Discovering heterogeneous subpopulations for fine-grained analysis of opioid use and opioid use disorders

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Abstract
The opioid epidemic in the United States claims over 40,000 lives per year, and it is estimated that well over two million Americans have an opioid use disorder. Overprescription and misuse of prescription opioids play an important role in the epidemic. Individuals who are prescribed opioids, and who are diagnosed with opioid use disorder, have diverse underlying health states. Policy interventions targeting prescription opioid use, opioid use disorder, and overdose often fail to account for this variation. To identify latent health states, or phenotypes, pertinent to opioid use and opioid use disorders, we use probabilistic topic modeling with medical diagnosis histories from a statewide population of individuals who were prescribed opioids. We demonstrate that our learned phenotypes are predictive of future opioid use-related outcomes. In addition, we show how the learned phenotypes can provide important context for variability in opioid prescriptions. Understanding the heterogeneity in individual health states and in prescription opioid use can help identify policy interventions to address this public health crisis.

1 Introduction
Prescription opioids, such as Vicodin, Percocet, and Oxycontin, are commonly prescribed for chronic and acute pain and can be effective treatments. However, opioids are highly addictive, opioid use disorders (OUD) have become widespread, and in 2016 alone, the United States saw nearly 45,000 opioid-related drug overdose deaths [1]. While some populations are understood to be vulnerable (e.g., pregnant women, users of injection drugs [15]), existing policy interventions fail to meaningfully account for heterogeneity in patient populations and differences in underlying health status [3] [8]. In order to understand where avenues for effective interventions exist, it is important to accurately characterize variability in opioid use with respect to latent health status.
To address this, we learn diagnostic phenotypes of prescription opioid users to understand the heterogeneous underlying health conditions that individuals who are prescribed opioids have. Whereas existing work using machine learning to gain insight into the opioid epidemic has used text-based data mining to identify and analyze non-prescription use of opioids [11] and supervised methods to predict opioid use outcomes in a general population [7], our goal is to identify meaningful latent health states to understand variability in opioid use and opioid use disorders within diagnostic phenotypes. We use Latent Dirichlet Allocation (LDA) [6] to learn phenotypes from the diagnostic histories of all individuals who had at least one healthcare episode, filled a prescription opioid, and were not previously diagnosed or treated for an opioid use disorder.
We demonstrate that the learned phenotypes can be used to predict future OUD, long-term use of opioids (>180 days supply annually [4]), and opioid overdose. We also show that the learned phenotypes are associated with differences in opioid prescription filling behavior. Finally, we show how examining variation in filled opioid prescriptions within phenotypes can shed light on differences in opioid use for individuals with and without opioid use disorders.

2 Data
Population-level insurance claims data Our data come from the Massachusetts All Payer Claims Database and capture almost all healthcare interactions from residents of Massachusetts for 2010-2014—a period during which OUD prevalence and opioid overdose deaths more than doubled [13]. By 2015, OUD prevalence in Massachusetts for people over age 11 was 4.6% [5].

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The data, collected and provided by the Massachusetts Center for Health Information and Analysis, include medical and pharmacy claims from private and public payers. These data are date-stamped, and include diagnoses, prescriptions and refills, member insurance eligibility information, and more.

**Inclusion criteria** To mitigate the effects of censoring (data before 2010 and after 2014 are unobserved, and data after earliest OUD diagnosis are ignored), we focus on claims from 2011. We use only data from individuals who had insurance eligibility starting prior to 2011 (6.6 million), and filtered for individuals who had at least one healthcare visit in 2011 (4.9 million remaining), were not observed to have OUD in 2011 or before (4.7 million remaining), and who filled an opioid prescription for oral or transdermal opioids in 2011 [19] (1.8 million remaining). This ensures that each individual has at least one year of diagnostic history, and prevents us from removing too many of the individuals diagnosed with OUD in future years. We identified individuals with OUD based on ICD-9 diagnosis codes for opioid abuse, opioid dependence, opioid abuse or dependence in remission, and opioid poisoning and filled prescriptions for OUD or overdose treatment (buprenorphine, methadone, naloxone). For ease of exposition, we refer to diagnosis and/or treatment of opioid use disorder as OUD in the remainder of the paper.

**Data Processing** We construct documents describing the diagnostic histories of each individual using a binary representation for whether or not each ICD-9 diagnosis code was assigned at any point in 2011. We use binary occurrences rather than counts, because counts reflect the interaction between utilization of health services attributable to access/tendency to go to the doctor, and utilization attributable to health state. A binary representation forces the phenotypes to focus on learning health state from co-occurrence of distinct diagnoses.

The data were divided into a 60/20/20 training/validation/test split, stratified by whether or not the individual was diagnosed or treated for OUD. Diagnosis codes that occurred in fewer than 3 individuals or in more than 99% of individuals in the training data were filtered out. This resulted in approximately 13,000 diagnosis codes in the final vocabulary. Table 1 describes the overall cohort demographics and outcome incidence, as well as the breakdown for the training, validation, and test sets.

|                     | N      | n_{OUD} | n_{long-term use} | n_{overdose} | Age (%) [0, 21] [21, 44] [44, 64] [64, 75] (75,) | Gender, F | Medicaid (%) |
|---------------------|--------|---------|-------------------|--------------|-------------------------------------------------|-----------|--------------|
| Training            | 1,098,687 | 33,555 (3.1%) | 50,364 (4.6%) | 2,874 (0.3%) | 13.9 33.5 37.5 12.7 2.3 | 57.9 | 19.1 |
| Validation          | 366,230  | 11,185 (3.1%) | 16,961 (4.6%) | 955 (0.3%)  | 13.8 33.6 37.6 12.6 2.4 | 57.9 | 19.0 |
| Test                | 366,230  | 11,185 (3.1%) | 16,623 (4.5%) | 928 (0.3%)  | 13.9 33.7 37.4 12.7 2.4 | 57.9 | 19.1 |
| Overall             | 1,831,147 | 55,925 (3.1%) | 83,948 (4.6%) | 14,757 (0.3%) | 13.9 33.6 37.5 12.7 2.4 | 57.9 | 19.1 |

3 Methods

**Learning Phenotypes** We use the gensim [17] implementation of Latent Dirichlet Allocation (LDA) to learn phenotypes from the diagnostic histories of individuals who were prescribed opioids. Probabilistic topic modeling methods such as LDA have been shown to learn meaningful subtypes from clinical notes [10], clinical order patterns [8], billing codes [9], and multimodal Electronic Health Record data [16]. We use an asymmetric prior on $\alpha$ to account for differences in prevalence of particular conditions. This is similar to how stopwords can be accounted for in text [21]. For each individual, LDA takes as input the set of diagnosis codes and learns *topics (phenotypes)*, where each topic is a distribution over diagnosis codes, and each individual is a distribution over topics.

**Predictive Models** We train L2-regularized logistic regression models on the training data to predict future opioid use-related outcomes. We incorporate an asymmetric cost parameter to weight examples from the minority class as more important during training, due to the high class imbalance. Values for the regularization parameter and for the asymmetric cost parameter are selected using 5-fold cross-validation on the training set.

**Selecting Number of Topics** We explore number of topics between 10 and 90 in increments of 5. All topic models are trained using only the training data. Predictive models for OUD are trained using the topic distributions, as described in the previous section. The number of topics that results in the best performance on the validation set is 80 (Figure A1).

Table 2 describes the top 5 and bottom 5 topics by enrichment for OUD. The enrichment of topic $t$ for label $y$ is defined as the weighted average of the topic presence for topic $t$, where the weight is the label $y$: $\sum_{i=1}^{n} \frac{y_i}{\sum_{j=1}^{n} y_j}$. The full set of topics is described in Table A1. Topics with diagnoses describing other substance use disorders (e.g., alcohol dependence, tobacco use disorder,
Table 2: Diagnostic phenotypes with most and least enrichment for future OUD diagnoses post 2011, with the top 3 ICD-9 diagnosis codes for each phenotype.

| Topic | Most Enriched for Future OUD | Least Enriched for Future OUD |
|-------|-----------------------------|-------------------------------|
| 32    | Tobacco use disorder, DMII wo cmp at st ucntr, Depressive disorder NEC | 29 Routine medical exam, Vaccin for influenza, Scn malig neop-prostate |
| 59    | Alcohol abuse-unspec, Alcols dep NEC/NOS-unspec, Hpt C w/ hep at comn NOS | 3 Sebaceous cyst, Scar & fibrosis of skin, Benign neo skin arm |
| 54    | Altered mental status, Muscle weakness-general, Abnormality of gait | 45 Senile nuclear cataract, Tear film insuffic NOS, Oph & related to risk |
| 4     | Post-proc states NEC, Acq absence of organ NEC, Macular degeneration NOS | 47 Screen mammogram NEC, Routine gyn examination, Bone & cartilage dis NOS |
| 25    | Tobacco use disorder, Long-term use meds NEC, History of tobacco use | 78 Other seborheic keratosis, Actinic keratosis, Benign neo skin trunk |

and long-term use of medications in topics 32, 59, and 25) are highly enriched for OUD. In contrast, topics describing routine exams (e.g., topics 29 and 47) are not highly enriched for OUD. These observations are in accordance with prior knowledge about individuals with OUD [2, 20].

4 Results

Diagnostic phenotypes can predict OUD-related outcomes

We demonstrate that our learned phenotypes capture meaningful patient health states relating to opioid use and OUD by predicting three outcomes post-2011 related to opioid use: 1) OUD, 2) long-term opioid use, and 3) opioid overdose. Using these phenotypes, learned from diagnoses alone, we are able to predict future opioid use related outcomes with high AUC (> 0.8). Importantly, we do not use prescription opioids or other medications as features in the learning process.

We compare performance against models using demographic information (features described in Table 1) and models combining demographic information with the learned diagnostic phenotypes. Performance on these tasks is shown in Figure 1. 95% confidence intervals were constructed from model performance on 100 stratified, bootstrapped samples of the test set. Improvements in performance using diagnostic phenotypes vs. demographics are statistically significant, as are improvements in performance when adding demographics to diagnostic phenotypes compared to using diagnostic phenotypes alone (paired t-test on bootstrapped samples, \( p < 0.001 \)).

While these supervised models indicate that diagnostic phenotypes are important in predicting opioid use-related outcomes, the labels we use may not be reliable [12]. For example, not all individuals who have OUD are diagnosed or treated for it, and not all opioid overdose events may be recorded in the claims data we are looking at.

![Figure 1: Performance results for future long-term use, OUD, and overdose. AUCs and 95% confidence intervals using demographic information, diagnostic phenotypes.](image)

Using Diagnostic Phenotypes to Gain Insight

Analyses of the unsupervised diagnostic phenotypes can also be used to lend insight into risk factors of OUD and avenues for intervention. As one example, we analyze variation in days supply of opioid prescriptions within diagnostic phenotypes. Figure 2 illustrates each topic’s enrichment for total days supply (calculated as described in Section 5) of opioid prescription fills in 2011. A dashed line is drawn to indicate the average total days supply (14 days) for prescription opioids in 2011. Topics with enrichment values above the line indicate above-average days supply. For example, topics 52 and 14 (back pain, chronic pain), topic 1 (Osteoarthrosis, joint replacement), and topic 32 (tobacco use disorder) are highly enriched for days supply. On the other hand, topics 30 (pregnancy) and 56 (routine gynecological exam) have lower enrichment for days supply. These enrichment values show that chronic conditions are associated with chronic usage (higher days supply), whereas acute conditions or more routine events are associated with lower than average days supply.

Figure 2 illustrates the variation in usage and outcomes within health status across three topics with low (pregnancy), average (chronic kidney disease) and high (lower back pain) enrichment for days supply of opioids in 2011. Individuals were assigned to the diagnostic phenotype with the highest probability.
Discussion & Future Work

In this work, we characterize diagnostic phenotypes in individuals who have filled an opioid prescription and have not yet been diagnosed or treated for opioid use disorder or a related outcome. We demonstrate that meaningful phenotypes can be discovered from diagnostic claims data using Latent Dirichlet Allocation, and that these phenotypes are predictive of (observed) OUD, long-term use of opioids, and opioid overdose in future years (2012-2014). We additionally show that these learned phenotypes can enable fine-grained analysis of opioid use and opioid use disorders. Labels for opioid use disorder are imperfectly observed, and so we do not use them for explicit training of our diagnostic phenotypes.

There are a number of limitations to and future directions for this work. First, diagnoses capture information relevant to individual health, but procedures and other prescription medication can also help inform our learned phenotypes. Second, by only considering whether or not a diagnosis is present in the year, we remove considerations of health services utilization and access. But, differences in access and utilization can be potential confounders and we plan to model these characteristics directly. Finally, we present a qualitative illustration of differences in opioid use in individuals who do and do not have an observed future diagnosis of OUD, conditioned on diagnostic phenotype; future work will investigate quantitative differences, and soft groupings (rather than hard assignments) of individuals to phenotypes.

While pathways to addiction, treatment, and addiction recovery are poorly understood, understanding the heterogeneous health states of individuals who are prescribed opioids will generate new understanding of opioid use and opioid use disorders. Characterizing this heterogeneity can help us identify vulnerable populations and potential policy levers to address overprescription and misuse of opioids.
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Appendix

Predicting OUD to select number of topics

Figure A1: Change in AUC for predicting opioid use disorder or treatment after 2011 using topics learned from diagnostic histories in 2011. The red line depicts performance on the training set, and the blue line depicts performance on the validation set.

Table A1: Descriptions of learned topics (top 3 ICD-9 diagnosis codes).

| Topic | $\alpha$ | Description (Top 3 ICD-9 Codes) |
|-------|---------|---------------------------------|
| 0     | 0.034   | Generalized hyperhidrosis, Counseling NOS, Non-healing surgical wound |
| 1     | 0.070   | Osteoarthrosis NOS-unspec, Joint replaced knee, Aftercare joint replace |
| 2     | 0.090   | Screen lipid disorders, Rhinitis due to pollen, Screen-diabetes mellitus |
| 3     | 0.069   | Sebaceous cyst, Scar & fibrosis of skin, Benign neo skin arm |
| 4     | 0.043   | Post-proc states NEC, Acq absence of organ NEC, Macular degeneration NOS |
| 5     | 0.174   | Eye & vision examination, Myopia, Presbyopia |
| 6     | 0.072   | Dermatophytosis of nail, Pain in limb, Ingrowing nail |
| 7     | 0.640   | Hypertension NOS, Hyperlipidemia NEC/NOS, Pure hypercholesterolem |
| 8     | 0.097   | Palpitations, Overweight, Abnormal weight gain |
| 9     | 0.079   | Carpal tunnel syndrome, Joint pain-hand, Pain in limb |
| 10    | 0.074   | Vaccination for Td-DT, Other specif counseling, Need prphyl vc vrl hepat |
| 11    | 0.057   | Absence of menstruation, Contraceptive mangmt NEC, Pregnancy test negative |
| 12    | 0.113   | Asthma NOS, Shortness of breath, Respiratory abnorm NEC |
| 13    | 0.075   | Excessive menstruation, Menstrual disorder NEC, Irregular menstruation |
| 14    | 0.138   | Backache NOS, Lumbago, Chronic pain NEC |
| 15    | 0.103   | Diarrhea, Nausea with vomiting, Noninf gastroenterit NEC |
| 16    | 0.046   | Abdominal pain rt upr quad, Cholelithiasis NOS, Herpes zoster NOS |
| 17    | 0.055   | Calculus of kidney, Abdominal pain oth spcf st, Hydronephrosis |
| 18    | 0.040   | Follow-up exam NEC, Female infertility NOS, Superficial inj cornea |
| 19    | 0.110   | Pain in limb, Joint pain-ankle, Hypermetropia |
| 20    | 0.202   | Acute pharyngitis, Acute uri NOS, Cough |
| 21    | 0.128   | Chest pain NOS, Chest pain NEC, Shortness of breath |
| 22    | 0.093   | Chr airway obstruct NEC, Pneumonia, organism NOS, Other lung disease NEC |
| 23    | 0.057   | Cellulitis NOS, Leukocytosis NOS, Oth nspcf finding blood |
| 24    | 0.130   | Abdominal pain unspcf site, Constipation NOS, Abdominal pain oth spcf st |
| 25    | 0.096   | Tobacco use disorder, Long-term use meds NEC, History of tobacco use |
| 26    | 0.080   | Lower leg injury NOS, Sprain of ankle NOS, Joint pain-ankle |
| 27    | 0.154   | Dermatitis NOS, Nonspecific skin erupt NEC, Acne NEC |
| 28    | 0.135   | Headache, Migrne unsp wo ntrc mgrn, Skin sensation disturb |
| 29    | 0.497   | Routine medical exam, Vaccin for influenza, Scrn malig neop-prostate |
| 30    | 0.031   | Supervis oth normal preg, Deliver-single liveborn, Preg state, incidental |
| 31    | 0.141   | Acute sinusitis NOS, Allergic rhinitis NOS, Viral infection NOS |
| 32    | 0.056   | Tobacco use disorder, DMII wo cmp nt st uncntr, Depressive disorder NEC |
| 33    | 0.113   | Oth spcf preop exam, Preop cardiovsclr exam, Preop exam unspcf |
| 34    | 0.059   | Enlargement lymph nodes, Observ-suspect cond NEC, Antineoplastic chemo enc |
Swelling of limb, Edema, Pain in limb
DMII wo cmp nt st uncnt, DMII wo cmp uncntrld, DMII neuro nt st uncntrl
Cervicalgia, Cervical spondylosis, Brachial neuritis NOS
Impacted cerumen, Hearing loss NOS, Sensoneur hear loss NOS
BPH w/o urinary obs/LUTS, Elvtd prostate spcf antgn, Malign neopl prostate
Osteoporosis NOS, Pain in thoracic spine, Idiopathic scoliosis
Dizziness and giddiness, Syncope and collapse, Insect bite NEC
Abn blood chemistry NEC, Chronic liver dis NEC, Abn liver function study
Fem genital symptoms NOS, Ovarian cyst NEC/NOS, Uterine leiomyoma NOS
Chronic sinusitis NOS, Nasal & sinus dis NEC, Chronic rhinitis
Senile nuclear cataract, Tear film insuffic NOS, Opn angl brderln lo risk
Screen mammogram NEC, Routine gyn examination, Bone & cartilage dis NOS
Hypopotassemia, Tachycardia NEC, Hyposmolality
Cor ath unsp vsl ntv/gft, Crnry athrscl natve vssl, Mitral valve disorder
Lumbar pain NOS, Cough, Impotence, organic orig
Head injury NOS, Pain in limb, Joint pain-up/arm
Lumbar disc degen, Lumbago, Lumbosacral spondylosis
Lyme disease, Cellulitis of arm, Follow-up exam NOS
Altered mental status, Muscle weakness-general, Abnormality of gait
Myalgia and myositis NOS, Somat dysfunc lumbar reg, Spasm of muscle
Routine gyn examination, Screen mal neop-cervix, Vaginitis NOS
Disorder of thyroid NOS, Regional enteritis NOS, Ulcerative colitis unspcf
Muscle weakness-general, Abnormality of gait, Convulsions NEC
Alcohol abuse-unspec, Alcoh dep NEC/NOS-unspec, Hpt C w/o hepat coma NOS
Idio periph neurphy NOS, Mononeuritis NOS, Mal neo bronch/lung NOS
Joint pain-l/leg, Osteoarthros NOS-l/leg, Joint effusion-l/leg
Routin child health exam, Otitis media NOS, Otalgia NOS
Obesity NOS, Obstructive sleep apnea, Morbid obesity
Hemorrhoids NOS, Visual disturbances NEC, Rectal & anal hemorrhage
Lump or mass in breast, Malign neopl breast NOS, Hx of breast malignancy
Fam hx-diabetes mellitus, Fam hx-cardiovas dis NEC, Sprain hip & thigh NOS
Long-term use antiocoagul, Therapeutic drug monitor, Atrial fibrillation
Local suprficial swellng, Insertion of iud, Iud surveillance
Aftr-catar obscur vision, Local skin infection NOS, Ulcer other part of foot
Esophageal reflux, Gstr/ddnts NOS w/o hmrhg, Diaphragmatic hernia
Urin tract infection NOS, Dysuria, Urinary frequency
Anxiety state NOS, Depressive disorder NEC, Dysthymic disorder
Anemia NOS, Abnormal loss of weight, Iron defic anemia NOS
Prim cardiomypathy NEC, CHF NOS, Atrial fibrillation
Joint pain-shlder, Rotator cuff synd NOS, Shoulder region dis NEC
Abdominal pain rt lwr quad, Spondylolisthesis, Acute appendicitis NOS
Screen malig neop-colon, Dvrtclo colon w/o hmrhg, Benign neoplasm lg bowel
Other sborheic keratosis, Actinic keratosis, Benign neo skin trunk
Vaccn/inoc viral dis NEC, Need prphyl vc varicella, Need prphyl vc vrl hepat