | Max | Min | Num. words Mean | Max | Min | Num. tokens Mean | Max | Min |
|-------------------|-----------------|-----|-----|-----------------|-----|-----|------------------|-----|-----|
| ACT (training)    | 1229.6          | 52,491.0 | 0   | 216.9          | 9350.0 | 0   | 260.8           | 10,946.0 | 0   |
| Gen. Pop. (training) | 1324.9         | 76,831.0 | 0   | 233.0          | 15,029.0 | 0   | 276.9           | 17,422.0 | 0   |
| Gen. Pop. (validation) | 1118.7         | 58,080.0 | 0   | 196.9          | 9588.0 | 0   | 234.9           | 11,251.0 | 0   |

Table 3  Cohort demographics

| ACT cohort | General population |
|------------|--------------------|
| Total people | 1473 100 | 2391 100 |
| Age at index |
| 65–69 | 14 0.95 | 456 19.07 |
| 70–74 | 107 7.26 | 515 21.54 |
| 75–79 | 260 17.65 | 461 19.28 |
| 80–84 | 395 26.82 | 450 18.82 |
| 85+ | 697 47.32 | 509 21.29 |
| Sex |
| Female | 954 64.77 | 1419 59.35 |
| Male | 519 35.23 | 972 40.65 |
| Race |
| American Indian/Alaska native | 8 0.54 | 26 1.09 |
| Asian | 40 2.72 | 104 4.35 |
| Black or African American | 61 4.14 | 51 2.13 |
| Native Hawaiian or Other Pacific Islander | 3 0.2 | 1 0.04 |
| Other | 10 0.68 | 15 0.63 |
| Unknown or not reported | 27 1.83 | 46 1.92 |
| White | 1324 89.88 | 2148 94.06 |
| Ethnicity |
| Hispanic or Latino | 37 2.51 | 94 3.93 |
| Not Hispanic or Latino | 1417 96.2 | 2249 94.06 |
| Unknown/not reported ethnicity | 19 1.29 | 48 2.01 |
| Neighborhood income |
| < $25,000 | 6 0.41 | 21 0.88 |
| ≥ $25,000 | 1409 95.66 | 2351 98.33 |
| Missing | 58 3.94 | 19 0.79 |
| Neighborhood education |
| < 25%college | 209 14.19 | 795 33.25 |
| ≥ 25%college | 1206 81.87 | 1577 65.96 |
| Missing | 58 3.94 | 19 0.79 |

This project was approved by the Kaiser Permanente Washington institutional review board.
Results

Corpus

There were 143,153 notes for 1473 ACT patients and 23,579 notes for 2391 general population patients. Table 2 shows the characteristics of the notes across corpora. Overall there were 1365,406 unique occurrences of the 42 concepts. The most frequently mentioned concepts were S_EXCL (exclude based on stroke noted, \(n = 373,418\)), WITHX (patient is accompanied by a loved one, \(n = 227,272\)), RESPONS (language noting a family member is taking responsibility for the care plan, \(n = 143,729\)) and NEGATE (clinician advising patient not to forget to do something such as take their hypertension medication, \(n = 131,262\)). Concepts affirmatively characterizing behaviors or symptoms of MCI were less common.

Population

Table 3 shows the demographic characteristics of the ACT cohort and general population cohort. We initially identified 15,396 people in the general population that were aged 65 years or more with an MMSE or MoCA score. Of these, 2071 were excluded because they were not continuously enrolled for 2 years prior to the index date on which the instrument was completed. Of the remaining 13,325 individuals, 5979 were excluded for a diagnosis of ADRD, 938 for a diagnosis of psychosis, 693 for a diagnosis of MCI, and 1739 for bipolar disorder. Of the remaining 6858, a further 488 were excluded for antipsychotic medication use and 386 who were enrolled in the ACT study. Finally, 711 were excluded because they had no notes with clinical text in the two years prior to their index test producing a final general population cohort of 2391.

The prevalence of MCI (as measured by test scores) varied across the cohorts. In the ACT training data, the prevalence of MCI was 50.03%. In the general population training data, the prevalence of MCI was 42.9% and in the general population validation data set the prevalence was 29.8%.

Table 4 shows the observed prevalence of MCI by age group and sex in the ACT cohort and General Population cohorts.

Table 5 shows the results of the logistic LASSO model. Age is a well-known predictor of cognitive impairment and this is borne out in the current study. With a coefficient of 0.023 per year, the coefficient for an individual aged 70 years would be 1.61. Stated another way, 8 years of aging is about the same in terms of MCI risk as documentation of communication going through family members.

| Table 4 | MCI prevalence |
|---------|----------------|
|         | ACT cohort     | General population |
|         | \(\text{MCI} (-)\) | \(\text{MCI} (+)\) | \(\text{MCI} (-)\) | \(\text{MCI} (+)\) |
| Age     | \begin{align*} \text{65–69} & \text{n} = 9, 5, \text{371, 85} \\ \text{%} & 64.3, 35.7, 81.4, 18.6 \end{align*} \\ | | \begin{align*} \text{70–74} & \text{n} = 57, 51, \text{407, 108} \\ \text{%} & 52.8, 47.2, 79.0, 21.0 \end{align*} | | \begin{align*} \text{75–79} & \text{n} = 136, 123, \text{318, 143} \\ \text{%} & 52.5, 47.5, 69.0, 31.0 \end{align*} | | \begin{align*} \text{80–84} & \text{n} = 194, 200, \text{270, 180} \\ \text{%} & 49.2, 50.8, 60.0, 40.0 \end{align*} | | \begin{align*} \text{85+} & \text{n} = 341, 357, \text{283, 226} \\ \text{%} & 48.9, 51.1, 55.6, 44.4 \end{align*} |
| Sex     | \begin{align*} \text{Male} & \text{n} = 260, 259, \text{693, 279} \\ \text{%} & 50.1, 49.9, 71.3, 28.7 \end{align*} | | \begin{align*} \text{Female} & \text{n} = 477, 477, \text{956, 463} \\ \text{%} & 50.0, 50.0, 67.4, 32.6 \end{align*} | | Total   | \begin{align*} \text{n} = 737, 736, \text{1649, 742} \\ \text{%} & 50.0, 50.0, 69.0, 31.0 \end{align*} |

| Table 5 | Variables retained in the prediction model |
|---------|------------------------------------------|
| Variable (intercept) | Description | Coefficient |
| ICD_EXCL | Dementia ICD9 codes in text but not structured data | 0.634 |
| DEMENTIA | Severe dementia | 0.596 |
| DONEPEZIL | Discussion of Aricept, donepezil (but not prescribed or used) | 0.568 |
| OTHER_SA | Communication goes through family members | 0.17 |
| RACE | Black race | 0.134 |
| DECLINE | Declining memory/cognitive abilities | 0.082 |
| BEHAVIOR SUM | Sum of presence of behavioral concepts | 0.076 |
| AGE | Age at index (per year) e.g. For age 70 the coefficient = 1.61 | 0.023 |
| CALLED | Reference to family member calling about patient’s memory | 0.012 |
Of the concepts identified in encounter notes, mention of donepezil, text indicating severe dementia, and problem list codes for dementia in text (but not structured data) were the strongest coefficients. With a coefficient of 0.134, Black race was also a significant predictor of MCI. On the other hand, variables such as communication through family members, and declining cognitive abilities had relatively weak coefficients. Concepts such as wandering, and hallucinations were not retained by the model.

Figure 1 shows the ROC curve characterizing performance of the model created using logistic LASSO. The area under the curve (AUC) for the validation data set is 0.67. Sensitivity analyses using only demographic variables produced an AUC of 0.598 suggesting that the NLP-derived variables significantly improve predictive ability over demographics alone. Because there is always a trade-off between sensitivity and specificity, Table 6 presents sensitivity, specificity, PPV, NPV across a wide range of cut-points (corresponding to different probabilities of correct classification). The prediction model generates a probability of MCI present at index date (which ranges from 0 to 1). For example, a cutoff of 0.3 corresponds to a 30% predicted probability of MCI diagnosed at index date. Setting the cutoff for correct classification in the general population validation cohort to 0.60 yields sensitivity of 0.02, specificity of 0.70, PPV of 0.70, NPV of 0.70 and F1 score of 0.04.

**Discussion**

Several studies report increased health care utilization and costs of care prior to diagnosis of Alzheimer’s Disease or Dementia [65–71]. While the largest increases appear to occur in the 3–6 months prior to diagnosis

![ROC curve for training and validation cohorts. Green dotted line: ACT + general population training. Light green dotted line: ACT training. Orange dotted line: general population 60% training sample. Blue dotted line: general population 40% validation sample. Gray dotted line: demographic variables only. ACT + general population 60% training: AUC = 0.716 (0.695, 0.736). ACT alone: AUC = 0.700 (0.673, 0.726). General population, 60% Training: AUC = 0.698 (0.663, 0.731). General population, 40% validation: AUC = 0.670 (0.638, 0.702). Demographics only (no NLP variables): AUC = 0.598 (0.576, 0.621)]
other studies report significant increases in utilization in the 1–3 years prior. Our study focused on the identification of mild cognitive impairment (rather than Alzheimer’s or Dementia) in the absence of screening to identify individuals on a trajectory of cognitive decline as early as possible. Early identification may help focus health care resources because identifying individuals as early as possible enables clinicians to offer patients education about the disease process and caregiver support interventions that reduce the burden of disease. Early identification also gives patients time to complete advanced directives and other end of life planning while they are still cognitively capable of doing so.

**General performance of the prediction model**

Among the 42 concepts identified by clinical experience and manual chart review, concepts that negated or ruled-out cognitive impairment were documented more frequently than those that positively identified individuals. The more common documentation of negating concepts is reflected in the very high specificity of the model across cohorts. It is also notable that the total amount of EHR information available (driven by the number of EHR notes available) was much greater for ACT than general population patients. One possible reason for the relatively modest performance of the prediction model in the validation data set may be that individuals in the general population had fewer contacts with the health system and therefore had less documentation in the EHR. It is well known that the stage of first presentation of cognitive decline varies greatly among individuals. Some patients seek care (or divulge cognitive issues) when symptoms are quite mild while others seek care only after symptoms are severe. Patients in the ACT cohort were assessed every 6 months for cognitive function and were cognitively intact at baseline according to inclusion criteria. Our approach is only useful for early detection and intervention insofar as people make health care visits and documentation of mild symptoms exists in the EHR—especially in the absence of regular, standardized screening. Previous studies have reported a bolus of health care utilization in the months leading up to an Alzheimer’s Disease or dementia diagnosis [66, 69] but not a diagnosis of mild cognitive impairment.

While an AUC of 0.67 is generally considered moderate test performance, it is also comparable to several tests that are widely used in clinical practice. For example, Veltri and Miller [72] reported an AUC of 0.632 for total prostate specific antigen (tPSA) in differentiating benign from malignant prostate tumors in a sample of 4870 patients. Similarly, Flueckiger and colleagues [73] reported an AUC of 0.716 for the revised Framingham Stroke Risk Score. The AUC for the Papanicolaou smear in detecting cervical intraepithelial neoplasia is 0.689 [74].

**Concepts retained by the prediction model**

It is well known that risk of cognitive impairment increases with age and this is reflected in the magnitude of the coefficient for age in the LASSO model. Adjusting for age, the concepts mostly strongly associated with positive MoCA and MMSE scores were related to more

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| Cohort                | Cutoff | Sensitivity | Specificity | PPV    | NPV    | F1 Score |
|-----------------------|--------|-------------|------------|--------|--------|----------|
| ACT + Gen. Pop. training | 0.3    | 0.95        | 0.17       | 0.46   | 0.83   | 0.62     |
|                       | 0.4    | 0.63        | 0.69       | 0.6    | 0.71   | 0.61     |
|                       | 0.5    | 0.37        | 0.9        | 0.73   | 0.66   | 0.49     |
|                       | 0.6    | 0.24        | 0.96       | 0.81   | 0.63   | 0.37     |
| ACT training          | 0.3    | 0.99        | 0.04       | 0.51   | 0.76   | 0.67     |
|                       | 0.4    | 0.75        | 0.52       | 0.61   | 0.68   | 0.67     |
|                       | 0.5    | 0.49        | 0.82       | 0.73   | 0.62   | 0.59     |
|                       | 0.6    | 0.34        | 0.92       | 0.80   | 0.58   | 0.48     |
| Gen. Pop. training    | 0.3    | 0.88        | 0.31       | 0.38   | 0.84   | 0.53     |
|                       | 0.4    | 0.37        | 0.86       | 0.57   | 0.74   | 0.45     |
|                       | 0.5    | 0.11        | 0.98       | 0.75   | 0.70   | 0.19     |
|                       | 0.6    | 0.02        | 1.00       | 1.00   | 0.68   | 0.04     |
| Gen. Pop. validation  | 0.3    | 0.87        | 0.32       | 0.35   | 0.85   | 0.50     |
|                       | 0.4    | 0.32        | 0.88       | 0.53   | 0.75   | 0.40     |
|                       | 0.5    | 0.09        | 0.97       | 0.56   | 0.71   | 0.16     |
|                       | 0.6    | 0.02        | 1.00       | 0.70   | 0.70   | 0.04     |

* Cutoffs are the various probabilities that the researcher or health system would choose as a threshold to classify someone as “positive” for MCI.
severe cognitive deficits. These included mentions of (but not the use of) donepezil, severe cognitive decline, and free text diagnosis codes from the problem list (but not included as formal diagnoses). This suggests that the model performs better when patients have more advanced cognitive impairment at assessment and therefore more documentation of symptoms and complaints. This may happen when patients wait to seek help until their functioning is significantly impacted. The utility of our approach in detecting cognitive impairment early depends on patients making visits and clinicians documenting mild symptoms.

The second general class of concepts retained in the model are related to communication and/or concern by family members about the patient. Both the occurrence of such communication and the cumulative amount of this communication (as measured by the aggregate variable Behavior Sum) were retained as significant predictors. This result is interesting from a clinical intervention perspective because signals/alerts for follow-up could be generated for case managers or physicians when the volume of communication by family members about the patient increases (both about memory and physical conditions).

The final interesting result is the retention of black race in the prediction model. Like the variables retained for evidence of more severe cognitive impairment discussed above, one interpretation of this result is that African American individuals are less likely to have their cognitive status discussed during an office visit until the disease has progressed to significant impairment. It may also be true that MoCA or MMSE measurement of African Americans may tend to be delayed until significant impairment exists relative to measurement of individuals of other races.

**Limitations**

This study has some important limitations. First, we conducted the study in one health system and the documentation of symptoms and complaints is likely to differ across health systems. Thus, the performance of the prediction model may be better or worse if these analyses were replicated elsewhere. Second, the training of the prediction model to ACT participants was both a strength and weakness. Research participants may not be representative in terms of visit frequency, education, and other characteristics. On the other hand, we leveraged ACT patients’ CASI scores and known periods of intact cognitive status to train the prediction model. We observed that ACT participants had significantly more contact with the health system (separate from their participation in research) and thus more documentation with which to train the model than was available in the general population.

Third, we did not evaluate the performance of the NLP system in correctly identifying concepts contained in notes. This would require comparing the automated identification in the study corpus to a reference corpus which we did not have or create. Instead, we focused on comparing our automated identification to the standardized measures of cognitive function. Similarly, we did not conduct inter-rater reliability analysis of notes that were manually annotated for concept discovery.

Fourth, there is potential for measurement error and bias in the general population of individuals with MoCA or MMSE scores. These screening instruments are not equivalent and have different performance characteristics. Moreover, a positive screen is not sufficient to diagnose mild cognitive impairment (though positive scores are routinely used to give diagnoses and refer patients to specialty care). Also, these instruments are administered when clinicians suspect cognitive impairment or want to rule-out impairment when patients or family members report symptoms, as opposed to being used for universal screening. While this bias exists, it is unlikely to have affected our results significantly because 69.0% of the MoCA and MMSE scores in the general population were negative. Also, the specificity of the model was much higher than the sensitivity. Measurement bias (by selective administration) would be more worrisome if the sensitivity of the model were very high. It is also worth noting that the prevalence of cognitive impairment increases with age. A test with the same sensitivity and specificity administered in a population with a higher prevalence will produce a higher positive predictive value and lower negative predictive value [75]. The prevalence of MCI in our training data set was intentionally set to 50% (by matching); however, the prevalence of MCI in the tested general population was only 31%.

Finally, we only calibrated one prediction model using a LASSO approach. It is possible that a different approach (such as a random forest model or neural network model) would perform better. We did not pursue these other models (and compare performance) for two reasons. First, the computational resources needed to estimate the more complicated models greatly exceed those available to healthcare systems and clinics who would use these predictive models. Second, LASSO models can be implemented natively in many electronic health records (EHR). This capability enables prediction models to be updated natively within the EHR as new healthcare utilization data become available. We are interested in ML approaches that can be implemented in the real world and change clinical care.
Conclusion
We were able to identify concepts appearing in clinical notes that are predictive of individuals developing mild cognitive impairment at a future date. The model performs moderately well in predicting MCI; however, performance may be improved by including covariates identified here with structured data in the medical record such as other diagnoses, injuries (e.g., falls), and patterns of utilization (e.g., increases in primary care visits). The success of future work on predictive modeling of cognitive impairment is likely to depend on a machine learning approach that incorporates multiple sources of data and discovering previously unidentified features.

Abbreviations
ACT: Adult Changes in Thought study; ADRD: Alzheimer’s Disease and Related Dementias; AUC: Area under the curve; BRAT: Brat rapid annotation tool; CASI: Cognitive Abilities Screening Instrument; CUI: Concept unique identifier; EHR: Electronic health record; Gen. Pop.: General population; KPWA: Kaiser Permanente Washington; LASSO: Least absolute shrinkage and selection operator; MoCA: Montreal Cognitive Assessment; NLP: Natural language processing; PPV: Positive predictive value; ROC: Receiver operating curve; U.S.: United States; VDW: Virtual data warehouse.

Supplementary Information
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Author contributions
RF, DSC, PS, and MA contributed to the design and conduct of the study and participated in the interpretation of results and preparation of the manuscript. AG and TD conducted chart reviews of patients meeting criteria to train the NLP system. They participated in revisions to the manuscript. DJC conducted the statistical modeling and wrote the manuscript. AG and TD conducted chart reviews of patients meeting criteria to train the NLP system. They participated in revisions to the manuscript. CP was the program owner who created the analytic database and contributed to manuscript revisions. EJ conducted the statistical modeling and wrote the manuscript. All authors have read and approved the manuscript.

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Availability of data and materials
Data supporting the results reported in this article may be obtained upon request from the corresponding author. Please email robert.b.penfold@kp.org to request data. Because these data could compromise individual privacy, a signed data use agreement will be necessary to access the analytic file. We cannot make available the clinical free text from patient electronic health records.

Declarations

Ethics approval and consent to participate
This study was approved by the Kaiser Permanente Washington Health Research Institute Institutional Review Board. We obtained waivers of consent and HIPAA authorization to participate.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Additional file 1: NLP Dictionary.
Additional file 2: NLP Rule Definitions for Concept Unique Identifiers.
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