NBER WORKING PAPER SERIES

PREDICTING HIGH-RISK OPIOID PRESCRIPTIONS BEFORE THEY ARE GIVEN

Justine S. Hastings
Mark Howison
Sarah E. Inman

Working Paper 25791
http://www.nber.org/papers/w25791

NATIONAL BUREAU OF ECONOMIC RESEARCH
1050 Massachusetts Avenue
Cambridge, MA 02138
April 2019

We thank Miraj Shah for contributions to the project; Tom Coderre, Brandon Marshall, Susan Athey, and participants at the NBER conference on Machine Learning in Healthcare for helpful comments; and the Office of the Governor of Rhode Island and the Rhode Island Executive Office of Health and Human Services for supporting this research. We thank the Smith Richardson Foundation and the Laura and John Arnold Foundation for financial support. The views expressed herein are those of the authors and do not necessarily reflect the views of the National Bureau of Economic Research.

NBER working papers are circulated for discussion and comment purposes. They have not been peer-reviewed or been subject to the review by the NBER Board of Directors that accompanies official NBER publications.

© 2019 by Justine S. Hastings, Mark Howison, and Sarah E. Inman. All rights reserved. Short sections of text, not to exceed two paragraphs, may be quoted without explicit permission provided that full credit, including © notice, is given to the source.

Predicting High-Risk Opioid Prescriptions Before they are Given
Justine S. Hastings, Mark Howison, and Sarah E. Inman
NBER Working Paper No. 25791
April 2019
JEL No. D61,I1,I12,I18,Z18

ABSTRACT

Misuse of prescription opioids is a leading cause of premature death in the United States. We use new state government administrative data and machine learning methods to examine whether the risk of future opioid dependence, abuse, or poisoning can be predicted in advance of an initial opioid prescription. Our models accurately predict these outcomes and identify particular prior non-opioid prescriptions, medical history, incarceration, and demographics as strong predictors. Using our model estimates, we simulate a hypothetical policy which restricts new opioid prescriptions to only those with low predicted risk. The policy's potential benefits likely outweigh costs across demographic subgroups, even for lenient definitions of "high risk." Our findings suggest new avenues for prevention using state administrative data, which could aid providers in making better, data-informed decisions when weighing the medical benefits of opioid therapy against the risks.

Justine S. Hastings
Brown University
Department of Economics
64 Waterman Street
Providence, RI 02912
and NBER
justine_hastings@brown.edu

Sarah E. Inman
Columbia University
School of International and Public Affairs
420 West 118th Street
New York, NY 10027
sei2112@columbia.edu

Mark Howison
Research Improving People's Lives
1 Park Row, Suite 401
Providence, RI 02903
mhowison@ripl.org

A data appendix is available at http://www.nber.org/data-appendix/w25791

1 Introduction

Prescription opioids rank among the highest in terms of potential for dependence, abuse, and poisoning. In 2016, more Americans under the age of 50 died from drug overdoses than from car crashes or gun violence, a trend driven by increases in opioid overdoses (1). However, opioids may also be an important therapy for those who suffer from chronic pain. The majority of those prescribed opioids do not experience adverse outcomes; a survey of studies of opioid use found that rates of misuse, abuse, and addiction averaged between 8 percent and 12 percent (2). This rate is, however, higher than an early (and widely cited) claim that less than 1 percent of hospitalized patients receiving narcotics developed an addiction (3).

Moreover, many of those suffering from adverse outcomes were introduced to opioids through a legitimate opioid prescription. One study of six years of medical and pharmacy claims found that 79.9 percent of opioid abusers had a prescription prior to their first abuse diagnosis (4). Of the opioid abusers who did not themselves have a prior prescription, 50.8 percent had a family member with a prior prescription.

Given the risks and long-term consequences of adverse outcomes following legitimate opioid prescriptions, many providers now report a lack of confidence in managing their patients' chronic pain through opioid therapy (5). Providers could benefit from better information on the risks of initiating a patient on opioid therapy, especially when that patient has never received an opioid prescription before.

Prior studies have identified risk factors for opioid abuse and dependence through descriptive analysis and statistical modeling of both medical claims and electronic health records (6–10), and two studies have also evaluated the predictive performance of such models (11, 12). However, these studies focus on individuals already receiving opioid therapy and describe prescription patterns which are indicative of dependency and misuse within this subpopulation. Previous research has not yet developed a predictive model that is applicable to the larger population of potential recipients of opioid therapy.

In this study, we use novel integrated administrative data to estimate models of adverse opioid-related outcomes for Medicaid enrollees in Rhode Island and conduct policy simulations of restricting opioid prescriptions to only those with low predicted risk. By some estimates, the opioid epidemic created $5.5 billion in additional health care costs to the Medicaid program nationally in 2013 (13). Estimating our model on state administrative data provides an avenue for state policymakers to predict the risk associated with prescribing opioids to any potential Medicaid enrollee, which could be used to inform providers'

treatment decisions.

We use de-identified administrative records from the State of Rhode Island housed in a secure data enclave (14, 15). Personally identifiable information has been removed and replaced with anonymous identifiers so that researchers with approved access can join and analyze records associated with the same individual while preserving anonymity. Because this study does not involve data that is both identifiable and private, Brown University's Institutional Review Board does not classify it as research with human subjects. The database includes Medicaid records from 2005 to 2017, and data on major social benefit and insurance programs, employment, incarceration, and criminal history. We construct a panel data set of 70,153 individuals who received an opioid prescription in the Medicaid pharmacy claims between 2006 and 2012, out of 400,024 distinct Medicaid enrollees in this period. Further details are in Appendix Section 2 and Table S4.

We define an adverse opioid-related outcome as receiving a diagnosis of opioid dependence, abuse, or poisoning[1], or receiving treatment for an opioid use disorder in the five years following initial prescription. Figure S3 shows the cumulative frequency of adverse outcomes from the time of initial prescription, which peaks at 6.0 percent by year five.

We construct variables from observations in the twelve months prior to when an individual receives an opioid prescription. These include 71 variables for demographics, incarceration, citations, arrests, car crashes, wages, unemployment rates, household composition, and payments received from social benefit and insurance programs.

We construct 489 variables from Medicaid claims and enrollment records, for a total of 560 variables, as follows. First, we observe 8,494 distinct diagnosis codes and 6,507 distinct procedure codes in the Medicaid claims data. We use natural language processing topic modeling techniques to consolidate the codes into 200 topics, based on the codes' text descriptions and frequency. The topic models reduce the dimensionality of the diagnosis and procedure codes and model their co-occurrence. For example, the ten most frequent words in topic number 195 are "movements thoracic back accidents overexertion strenuous ligament neck site lumbar." The variable for topic number 195 measures how strongly this combination of diagnoses and procedures for accidental back and neck injury is represented in each individuals' medical history. Details

[1] This includes both opioid and heroin poisoning. See Appendix Section 2.2 for details.

on the topic modeling implementation appear in Appendix Section 3.1.

Second, the pharmacy claims data include 39,805 distinct drug product codes. We use existing pharmacological classifications to consolidate these into prior prescriptions indicators for 262 drug categories.

We estimate predictive models using machine learning algorithms which search over variables and functions of those variables to maximize out-of-sample predictive fit. These algorithms vary in complexity and interpretability (16), so we fit three kinds of models: a regularized regression, an ensemble, and a neural network. The complexity of regularized regressions is limited to functions of variables the researcher specifies in advance. However, each variable's contribution to prediction is easily interpreted. At the other extreme, neural networks can adaptively model complex non-linearities and interactions between variables, potentially delivering a higher predictive fit, but with greatly reduced interpretability (17).

For the regularized regression, we use a LASSO which searches over a large number of variables to identify the subset yielding highest out-of-sample predictive fit. The model is easily interpretable through a post-LASSO regression on the selected variables. However, the large set of variables we construct may include highly correlated pairs of variables, and a single LASSO could arbitrarily select one variable from such a pair. Therefore, we use a bootstrapped LASSO (BOLASSO) which retains the variables that are consistently selected among 100 bootstrap replicates (18). For the ensemble model, we average the predictions across these 100 bootstrap replicates. For the neural network, we use a recurrent neural network which can explicitly model the time dependence of the variables (19). Appendix Section 4 contains details on model implementation.

We use the model predictions to describe the potential costs and benefits of a hypothetical policy that identifies high-risk individuals before their initial prescription, prevents those prescriptions, and (we assume) also prevents their adverse outcomes. Such a hypothetical policy is supported by recent findings that predictive screening tools for opioid use disorder help primary care providers improve clinical outcomes (20), and by advice that clinicians consider patient risk before initiating opioid therapy (21). It also has similarities to the Centers for Disease Control's Patient Review and Restriction Program for limiting opioid prescriptions (22).

To simulate policy impact, we define a predicted risk threshold above which the policy would restrict opioid prescriptions. The costs and benefits then depend on how accurately our model classifies individuals

at this threshold. We define two costs: C_A denotes the cost to an individual and to society of an adverse outcome, and C_H denotes the hassle cost an individual experience from receiving an alternative therapy to opioid therapy. Assuming the policy will prevent adverse outcomes, it will save the cost $C_A - C_H$ for each True Positive (TP) who is predicted as high-risk and would have had an adverse outcome. False Positives (FP) accrue C_H because they are incorrectly classified as high-risk and prevented from obtaining an opioid prescription. The policy misses the potential savings of C_A for the false negatives, those who are incorrectly classified as low-risk but have an adverse outcome. However, there is no net change since these costs would accrue in the absence or presence of the policy. Finally, the true negatives are predicted as low-risk, do not have an adverse outcome, and accrue neither cost.

The net benefit of the hypothetical policy is, therefore, $TP(C_A - C_H) - FP \cdot C_H$. It is positive when $TP/(FP + TP) > C_H / C_A$. This captures the tradeoff between model accuracy (the True Positive Rate) and the "cost ratio" C_H / C_A. If the hassle cost C_H is low relative to the adverse outcome cost C_A, then it will be beneficial to intervene with more individuals by setting a lower risk threshold and accepting a lower degree of classification accuracy. We use this framework to illustrate hypothetical policy tradeoffs and to measure fairness across marginalized subpopulations.

2 Results

2.1 Predictive performance

A common metric for assessing the performance of a machine learning model is the area under the receiver- operating characteristic curve (AUC). The AUC measures the probability that, given two randomly chosen individuals with different outcomes, the model will correctly assign a higher risk to the individual with the adverse outcome. A perfect classifier has an AUC of 1, and a classifier that chooses at random has an AUC of 0.5.

Our models achieve AUCs of 0.754 (95% C.I. 0.740 - 0.771) for the BOLASSO, 0.781 (95% C.I. 0.7690.795) for the LASSO ensemble, and 0.793 (95% C.I. 0.780 – 0.808) for the neural network. The gains to the neural network are small and not significantly different from the LASSO ensemble; the loss in interpretability does not deliver gains in predictive power.

Figure 1 shows the distribution of true outcomes by predicted risk decile for each model. Within

the top three risk deciles, the fraction of true outcomes predicted by all of the models is greater than the base rate of outcomes among the entire population, which is 0.06.

2.1 Interpreting model results

Figure 2 shows the distribution of odds ratios from the post-BOLASSO regression for the 89 variables which the BOLASSO model selected as the strongest, consistent predictors from the full set of 560 variables across the 100 bootstrap replicates. BOLASSO helps to identify consistent covariates, avoiding arbitrary choices among highly correlated pairs. While the coefficients on the selected variables do not necessarily have a causal interpretation, they pick up factors which are strong predictors among observables. For example, observed claims for routine preventative health may themselves lower risk through increased or more frequent interactions with medical professionals, or they may proxy for attention to personal health or responsibility which is the true unobserved underlying factor that reduces risk. In a predictive model, our primary goal is to understand the observables that predict risk so we can design more effective policy. Understanding these predictors can, however, also point us in the direction of potential causal relationships and underlying mechanisms for further study.

Overall, the variables with the largest odds ratios were release from prison (1.929), and prior prescriptions for antipsychotics (1.317), centrally-acting muscle relaxants (1.296), benzodiazepines (1.213), and opiate agonists (1.196). Individuals who were released from prison in the prior year are estimated as 92.9 percent more likely to have an adverse outcome if given an initial prescription, all else equal. The coefficient on opioid agonists indicates that prior prescriptions from drugs such as cough syrups and mild painkillers with small dosages of an opioid ingredient (see Table S5) are positive risk factors, even though these drugs are not considered strong enough for chronic opioid therapy.

Variables with the smallest odds ratios (indicating decreased risk) were enrollment in Medicaid with a payer code for the Rhode Island Pharmaceutical Assistance to the Elderly program (0.008 – indicating an almost complete reduction in risk), the categorically-needy Medicaid eligibility criterion (0.136), Hispanic race (0.245), missing race (0.305), and missing marital status (0.350). Because we use modal race and marital status across all administrative sources, these missing indicators are likely proxies for individuals who are enrolled only in Medicaid and not in other state services where race and marital status are reported.

The majority of variables (72) are derived from Medicaid records. Of these, four are derived from Medicaid enrollment characteristics (such as eligibility criteria), one is total pharmacy payments, and four

are for prior prescriptions. The remainder of the Medicaid predictors are diagnosis/procedure topics. Some of the significant themes among the selected topics include: injuries and pain (+); mental health (+); HIV (+); cardiovascular health (+); contraceptives (-); tobacco and alcohol use (+); cancer (-); routine examinations (-); and mammograms (-).

2.2 Cost ratio

Figure 3 shows the break-even cost ratio C_H/C_A at which the hypothetical policy is cost neutral across cumulative risk deciles using predictive risk from the neural network model. In the top risk decile, the break-even ratio is 0.233: it is net beneficial to recommend against opioid prescriptions for individuals in the top decile if the C_H is less than 23.3 percent of C_A. It is net beneficial to intervene with the entire population if C_H is less than 6.0 percent of C_A.

The existing literature provides guidance on reasonable estimates for C_H and C_A. In 2015, 33,091 people died from drug overdoses involving opioids (23), and 2,375,000 individuals over the age of 12 had an opioid use disorder (24). The U.S. Department of Transportation's Value of a Statistical Life is $10.1 million. Florence *et al*. (13) estimate the aggregate annual societal cost of an opioid use disorder to be $61,297 (including additional cost of health care, substance abuse treatment, lost productivity, and criminal justice activities). Weiss and Rao (25) estimate a 50 percent recovery probability after one year of medication-assisted treatment. Using these statistics, with the simplifying assumption that once an individual receives a prescription, they either overdose resulting in death, become dependent but successfully recover after one year of treatment, or continue to be dependent for ten years, we estimate a ballpark present discounted value of $450,000 for C_A.

Hassle costs are more difficult to quantify. They may include lost productivity due to chronic pain after receiving an alternative therapy. The economic cost of pain in the United States is conservatively estimated at $560 to $635 billion (2010 dollars), with a value of lost productivity from $299 to $335 billion (26). Treating pain compassionately is a moral imperative for physicians, who must balance protecting those experiencing chronic pain with the significant risk of harm that opioids can cause individuals, their families, and their communities (27).

However, recent research suggests that opioid therapy may not be more effective at pain relief than non-opioid therapy in both the short- and long-term. A randomized trial comparing opioid therapy to non-

opioid therapy for acute short-term pain found similar levels of pain relief between the two treatments (28). Observational studies of restricting opioid therapy and offering non-opioid therapy over longer periods of time also show no advantage for opioid treatment in terms of pain relief, with some patients on higher-potency opioids reporting more psychological impairment than those on lower-potency opioids (29, 30).

This suggests that the C_H is likely lower than \$104,850 (23.3 percent of \$450,000), meaning that a low risk threshold that maximizes true positives at the cost of increased false positives could be optimal. These findings support a belief among some within the medical community that the risks of opioid prescription outweigh the benefits in many cases of prescription outside of cancer or palliative care (31). A benefit of structuring our cost-benefit analysis in terms of the cost ratio is that a risk threshold can easily be reevaluated as better data on these costs become available.

2.3 Fairness

In addition to evaluating the costs and benefits of the hypothetical policy, our model can help policymakers examine measures of "fairness" – the extent to which the benefits versus costs of a policy accrue disproportionately to marginalized groups. The model's false discovery rate (FDR) provides such a measure. It is defined as the fraction of false positives among all individuals who are predicted to have an adverse outcome. Figure 4 shows the FDR in the highest risk quintile by race, incarceration history, and disability status.

While members of minority groups (African-American, Hispanic) have a higher point estimate for FDR in the highest risk quintile of our model, the variance in the estimates is high and the difference is not significant. The previously incarcerated have a significantly lower FDR, and there is no significant difference by disability status. Therefore, we do not find evidence of unfairness using the FDR.

3 Discussion

Prevention and treatment policies can be complementary approaches to opioid use disorders. Treatment can help the many individuals already suffering from adverse outcomes, while prevention can stem the growth of new cases of opioid dependence, abuse, or poisoning.

The proven standard treatment for opioid use disorder is medication-assisted treatment (MAT) (32–34). However, it faces two significant hurdles. First, MAT is not widely available to those with opioid use

disorders; only 36 percent of substance abuse treatment facilities offering one of three different kinds of medication treatment (35). Second, even when those suffering from opioid use disorders can be connected to treatment, the costs associated with treatment are high and recovery from an opioid use disorder is challenging. The probability of recovery after a year of MAT is estimated at 50 percent (25).

Prevention strategies can help prevent further cases of opioid use disorder. Current strategies are primarily designed around reducing the quantity or potency of opioid prescriptions to curb misuse and prevent poisoning among those with existing opioid use disorders.[2] These strategies are especially complementary to a treatment approach. A recent study suggests that limiting opioid availability for those with an existing disorder may increase the use of illicit drugs such as heroin.[3]

The most widespread approach to preventing misuse by those with a disorder has been the deployment of state-level prescription drug monitoring programs (PDMPs). These electronic data systems present data on the prescription history of controlled drugs to providers, and are now in use in almost every state (34). They have been shown to reduce prescription rates of opioids and increase provider comfort in prescribing opioids, as providers can be reassured that they are not enabling risky opioid-related behaviors such as doctor shopping or overlapping prescriptions (38, 39).

These strategies are reactive rather than proactive; they target individuals who have already begun opioid treatment and have likely developed dependency based on risky prescription behavior. Our models complement these policies by providing an opportunity to predict high-risk prescriptions among the larger population of potential patients who have yet to be given an initial opioid prescription.

Our models and hypothetical policy aim to prevent dependency before it occurs. This is complementary to existing efforts and could make use of the infrastructure already in place, such as the PDMPs. For example, a PDMP could implement our modeling approach to show providers a risk categorization for all patients (e.g. a red, yellow, or green indicator for predicted risk). This could increase information available to providers, expand the population covered by the PDMP, and help providers consider the benefits and risks of initiating opioid therapy with a new patient.

[2] For example, a major health insurer's effort to reduce extended-release oxycodone prescription by requiring prior authorization, which led to an increase in the rate of short-acting opioid prescriptions and no overall change in the total morphine milligram equivalents prescribed (36).

[3] Abuse-deterrent reformulations of prescription opioids were developed to make it more difficult to crush or dissolve pills to release the drug more quickly. Unfortunately, recent evidence suggests that the introduction of abuse-deterrent prescription opioids into the market caused opioid abusers to substitute away from prescription opioids to heroin, with differential increases in fatal heroin poisonings (37).

A limitation of our study is that it is restricted to the population of Medicaid enrollees. Expanding the study to a data source such as an all-payers claims database would improve representativeness by including Medicare enrollees and the privately insured. However, a strength of restricting our study to the Medicaid population is our ability to securely join claims data to additional administrative records, which could be challenging with an all-payers claim database.

Our definition of adverse outcomes is limited by the accuracy of diagnosis codes in the Medicaid records. In particular, prior studies have found that opioid-related diagnoses can be underreported because of their potential stigma (40, 41). To address this limitation, we added an adverse outcome based on procedure codes for the treatment of opioid use disorder, which could indicate an adverse outcome even in the absence of a diagnosis.

Including treatment as an indicator of adverse outcomes is also a limitation. As noted in prior work, receiving treatment for an opioid use disorder is a positive outcome conditional on already having a disorder (41, 42). However, the goal of this study is to suggest opportunities for prevention by examining whether individuals at a high risk of developing an adverse outcome can be identified with confidence before they are given a prescription using administrative data. This complements important research being done on successfully treating opioid use disorders after they have occurred (43).

4 Conclusion

The opioid epidemic is a complex public health challenge for which prevention and treatment are complementary approaches. Our results demonstrate the feasibility of a new approach to prevention based on intervening with high-risk initial prescriptions through predictive modeling. Our data-driven, machine-learning approach to modeling adverse outcome risk provides new insights into the benefits, costs, and fairness of policies limiting opioid prescriptions. Intervening at the earliest stage, before an individual receives an initial opioid prescription, has the potential to prevent future treatment costs and recovery challenges and, ultimately, the life-long consequences of opioid use disorders.

Acknowledgments

We thank the Smith Richardson Foundation and the Laura and John Arnold Foundation for financial support. We thank Miraj Shah for contributions to the project; Susan Athey, Tom Coderre, Brandon Marshall, and participants at the NBER conference on Machine Learning in Healthcare for helpful comments; and the Office of the Governor of Rhode Island and the Rhode Island Executive Office of Health and Human Services for supporting research to improve fact-based policymaking.

Data are available through individual data sharing agreements with each of the following Rhode Island agencies and municipal police departments: RI Department of Corrections, RI Department of Labor and Training, RI Executive Office of Health and Human Services, RI State Police, Central Falls Police Department, Cranston Police Department, Cumberland Police Department, Middletown Police Department, Narragansett Police Department, Providence Police Department, Warwick Police Department, Woonsocket Police Department.

AHFS® Pharmacologic/Therapeutic Classification© used with permission. © 2017, the American Society of Health-System Pharmacists, Inc. (ASHP). The Data is a part of the AHFS Drug Information®; ASHP is not responsible for the accuracy of transpositions from the original context.

References

[1] Kaplan S (2017) C.D.C. Reports a Record Jump in Drug Overdose Deaths Last Year. *The New York Times* (Nov. 3, 2017).

[2] Vowles KE, et al. (2015) Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain* 156(4):569–576.

[3] Porter J, Jick H (1980) Addiction rare in patients treated with narcotics. *New England Journal of Medicine* 302(2):123.

[4] Shei A, et al. (2015) Sources of prescription opioids among diagnosed opioid abusers. *Current Medical Research and Opinion* 31(4):779–784.

[5] Pearson A, Moman R, Moeschler S, Eldrige J, Hooten WM (2017) Provider confidence in opioid prescribing and chronic pain management: results of the Opioid Therapy Provider Survey. *Journal of Pain Research* 10:1395–1400.

[6] White AG, Birnbaum HG, Schiller M, Tang J, Katz NP (2009) Analytic models to identify patients at risk for prescription opioid abuse. *American Journal of Managed Care* 15(12):897–906.

[7] Sullivan MD, et al. (2010) Risks for possible and probable opioid misuse among recipients of chronic opioid therapy in commercial and medicaid insurance plans: The TROUP Study. *Pain* 150(2):332–339.

[8] Palmer RE, et al. (2015) The prevalence of problem opioid use in patients receiving chronic opioid therapy: computer-assisted review of electronic health record clinical notes. *Pain* 156(7):1208–1214.

[9] Yang Z, et al. (2015) Defining Risk of Prescription Opioid Overdose: Pharmacy Shopping and Overlapping Prescriptions Among Long-Term Opioid Users in Medicaid. *Journal of Pain* 16(5):445–453.

[10] Brat GA, et al. (2018) Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. *BMJ* 360:j5790.

[11] Dufour R, et al. (2014) Understanding predictors of opioid abuse: predictive model development and validation. *American Journal of Pharmacy Benefits* 6(5):208–216.

[12] Hylan TR, et al. (2015) Automated Prediction of Risk for Problem Opioid Use in a Primary Care Setting. *Journal of Pain* 16(4):380–387.

[13] Florence CS, Zhou C, Luo F, Xu L (2016) The economic burden of prescription opioid overdose, abuse, and dependence in the United States, 2013. *Medical Care* 54(10):901–906.

[14] Hastings JS, Howison M, Lawless T, Ucles J, White P (2019) Unlocking Data to Improve Public Policy. *OSF Preprints* 28krq. Preprint, posted March 15, 2019.

[15] Hastings J (2019) Fact-Based Policy: How Do State and Local Governments Accomplish It? *The Hamilton Project (Brookings Institution)* Policy Proposal 2019-01.

[16] Hastie T, Tibshirani R, Friedman J (2009) *The Elements of Statistical Learning*. (Springer-Verlag, New York), second edition.

[17] LeCun Y, Bengio Y, Hinton G (2015) Deep learning. *Nature* 521(7553):436–444.

[18] Bach FR (2008) Bolasso: Model Consistent Lasso Estimation Through the Bootstrap in *Proceedings of the 25th International Conference on Machine Learning*, ICML '08. (ACM, New York, NY, USA), pp. 33–40.

[19] Hochreiter S, Schmidhuber J (1997) Long Short-Term Memory. *Neural Computation* 9(8):1735–1780.

[20] Lee C, Sharma M, Kantorovich S, Brenton A (2018) A Predictive Algorithm to Detect Opioid Use Disorder: What Is the Utility in a Primary Care Setting? *Health Services Research and Managerial Epidemiology* 5:1–8.

[21] Agarin T, Trescot A, Agarin A, Lesanics D, Decastro C (2015) Reducing Opioid Analgesic Deaths in America: What Health Providers Can Do. *Pain Physician* 18(3):E307–E322.

[22] Centers for Disease Control and Prevention (2013) Patient Review & Restriction Programs: Lessons learned from state Medicaid programs, Technical Report CS240524.

[23] National Institute on Drug Abuse (2017) National Overdose Deaths from Select Prescription and Illicit Drugs. https://www.drugabuse.gov/sites/default/files/overdose data 1999-2015.xls (Accessed March 25, 2019).

[24] Center for Behavioral Health Statistics and Quality (2017) 2016 National Survey on Drug Use and Health: Detailed Ta- bles. https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2016/NSDUH-DetTabs-2016.pdf (Accessed March 25, 2019).

[25] Weiss RD, Rao V (2017) The Prescription Opioid Addiction Treatment Study: What have we learned. *Drug & Alcohol Dependence* 173:S48–S54.

[26] Gaskin DJ, Richard P (2012) The Economic Costs of Pain in the United States. *The Journal of Pain* 13(8):715–724.

[27] Califf RM, Woodcock J, Ostroff S (2016) A Proactive Response to Prescription Opioid Abuse. *New England Journal of Medicine* 374(15):1480–1485.

[28] Chang AK, Bijur PE, Esses D, Barnaby DP, Baer J (2017) Effect of a Single Dose of Oral Opioid and Nonopioid Analgesics on Acute Extremity Pain in the Emergency Department: A Randomized Clinical Trial. *JAMA* 318(17):1661–1667.

[29] Shimoni Z, Varon D, Froom P (2018) Minimal Use of Opioids for Pain Relief in an Internal Medicine Department. *Southern Medical Journal* 111:288–292.

[30] Elsesser K, Cegla T (2017) Long-term treatment in chronic noncancer pain: Results of an observational study comparing opioid and nonopioid therapy. Scandinavian Journal of Pain 17(1):87–98.

[31] Chou R, et al. (2009) Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. The Journal of Pain 10(2):113–130.e22.

[32] Barry CL (2017) Fentanyl and the Evolving Opioid Epidemic: What Strategies Should Policy Makers Consider? *Psychiatric Services* 69(1):100–103.

[33] Mohlman MK, Tanzman B, Finison K, Pinette M, Jones C (2016) Impact of Medication-Assisted Treatment for Opioid Addiction on Medicaid Expenditures and Health Services Utilization Rates in Vermont. *Journal of Substance Abuse Treatment* 67:9–14.

[34] Volkow ND, McLellan AT (2016) Opioid Abuse in Chronic Pain — Misconceptions and Mitigation Strategies. *New England Journal of Medicine* 374(13):1253–1263.

[35] Mojtabai R, Mauro C, Wall MM, Barry CL, Olfson M (2019) Medication Treatment For Opioid Use Disorders In Substance Use Treatment Facilities. *Health Affairs* 38(1):14–23.

[36] Barnett ML, et al. (2018) A Health Plan's Formulary Led To Reduced Use Of Extended-Release Opioids But Did Not Lower Overall Opioid Use. *Health Affairs* 37(9):1509–1516.

[37] Alpert A, Powell D, Pacula RL (2017) Supply-Side Drug Policy in the Presence of Substitutes: Evidence from the Introduction of Abuse-Deterrent Opioids, (National Bureau of Economic Research), Working Paper 23031.

[38] Lin DH, et al. (2017) Physician attitudes and experiences with Maryland's prescription drug monitoring program (PDMP). *Addiction* 112(2):311–319.

[39] Wen H, Schackman BR, Aden B, Bao Y (2017) States With Prescription Drug Monitoring Mandates Saw A Reduction In Opioids Prescribed To Medicaid Enrollees. *Health Affairs* 36(4):733–741.

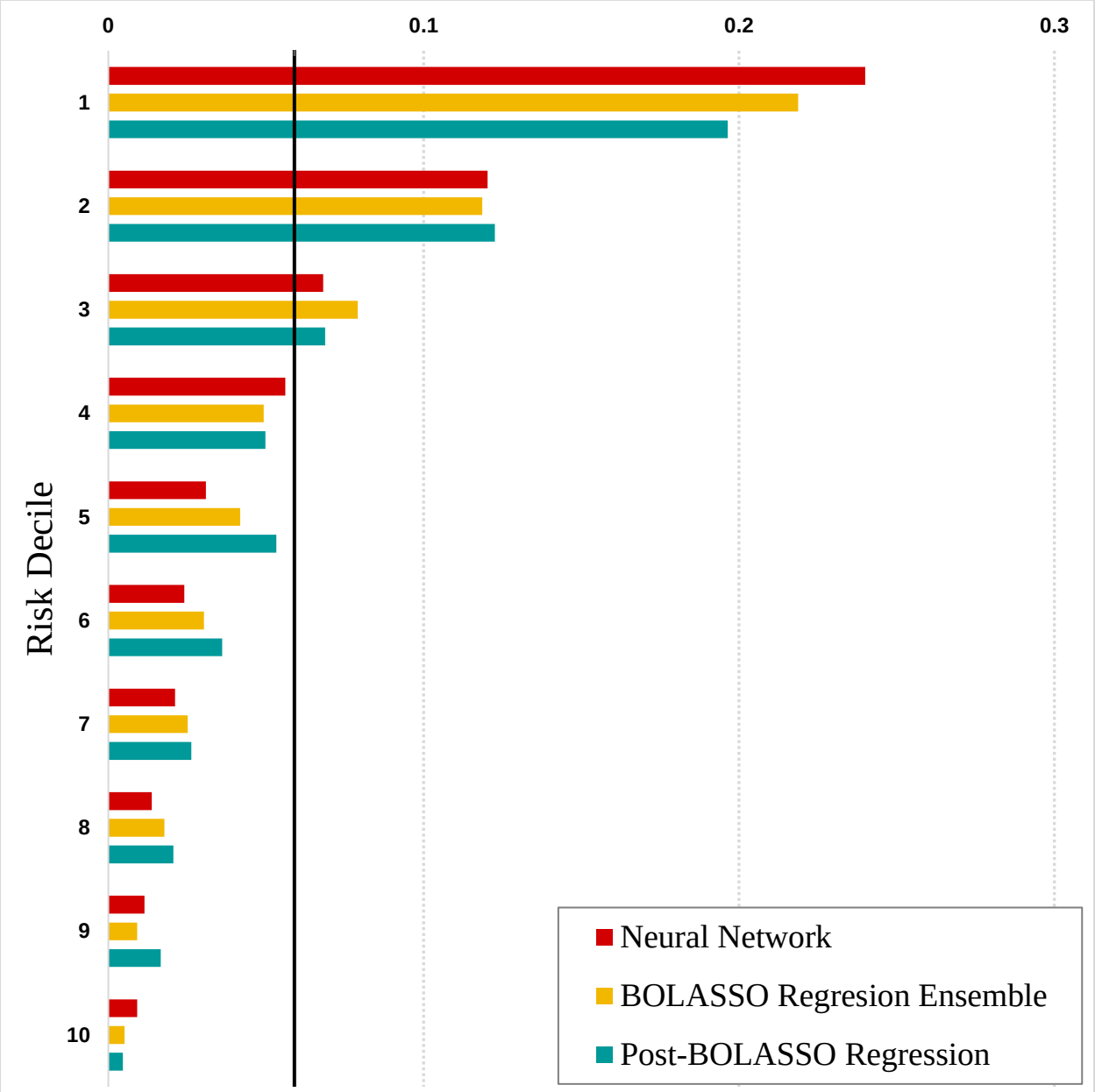
[40] Carrell DS, et al. (2015) Using natural language processing to identify problem usage of prescription opioids. *International Journal of Medical Informatics* 84(12):1057–1064.

[41] Barocas JA, et al. (2018) Estimated Prevalence of Opioid Use Disorder in Massachusetts, 2011–2015: A Capture–Recapture Analysis. *American Journal of Public Health* 108(12):1675–1681.

[42] Hadland SE, et al. (2018) Receipt of Timely Addiction Treatment and Association of Early Medication Treatment With Retention in Care Among Youths With Opioid Use Disorder. *JAMA Pediatrics* 172(11):1029–1037.

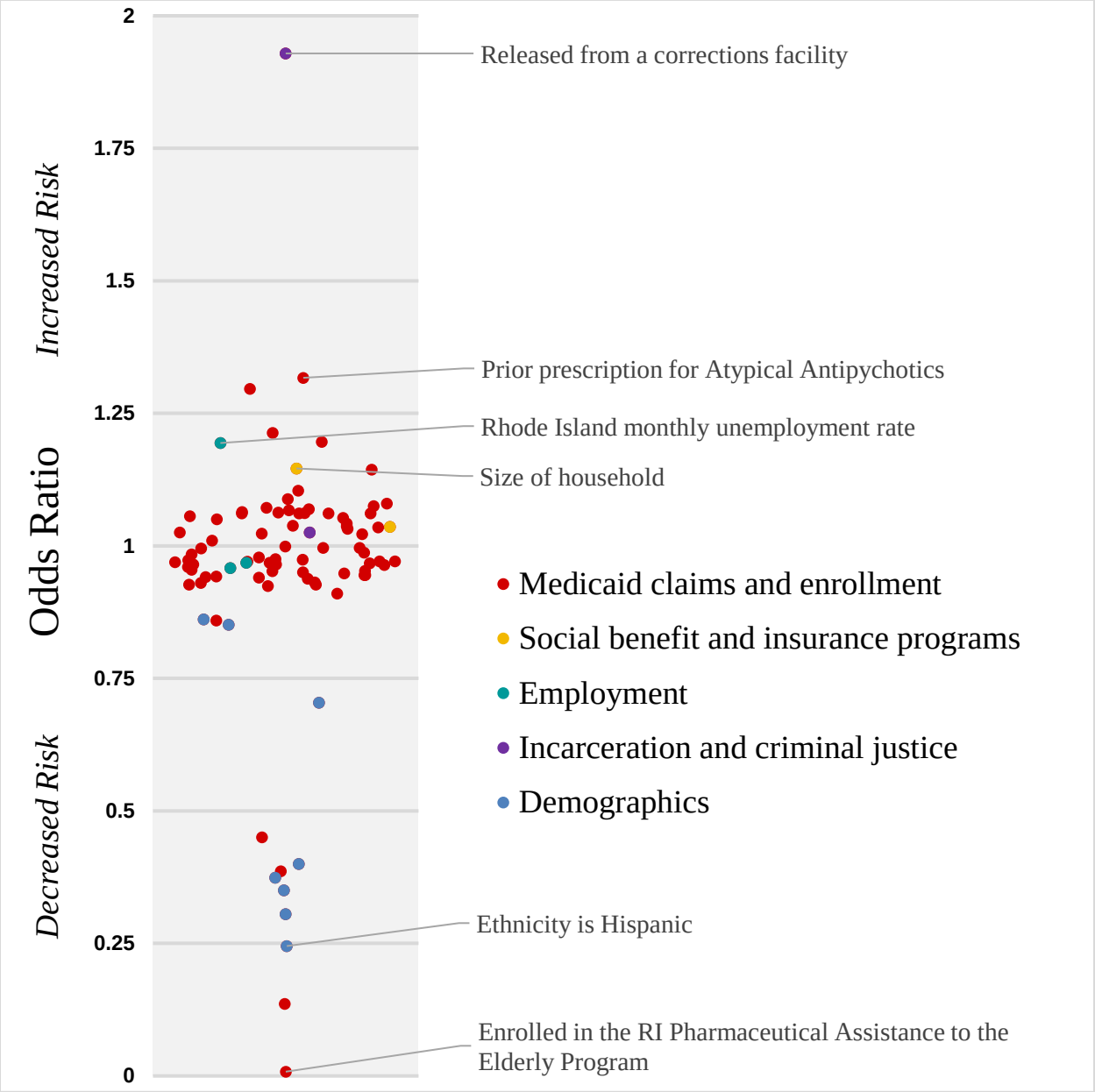
[43] Green TC, et al. (2018) Postincarceration Fatal Overdoses After Implementing Medications for Addiction Treatment in a Statewide Correctional System. *JAMA Psychiatry* 75(4):405–407.

Figure 1: The fraction of true outcomes by risk decile in the test sample.



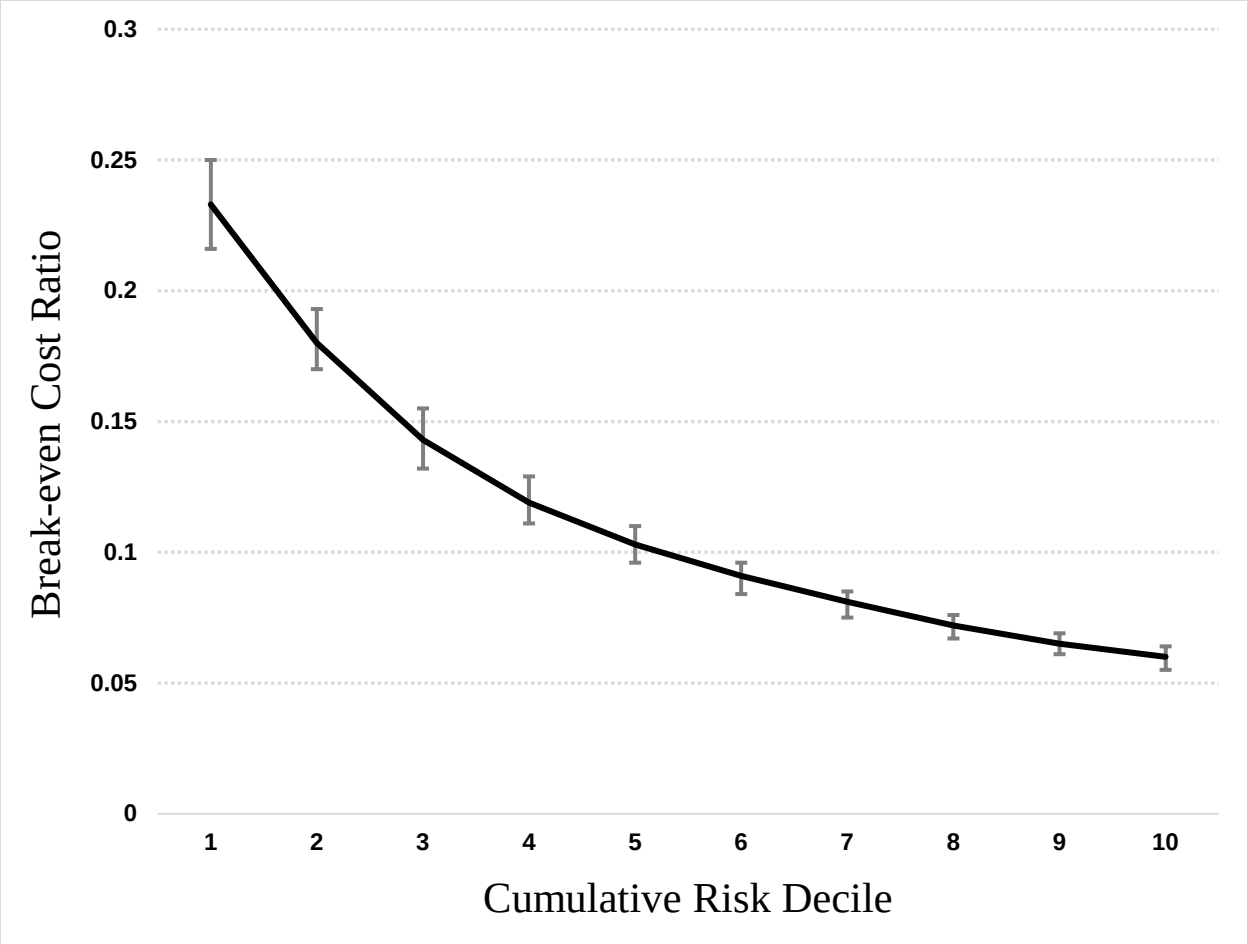
Note: The vertical black line indicates the base rate of outcomes among the entire population, which is 0.06.

Figure 2: Odds ratios from the post-BOLASSO regression.



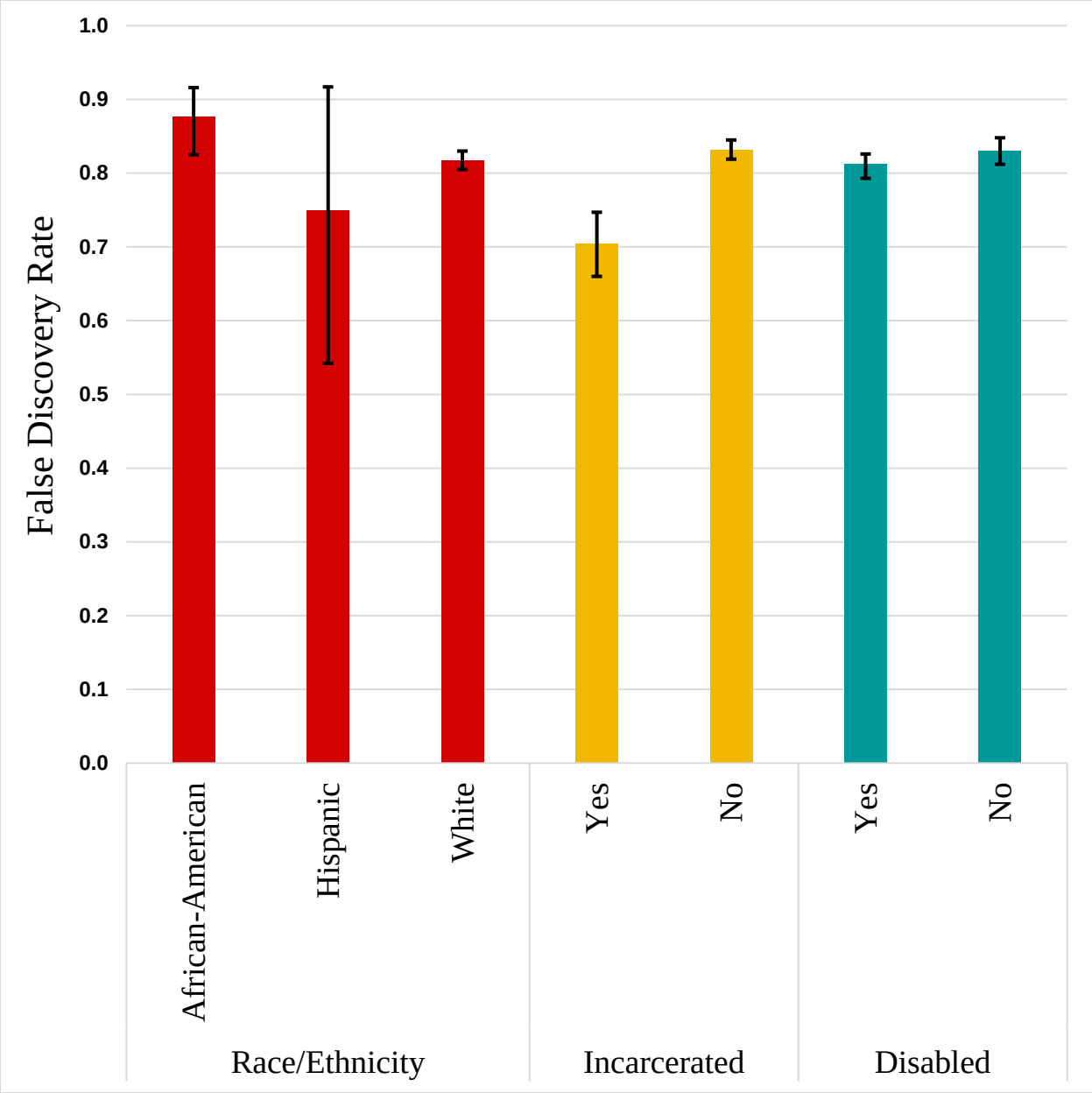
Note: The full regression output is available in Table S6.

Figure 3: The break-even cost ratio by cumulative risk decile.



Note: The break-even cost ratio is the point at which the hypothetical policy becomes cost neutral. If the hassle cost is less than this ratio times the adverse outcome cost, than the policy will be net beneficial. Lower hassle costs are required to make the policy net beneficial among lower risk scores. Error bars indicate the 95% confidence interval calculated from 100 bootstrap replicates.

Figure 4: The false discovery rate for the highest risk quintile.



Note: The false discovery rate is defined as the fraction of false positives among all individuals who are predicted to have an adverse outcome, which is the population that the hypothetical policy would affect. Error bars indicate the 95% confidence interval calculated from 100 bootstrap replicates.

Appendix

1 Experimental Design

Our objective was to define a panel of Rhode Island Medicaid recipients who received an initial opioid prescription under Medicaid coverage; define adverse outcomes of opioid dependence, abuse, or poisoning; and model and assess the accuracy of predictions of adverse outcomes using information known only prior to the initial prescription. Data were split into randomly-sampled training, validation, and testing sets using the ratio 50:25:25 at the beginning of the study. We report the results of model predictions on the testing set, which was withheld from analysis prior to the preparation of the manuscript.

Data are from the period 2005-2017, and include Rhode Island administrative records from the Department of Human Services (DHS), Department of Labor and Training (DLT), Department of Corrections (DOC), Medicaid program (under the Executive Office of Health and Human Services), and police agencies (including the Rhode Island State Police and eight municipal police departments).

Although our data span the years 2005 to 2017, we construct a panel of individuals with initial prescriptions between 2006 and 2012 to allow for the construction of variables a year before the initial prescription and to define outcomes up to five years after the initial prescription.

2 Panel and Outcome Definitions

2.1 Opioid Prescriptions

To define our panel, we first establish which pharmacy claims correspond to opioid prescriptions. The primary identifier for the dispensed drug is a standardized 11-digit National Drug Code (NDC) from the U.S. Food and Drug Administration's NDC Directory.[1] This directory is only available as a current snapshot, and because our claims data start in 2005, there are many unmapped NDCs to the current directory. Out of approximately 14.8 million pharmacy claims between 2006 and 2012, only 66.8 percent join to the current directory. Therefore, we construct a historical NDC directory using a data mining framework that downloads and collates all available Internet Archive snapshots of the FDA's NDC website since 2000.[2] This historical directory also includes full ingredient lists for each NDC, standardized to milligrams. Using this improved directory, 88.1 percent of pharmacy claims between 2006 and 2012 map to an NDC entry.

We define an opioid prescription as any claim for a drug containing an opioid ingredient at or above the recommended starting dose when initiating opioid therapy for chronic pain management, as established in Washington State's 2015 prescribing guideline and further cited in the Centers for Disease Control's 2016 prescribing guideline.[3,4] Table S1 lists these ingredients and the minimum amounts we use to define an opioid drug. Of the 4,359 drugs containing one of these ingredients, 4,175 meet the minimum threshold amount and appear in 3.9 percent of claims.

Additionally, we define a recovery prescription as any NDC containing one of four ingredients commonly used in medication-assisted treatment of an opioid use disorder, which identifies 412 such drugs that appear in 0.5 percent of claims. These prescriptions may indicate that an individual has a preexisting opioid use disorder.

2.2 Outcomes

For each individual in our panel, we examine all of the Medicaid claims following their initial opioid prescription to construct indicator variables for four types of adverse outcomes: opioid dependence, opioid abuse, prescription-opioid poisoning and heroin poisoning. We include heroin poisoning as an outcome given the increasing use of heroin among those who abuse opioids, and the high proportion (greater than 80 percent) of joint heroin-prescription-opioid users who abused opioids prior to using heroin.[5]

We determine these outcomes from the claim's International Classification of Diseases (ICD) diagnosis codes, which are used by medical professionals to classify a patient's health conditions following an encounter. Because our data span the transition from the ICD-9 to ICD-10 classification, we include diagnosis codes from both. Table S2 lists the exact codes used to indicate each of these four diagnosis-related outcomes.

Not everyone with an opioid use disorder receives a diagnosis code. Though it is unknown precisely what fraction of opioid use disorders go undiagnosed, Carrell *et al*. found that diagnosis codes were missing for as many as a quarter of patients for whom their providers were aware of opioid abuse.[6] Similarly, a study by Barocas *et al*. estimated that only 44% of individuals with opioid use disorder were identified as such in claims and administrative records.[7] To address the challenges with diagnoses codes, we define a fifth treatment outcome using procedure codes related to the treatment of opioid use disorder, and more generally for drug rehabilitation and detoxification (Table S2). Finally, we define a sixth "any" outcome as the union of any of the diagnoses or treatment outcomes, to capture as broad a population of individual with opioid use disorder as possible. Data and measurement limitations notwithstanding, our model demonstrates that administrative data can be combined to form an accurate prediction of these outcomes, suggesting a feasible path forward for utilizing data to inform prescription risk. Figure S3 shows the accumulating fraction of adverse outcomes over the five-year period following initial prescription.

2.3 Final Panel

Out of 400,024 distinct Medicaid enrollees between 2006 and 2012, our panel initially contains 74,213 individuals who received at least one opioid prescription in that period. We exclude 511 individuals who received a recovery prescription before their initial opioid prescription, since this indicates they may have been seeking treatment for an opioid use disorder. We exclude 3,549 individuals with an adverse outcome prior to their initial opioid prescription, since we assume they were already receiving opioids from another source, such as through private insurance before enrolling in Medicaid. Our final panel includes 70,153 individuals. Table S4 shows the incidence of adverse outcomes among these individuals by baseline characteristics.

3 Variable Construction

We construct variables that summarize information known in the 12 months prior to the individual's initial prescription.

Using the demographics from the integrated RI 360 database,[8] we construct variables for (modal) age, sex, race, marital status, body mass index, and median income and fraction below the federal poverty line in the home Census block group. Using DHS data, we construct variables for household size and new births in the household, and monthly payments for the Supplemental Nutrition Assistance Program (SNAP), the Temporary Assistance for Needy Families (TANF), the General Public Assistance (GPA), the Child Care Assistance Program (CCAP), and State Supplemental Payment portions of Supplemental Security Income benefits. Using DLT data, we construct indicators for sector of work derived from the first two digits of industry codes assigned according to the North American Industry Classification System (NAICS); monthly payments for Temporary Disability Insurance (TDI) and Unemployment Insurance (UI); and quarterly

wage history, including average quarterly wages and variance, the number of employers and the number of hours worked (for hourly employees); the monthly unemployment rate in Rhode Island; and the annual national unemployment rate for two-digit NAICS industries that the individual has worked in. Using DOC data, we construct indicators for charges, seven categories of sentencing, and commitments and releases from prison. Using police data, we construct variables for arrests; the number of car crashes involved and injured in; and the number of and total fines for citations.

The largest set of variables comes from the Medicaid data. These include indicators for enrollment eligibility categories, plan type, and payer codes; number of claims and total bill and payment amounts for all claims and for Emergency Department claims; indicators for prescriptions in 262 drug categories from the AHFS Pharmacologic/Therapeutic Classification;[9] and topic models summarizing the concatenated text descriptions for all of the individual's ICD-9 diagnosis codes and HCPCS procedure codes.

3.1 Topic Modeling

We construct the topic models using a technique called non-negative matrix factorization (NMF), which is commonly used in text analysis to discover latent topic structure in documents.[10] In this application, we treat each individual's concatenated text descriptions of diagnosis and procedure codes as a document to learn the latent topic structure across individuals' health histories. Our topic models summarize 70,153 documents comprised of 16,367 distinct words from the code descriptions, after removing 173 uninformative words using a stopword list. The total corpus consists of over 20.5 million words.

NMF works by factorizing the non-negative $d \times t$ matrix of the documents' word frequencies into non-negative matrices $d \times t$ and $t \times w$, where d is the number of documents, w is the number of distinct words, and t is the number of topics. We apply a term frequency-inverse document frequency (TF-IDF) transformation to the $d \times t$ matrix to reweight the word frequencies by their overall frequencies in the entire corpus, which is common practice when implementing NMF. The $d \times t$ matrix represents the weighting of topics for each document, and the $t \times w$ matrix represents the weighting of words for each topic. We summarize each topic using the 10 words with the greatest frequency in the $t \times w$ matrix.

Because the number of topics *t is* not known *a priori*, we tune this parameter by finding the *t* with the best out-of-sample area under the operating-receiver characteristic curve (AUC) in a logistic regression that includes only the topic model variables. We use only the training set for this tuning, and further subdivide it in half into topic training and topic validation sets. The tuning achieves AUCs on the topic validation set of 0.660 for 10 topics, 0.674 for 20 topics, 0.703 for 50 topics, 0.714 for 100 topics, 0.716 for 200 topics, and 0.696 for 500 topics. Therefore, we select the model with 200 topics as the final variables.

3.2 Low-Dosage Opioids

Within the prescription drug categories, there is a category for opiate agonists. By construction of our panel, no individuals should have previously received an opioid prescription. However, the opiate agonist category includes 152 drugs that were not identified in the 4,175 opioid drugs from our historical NDC directory, and which are listed in Table S5. These drugs either contain an opioid ingredient at a lower amount than the minimum thresholds defined by the Washington State prescribing guidelines, or contain an ingredient not identified in those guidelines (e.g., "opium"). Therefore, the opiate agonist variable indicates that the individual received a drug that was not likely for initiating opioid therapy, but nonetheless contains a small amount of an opioid ingredient. Most of these drugs are over-the-counter cough syrups or painkillers combined with small amounts of an opioid ingredient. Of the 152, there are eight that are not present in the historical NDC directory, possibly because they were on the market for a short enough time that they do not occur in any of the available historical snapshots of the NDC directory.

3.3 Tensors

For our neural network models, we construct tensors of monthly values for a given variable for each of the individuals in our panel in the 12 months prior to the individual's initial prescription. Missing values are imputed using mean values from the training population.

The DHS tensor includes 13 variables for demographics (age and indicators for sex, race, and Spanish or Portuguese as a primary language) and monthly payments for the Supplemental Nutrition Assistance Program (SNAP), the Temporary Assistance for Needy Families (TANF), the General Public Assistance (GPA), the Child Care Assistance Program (CCAP), and State Supplemental Payment portions of Supplemental Security Income benefits.

The DLT tensor includes 31 variables for indicators for sector of work derived from the first two digits of industry codes assigned according to the North American Industry Classification System (NAICS); monthly payments for Temporary Disability Insurance (TDI) and Unemployment Insurance (UI); and quarterly wage history, including wage amount, the number of employers and the number of hours worked (for hourly employees).

The DOC tensor includes 16 variables for demographics (age and indicators for sex, race, Spanish as a primary language), and indicators for charges, seven categories of sentencing, and commitments and releases from prison.

The Medicaid tensor includes 683 variables for demographics (age and indicators for sex, race, and Spanish or Portuguese as a primary language); indicators for eligibility categories, plan type, and payer codes at each month of enrollment; number of claims and total bill and payment amounts for all claims and for Emergency Department claims; the number of prescriptions in each of 265 categories from the AHFS Pharmacologic/Therapeutic Classification; and indicators for ICD-9 diagnosis codes and HCPCS procedure codes for all codes that are correlated >0.02 with any adverse outcome in the training population.

The police tensor includes 42 variables for demographics (age and indicators for sex and officer-observed race); indicators for all arrests, DUI arrests, and domestic-offense arrests; the number of car crashes involved and injured in; the number of and total fines for citations; and the spatio-temporal intensity of calls for service in the individual's home Census block group for 29 categories of calls.

Finally, we construct an integrated tensor including all of the 785 variables from the DHS, DLT, DOC, Medicaid, and police tensors. The dimension of this integrated tensor are 70,153 individuals x 12 months x 785 variables.

4 Models

We estimate a range of predictive models using modern machine learning algorithms, which vary in both their complexity and interpretability. For example, a class of models called "regularized regression models" estimate standard linear models, but search over many potential explanatory variables, potentially more explanatory variables than available data observations, to maximize out-of-sample predictive fit and minimize over-fitting. Like ordinary least squares or logistic models, the model results are easy to interpret, but the complexity is limited to functions of variables the researcher specifies in advance. At the other extreme are artificial neural network models where the algorithm searches over non-linear transformations of layers of local linear regressions. The increased complexity allows the algorithm to search for arbitrary non-linearities and interactions between variables, but at a cost of greatly reducing the interpretability of

the model (e.g., it is difficult to simply measure which variables contribute most to predictive fit).

4.1 Regularized Regression

For our regularized regression, we use an algorithm called Bootstrap Least Absolute Shrinkage and Selection Operator (BOLASSO).[11] This algorithm is a generalization of the popular LASSO algorithm which is able to consistently identify a model even when predictors are highly correlated. The BOLASSO selects the predictors with non-zero coefficients that appear in at least 90% of bootstrapped LASSO models.

Following convention, we use BOLASSO to select the variables from among 560 variables which are persistently the strongest predictors of future adverse opioid outcomes, and we present results from a second-stage logistic regression of an indicator for future adverse outcomes on these selected variables, to describe the predictive power of each variable. Exhibit A6 lists the variables selected by the BOLASSO as occurring with a non-zero coefficient in more than 90 of the 100 LASSO bootstrap replicates, along with the regression results from the second-stage logistic regression. In addition to the second-stage logistic regression, we also construct a regression ensemble model that averages the predictions of all 100 bootstrap replicates in the BOLASSO.

We fit each LASSO bootstrap replicate on the training set using a regularized logistic regression implementation called the gamma LASSO, which was developed specifically to address the challenges of modeling sparse, high-dimensional data.[12] Since a predictive model fits idiosyncratic noise through increased complexity in the model's structure, machine learning techniques commonly penalize complexity in the models they produce through a process called regularization. We tune the regularization parameters for the gamma LASSO model through a parameter search over gamma values in [0, 1, 10] and a path of 100 lambda values, and we select the model with the best area under the receiver-operating characteristic curve (AUC) on the validation set. Regularization helps prevent overfitting to the training data and thus improves out-of-sample fit. We are primarily interested in out-of-sample performance since our goal is to use the model to inform successful policy interventions, which require making predictions on new observations.[13]

4.2 Neural Networks

We train a neural network model for each tensor using the Python package Keras,[14] which provides an interface to the TensorFlow library.[15] Specifically, we train a recurrent neural network (RNN), since RNNs have the ability to model temporal patterns in the input data. We input our training data into a two-layer network of 10x10 Long Short-Term Memory (LSTM)[16] units with the tanh activation function. We input the last LSTM layer into a dense layer that applies a sigmoid activation function to the weighted sum of the 10 inputs in order to produce a single predicted probability of adverse outcome. We employ regularization prior to each layer in the form of a dropout factor of 0.25, which causes a random deactivation of units within the layer during training with a fixed probability of 0.25.[17]

The neural networks are optimized to minimize the binary cross-entropy, also known as log-loss, on the training data. We use the Adam[18] optimization algorithm, training with a batch size of 16. We tune the model on the validation set by allowing the neural network to train for as many epochs as needed until the area under the receiver-operating curve (AUC) from predictions on the validation set does not improve by 0.001. Table S7 shows the AUC from predictions on the testing set for each data source and each individual outcome.

Notes

[1] U.S. Food & Drug Administration. National Drug Code Directory [Internet; cited 2019 Feb 19]; Available from: https://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm

[2] Research Improving People's Lives. Assembling a Historical National Drug Code Directory from the Internet Archive [Internet; cited 2019 Feb 19]; Available from: https://github.com/ripl-org/historical-ndc

[3] Agency Medical Directors' Group. Interagency Guideline on Prescribing Opioids for Pain. Olympia, WA: 2015 [cited 2019 Feb 19]. Available from: http://www.agencymeddirectors.wa.gov/Files/2015AMDG□pioidGuideline.pdf

[4] Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR Recomm Rep [Internet]. 2016 [cited 2019 Feb 19];65. Available from: https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm

[5] Jones CM. Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers – United States, 2002–2004 and 2008–2010. Drug Alcohol Depend. 2013 Sep;132(1–2):95–100.

[6] Carrell DS, Cronkite D, Palmer RE, Saunders K, Gross DE, Masters ET, et al. Using natural language processing to identify problem usage of prescription opioids. Int J Med Inform. 2015 Dec;84(12):1057–64.

[7] Barocas JA, White LF, Wang J, Walley AY, LaRochelle MR, Bernson D, et al. Estimated Prevalence of Opioid Use Disorder in Massachusetts, 2011–2015: A Capture–Recapture Analysis. Am J Public Health. 2018 Oct 25;108(12):1675–81.

[8] Hastings JS, Howison M, Lawless T, Ucles J, White P. Unlocking Data to Improve Public Policy. Communication of the ACM. Forthcoming.

[9] *AHFS® Pharmacologic/Therapeutic Classification*© used with permission. © 2017, the American Society of Health-System Pharmacists, Inc. (ASHP). The Data is a part of the *AHFS Drug Information*®; ASHP is not responsible for the accuracy of transpositions from the original context.

[10] Févotte C, Idier J. Algorithms for Nonnegative Matrix Factorization with the β-Divergence. Neural Computation. 2011 Jun 14;23(9):2421–56.

[11] Bach FR. Bolasso: Model Consistent Lasso Estimation Through the Bootstrap. In: Proceedings of the 25th International Conference on Machine Learning [Internet]. New York, NY, USA: ACM; 2008 [cited 2018 Feb 19]. p. 33–40. (ICML 08). Available from: http://doi.acm.org/10.1145/1390156.1390161

[12] Taddy M. One-step estimator paths for concave regularization. arXiv:13085623 [Internet]. 2016 May 1 [cited 2019 Feb 27]; Available from: http://arxiv. org/abs/1308.5623

[13] Kleinberg J, Ludwig J, Mullainathan S, Obermeyer Z. Prediction Policy Problems. Am Econ Rev. 2015 May;105(5):491–5.

[14] Chollet F, et al. Keras: The Python Deep Learning library [Internet; cited 2019 Feb 27]; Available from: https://keras.io/

[15] Abadi M, Barham P, Chen J, Chen Z, Davis A, Dean J, et al. TensorFlow: A System for Large-Scale Machine Learning. In: 12th USENIX Symposium on Operating Systems Design and Implementation (OSDI 16). 2016 [cited 2019 Feb 19] p. 265–83. Available from: https://www.usenix.org/conference/ osdi16/technical-sessions/presentation/abadi

[16] Hochreiter S, Schmidhuber J. Long Short-Term Memory. Neural Computation. 1997 Nov 1;9(8):1735–80.

[17] Srivastava N, Hinton G, Krizhevsky A, Sutskever I, Salakhutdinov R. Dropout: A Simple Way to Prevent Neural Networks from Overfitting. J Mach Learn Res. 2014 Jun 14;15:1929–58.

[18] Kingma DP, Ba J. Adam: A Method for Stochastic Optimization. arXiv:14126980 [Internet]. 2014 Dec 22 [cited 2019 Feb 19]; Available from: http://arxiv. org/abs/1412.6980

Table S1. Minimum amounts of ingredients in a drug to classify it as an opioid prescription or a recovery prescription.

Opioid Ingredient	***Minimum Amount (mg)***
Codeine	30.0
Fentanyl	0.0125
Hydrocodone	5.0
Hydromorphone	2.0
Meperidine*	0.0
Morphine	10.0
Oxycodone	5.0
Oxymorphone	5.0
Tapentadol	50.0
Tramadol	50.0

Recovery Ingredient°	***Minimum Amount (mg)***
Buprenorphine	0.0
Methadone	0.0
Naloxone	0.0
Naltrexone	0.0

* Meperidine has no recommended starting dose for treatment of chronic pain because of its risk for complications in older adults; therefore, we consider any amount as evidence that the drug is an opioid.

° We consider any amount of a recovery ingredient as evidence that the drug may have been used to treat a prior opioid use disorder.

Table S2. Diagnosis and procedure codes used to indicate adverse outcomes when occurring in any claim after the initial opioid prescription.

Outcome	*Code*	*Description*
Opioid Dependence	304.0	Opioid type dependence
	304.7	Combinations of opioid type drug with any other drug dependence
	F11.2*	Opioid dependence
Opioid Abuse	305.0	Nondependent opioid
	F11.1*	Opioid abuse
Prescription-Opioid Poisoning	965.00	Poisoning by opium (alkaloids), unspecified
	965.02	Poisoning by methadone
	965.09	Poisoning by other opiates and related narcotics
	970.1	Poisoning by opiate antagonists
	E850.1	Accidental poisoning by methadone
	E850.2	Accidental poisoning by other opiates and related narcotics
	E935.1	Methadone causing adverse effects in therapeutic use
	E935.2	Other opiates and related narcotics causing adverse effects in therapeutic use
	E940.1	Opiate antagonists causing adverse effects in therapeutic use
	T400*	Poisoning by, adverse effect of and underdosing of opium
	T402*	Poisoning by, adverse effect of and underdosing of other opioids
	T403*	Poisoning by, adverse effect of and underdosing of methadone
Heroin Poisoning	965.01	Poisoning by heroin
	E850.0	Accidental poisoning by heroin
	E935.0	Heroin causing adverse effects in therapeutic use
	T401*	Poisoning by and adverse effects of heroin
Treatment	J2310°	Naloxone HCI Injection, per 1 mg
	J2315°	Naltrexone injection, depot form, 1mg
	J0592°	Buprenorphine HCL injection, 0.1mg
	X0305°	Methadone detoxification – outpatient
	X0321°	Methadone maintenance, assessment and evaluation, counseling, treatment and review, and lab testing
	H0020°	Alcohol and or drug services; methadone administration and or service
	J1230°	Injection, methadone, up to 10mg
	83840°	Methadone
	946°	Alcohol and drug rehabilitation and counseling
	9464°	Drug rehabilitation
	9465°	Drug detoxification
	9466°	Drug rehabilitation and detoxification combined
	9467°	Alcohol and drug rehabilitation combined
	9468°	Alcohol and drug detoxification
	9469°	Combined alcohol and drug rehabilitation and detoxification

* ICD-10 diagnosis code

° HCPCS procedure code

Figure S3. Cumulative frequency of adverse outcomes over time since initial opioid prescription.

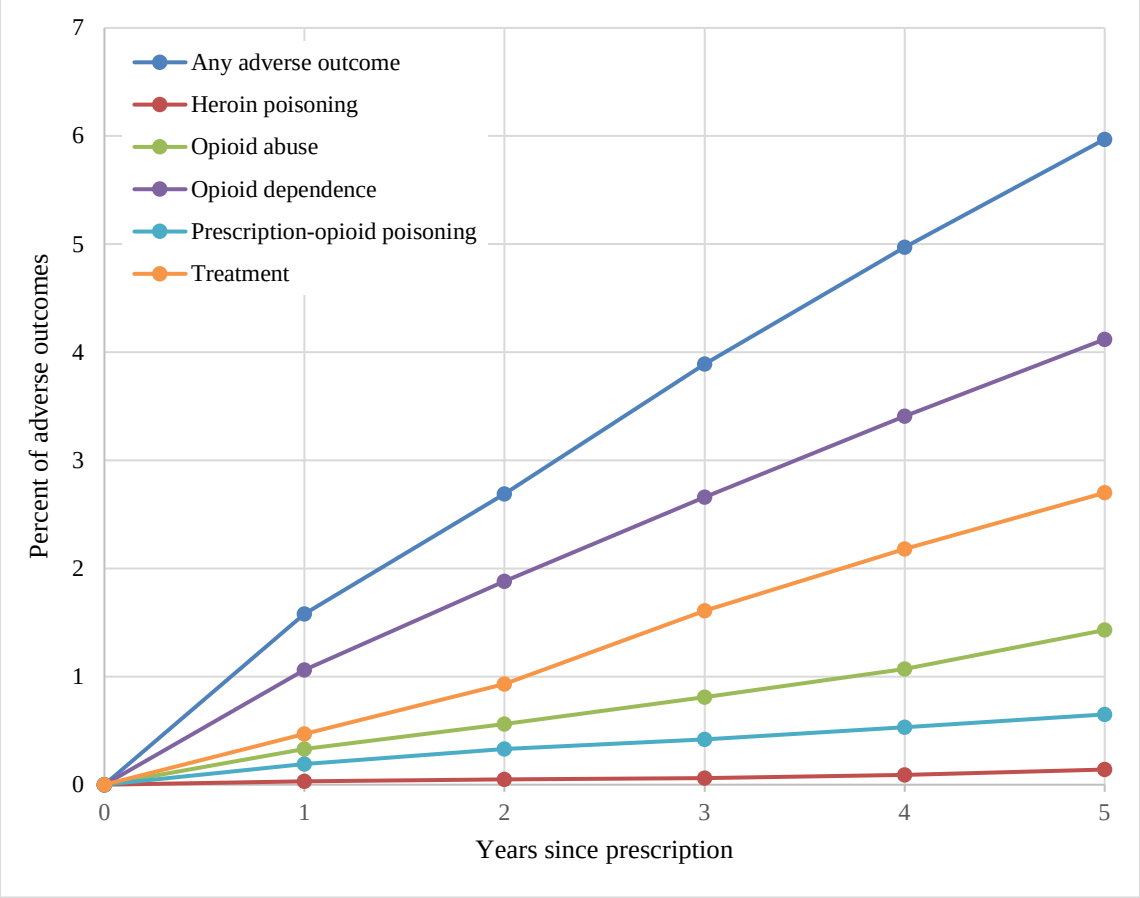


Table S4. Descriptive statistics for the final panel.

Variable	*Value*	*N*	*Outcome*
Age	<18	8501	**2.39%**
	18-45	43238	**6.79%**
	45-60	11802	**8.11%**
	61+	6531	**1.32%**
	NA	81	**4.94%**
Race/Ethnicity	White	40937	**8.14%**
	Black	7392	**4.33%**
	Hispanic	7634	**2.06%**
	Other	4765	**2.22%**
	NA	9425	**2.83%**
Sex	Female	47739	**5.14%**
	Male	22379	**7.73%**
	NA	35	**2.86%**
Marital status	Married	11975	**4.82%**
	Not married	39052	**7.94%**
	NA	19126	**2.65%**
Body mass index	Underweight (<18.5)	1139	**9.31%**
	Normal (18.5-25)	20073	**7.65%**
	Overweight (25-30)	15737	**6.12%**
	Obese (>30)	12590	**5.21%**
	NA	20614	**4.48%**
Blockgroup fraction of residents below FPL	At least 16.4%	11652	**5.36%**
	Otherwise	16565	**6.46%**
	NA	41936	**5.94%**
Average quarterly wages in previous year	<$2500	14624	**7.18%**
	$2500-$7500	14316	**4.52%**
	$7500-$15000	1477	**4.47%**
	>$15000	65	**3.08%**
	$0 or NA	39671	**6.10%**
Received SNAP in previous year	Yes	39678	**7.64%**
	No	30475	**3.78%**
Received SSI in previous year	Yes	1204	**8.80%**
	No	68949	**5.91%**
Received UI in previous year	Yes	6220	**6.62%**
	No	63933	**5.90%**
Received TDI in previous year	Yes	5538	**6.86%**
	No	64645	**5.89%**
Children in DHS household in previous year	0 or NA	4263	**2.67%**
	1	16006	**9.52%**
	2+	49884	**5.11%**

Table S5. Low-dosage prescription opioids identified by the AHFS Pharmacologic/Therapeutic Classification category for opiate agonists.

NDC Code	*Opioid Ingredients*	*Other Ingredients*
00037-2403	codeine phosphate (16mg)	aspirin (325mg) carisoprodol (200mg)
00054-0243	codeine sulfate (15mg)	
00054-0386	hydromorphone hydrochloride (1mg)	
00093-0050	codeine phosphate (15mg)	acetaminophen (300mg)
00121-0504	codeine phosphate (12mg)	aceteminophen (120mg)
00121-0775	codeine phosphate (10mg)	guaifenesin (100mg)
00121-1775	codeine phosphate (16mg)	guaifenesin (100mg)
00185-0749	codeine phosphate (16mg)	aspirin (325mg) carisoprodol (200mg)
00378-6117	oxycodone hydrochloride (4.8355mg)	aspirin (325mg)
00378-7103	oxycodone hydrochloride (2.5mg)	acetaminophen (325mg)
00378-8088	tramadol hydrochloride (37.5mg)	acetaminophen (325mg)
00406-0483	codeine phosphate (15mg)	acetaminophen (300mg)
00482-0440	codeine phosphate (10mg)	guaifenesin (300mg)
00482-0441*****		
00574-7040	opium (30-60mg) opium, powdered (60mg)	atropa belladonna (16.2mg) belladonna extract (16.2mg)
00574-7045	opium (30-60mg) opium, powdered (1.5%ww)	atropa belladonna (0.81%ww) atropa belladonna (16.2mg) belladonna (0.8-0.81%ww)
00574-7110	morphine sulfate (5mg)	
00591-0617*****		
00591-0820	oxycodone hydrochloride (4.5mg) ocycodone terephthalate (0.38-0.4mg)	aspirin (325mg)
00591-3551	oxycodone hydrochloride (4.8355mg)	aspirin (325mg)
00603-1020	codeine phosphate (12mg)	acetaminophen (120mg)
00603-1075	codeine phosphate (10mg)	alcohol, dehydrated (3.68-3.7%ww) guaifenesin (100mg)
00603-1078	codeine phosphate (10mg)	alcohol, dehydrated (1.9%ww) guaifenesin (100mg) pseudoephedrine hydrochloride (30mg)
00603-1329	codeine phosphate (10mg)	guaifenesin (100mg)
00603-1520	codeine phosphate (10mg)	chlorpheniramine maleate (2mg) pseudoephedrine hydrochloride (30mg)
00603-1585	codeine phosphate (10mg)	promethazine hydrochloride (6.25-6.3mg)
00603-1588	codeine phosphate (10mg)	phenylephrine hydrochloride (5mg) promethazine hydrochloride (6.25)
00603-2337	codeine phosphate (15mg)	acetaminophen (300mg)
00603-4978	oxycodone hydrochloride (2.5mg)	acetaminophen (325mg)
00603-9013	codeine phosphate (12mg)	acetaminophen (120mg)
00641-1130*****		
10135-0519*****		
13107-0058	codeine phosphate (15mg)	acetaminophen (300mg)
16571-0301	codeine phosphate (10mg)	guaifenesin (100mg) pseudoephedrine hydrochloride (30mg)
16571-0302	codeine phosphate (10mg)	guaifenesin (100mg)
46672-0561	codeine phosphate (12mg)	acetaminophen (120mg)
49884-0946	tramadol hydrochloride (37.5mg)	acetaminophen (325mg)
50383-0079	codeine phosphate (12mg)	acetaminophen (120mg)
50383-0087	codeine phosphate (10mg)	guaifenesin (100mg)
50383-0804	codeine phosphate (10mg)	promethazine hydrochloride (6.25mg)
50383-0805	codeine phosphate (10mg)	phenylephrine hydrochloride (5mg) promethazine hydrochloride (6.25mg)
53489-0159	codeine phosphate (15mg)	acetaminophen (300mg)
53746-0617	tramadol hydrochloride (37.5mg)	acetaminophen (325mg)
57664-0185	codeine phosphate (10mg)	promethazine hydrochloride (6.25mg)
57664-0537	tramadol hydrochloride (37.5mg)	acetaminophen(325mg)
57963-0103	codeine phosphate(10mg)	guaifenesin(100mg)
58177-0449*****		
58177-0620*****		

58177-0621*****		
58657-0500	codeine phosphate(10mg)	guaifenesin(100mg)
60432-0245	codeine phosphate(12mg)	acetaminophen(120mg)
60432-0606	codeine phosphate(10mg)	promethazine hydrochloride (6.25mg)
60505-2644	tramadol hydrochloride (37.5mg)	acetaminophen(325mg)
60505-7010	fentanyl (12ug)	
60951-0310	oxycodone hydrochloride (4.8355mg)	aspirin (325mg)
60951-0701	oxycodone hydrochloride (2.5mg)	acetaminophen(325mg)
63481-0121	oxycodone hydrochloride (4.8355mg)	aspirin (325mg)
63481-0627	oxycodone hydrochloride (2.5mg)	acetaminophen(325mg)
65162-0617	tramadol hydrochloride (37.5mg)	acetaminophen(325mg)
65162-0694	codeine phosphate(10mg)	phenylephrine hydrochloride (5mg) promethazine hydrochloride (6.25mg)
66594-0333	codeine phosphate(9mg)	pyrilamine maleate (8.33mg)
66689-0024*****		
68308-0840	oxycodone hydrochloride (2.5mg)	acetaminophen(325mg)
68308-0845	oxycodone hydrochloride (4.8355mg)	aspirin (325mg)
68382-0334	tramadol hydrochloride (37.5mg)	acetaminophen(325mg)
69543-0252	codeine phosphate(10mg)	guaifenesin(100mg)
69543-0253	codeine phosphate(10mg)	guaifenesin(100mg) pseudoephedrine hydrochloride (30mg)
76439-0252	codeine phosphate(10mg)	guaifenesin(100mg)
76439-0253	codeine phosphate(10mg)	guaifenesin(100mg) pseudoephedrine hydrochloride (30mg)

* NDC code exists in AHFS Pharmacologic/Therapeutic Classification but does not exist in NDC directory

Table S6. Regression output for the post-BOLASSO logistic regression

Variables	*Odds Ratio*	*95% C.I.*	*p-value*	*Bootstrap Frequency*
Released from a corrections facility	1.929	(1.585 - 2.349)	0.000	100%
Prior prescription for Atypical Antipychotics	1.317	(1.114 - 1.556)	0.001	97%
Prior prescription for Centrally Acting Skeletal Muscle Relaxants	1.296	(1.128 - 1.488)	0.000	100%
Prior prescription for Benzodiazepines	1.213	(1.065 - 1.383)	0.004	100%
Prior prescription for Opiate Agonists	1.196	(1.048 - 1.365)	0.008	100%
Rhode Island monthly unemployment rate	1.194	(1.134 - 1.257)	0.000	100%
Size of household	1.146	(1.085 - 1.210)	0.000	100%
Topic 124 (fluid combinations opioid body ph specimen breath ethanol single screen)	1.144	(1.111 - 1.178)	0.000	100%
Topic 128 (compulsive disorders examination diagnostic history status psychiatric com interview disposition)	1.104	(1.066 - 1.142)	0.000	97%
Total Medicaid pharmacy payments	1.088	(1.047 - 1.131)	0.000	100%
Topic 60 (bls service statue ground mile mileage transport support emergency life)	1.080	(1.042 - 1.119)	0.000	97%
Topic 24 (injection specify drug intramuscular infusion push intravenous diagnostic prophylactic therapeutic substance)	1.075	(1.037 - 1.114)	0.000	100%
Topic 42 (acute quantification function delta cirrhosis viral chronic liver hepatic coma)	1.072	(1.037 - 1.108)	0.000	100%
Topic 101 (symptoms oblique sacral pain referable canal back lumbosacral sciatica lumbar)	1.069	(1.031 - 1.108)	0.000	100%
Topic 82 (fractured periapical broken jaws sinus disorder dental caries teeth structures)	1.067	(1.035 - 1.101)	0.000	100%
Topic 34 (limb splint metacarpal static injury phalanges phalanx minimum finger fingers)	1.064	(1.025 - 1.104)	0.001	93%
Topic 166 (region spondylosis cervical spinal lumbosacral degeneration displacement myelopathy intervertebral disc)	1.063	(1.026 - 1.102)	0.001	98%
Topic 112 (household member able render incontinence care personal combined ad homemaker)	1.062	(1.025 - 1.099)	0.001	95%
Topic 154 (back hands struck accidents accidentally striking eyes injury fall wall)	1.061	(1.022 - 1.102)	0.002	99%
Topic 195 (movements thoracic back accidents overexertion strenuous ligament neck site lumbar)	1.061	(1.020 - 1.104)	0.003	95%
Topic 17 (periumbilic amylase erect decubitus constipation abdomen generalized epigastric site pain)	1.061	(1.018 - 1.105)	0.005	97%
Topic 90 (using cardiovascular maximal submaximal bicycle treadmill stress exercise study myocardial)	1.061	(1.017 - 1.106)	0.006	92%
Topic 70 (multiplex diagnosticsamplification amplification isolation purified highly nuclear acid nucleic diagnostics)	1.056	(1.008 - 1.107)	0.021	96%
Topic 49 (absolute count quantification cd non cells disease virus human immunodeficiency)	1.053	(1.017 - 1.089)	0.003	92%
Topic 175 (cyst scoliosis spinal therapy morbid canal physical back obesity cervicalgia)	1.050	(1.016 - 1.086)	0.004	100%
Topic 46 (sensitivity antibiotic definitive kit commercial isolate quantitative urine identification bacterial)	1.042	(0.997 - 1.089)	0.067	92%
Topic 197 (physician vitamin infliximab abdomen infusion small large site intestine enteritis)	1.038	(1.007 - 1.001)	0.018	92%
Topic 187 (generalized therapeutic intensive greater smoking cessation oppositional defiant tobacco disorder)	1.037	(1.001 - 1.073)	0.044	95%
Total Unemployment Insurance payments	1.036	(0.997 - 1.077)	0.074	93%

Topic 151 (nonobstetric stenosis enthesopathy minimum pelvic pain joint hip pelvic region)	1.035	(0.997 - 1.074)	0.075	93%
Topic 182 (systemic erythrocyte sedimentation cpk kinase ck creatine lupus erythematosus myositis)	1.032	(0.999 - 1.067)	0.061	93%
Topic 6 (caries viral asthmaunspecified infection evaluation management visit key emergency comp)	1.025	(0.981 - 1.072)	0.272	93%
Number of police citations	1.025	(0.992 - 1.058)	0.139	97%
Topic 74 (nonpsychotic obstruction allergy crisis tobacco airway radiological insomnia disorder depressive)	1.023	(0.986 - 1.062)	0.230	92%
Topic 18 (radiological less sinuses paranasal frontal anteroposterior lateral minimum examination views)	1.022	(0.974 - 1.072)	0.370	98%
Number of opioid prescriptions in household	1.010	(1.000 - 1.020)	0.048	100%
Topic 62 (skills visit physical therapeutic intervention individual assessment health therapy counseling)	0.999	(0.959 - 1.041)	0.957	95%
Topic 93 (tachycardia abnormal ekg palpitations tracing routine interpretation report leads electrocardiogram)	0.996	(0.951 - 1.045)	0.883	94%
Topic 126 (mtt mh psychosis treatment disorganized rn program chronic assertive paranoid)	0.996	(0.958 - 1.036)	0.845	92%
Topic 10 (mental single disorder depressive episode recurrent major affective behavior severe)	0.995	(0.956 - 1.036)	0.803	95%
Topic 92 (followed stem canal spinal material brain contrast imaging proton resonance)	0.987	(0.943 - 1.033)	0.561	93%
Topic 16 (schedule vaccine viral prophylactic inoculation vaccination subcutaneous intradermal administration percutaneous)	0.984	(0.916 - 1.056)	0.652	92%
Topic 57 (shl problems disorder treatment group processing auditory voice language speech)	0.978	(0.915 - 1.046)	0.524	95%
Topic 119 (scan swelling follow st compression responses maneuvers duplex extremity veins)	0.975	(0.928 - 1.025)	0.318	96%
Topic 54 (face injury soft cervical eyes swelling lump mass scalp head)	0.974	(0.929 - 1.022)	0.283	94%
Topic 125 (gait mileage statute ground mile emergency non chair wheel van)	0.973	(0.930 - 1.018)	0.238	99%
Topic 179 (emergency functions special ed encounter oppositional defiant transportation trip rehabilitation)	0.971	(0.912 - 1.035)	0.373	98%
Topic 4 (sealant evaluation periodic oral child adult application included topical fluoride)	0.971	(0.898 - 1.050)	0.460	96%
Topic 180 (conductive speech sensorineural recognition impedance tympanometry audiometry threshold testing loss)	0.970	(0.910 - 1.034)	0.351	98%
Topic 194 (hypometropia refractive eyes treatment evaluation continuation examination prog diagnostics initiation)	0.969	(0.915 - 1.025)	0.270	95%
Average quarterly wages	0.968	(0.919 - 1.020)	0.223	100%
Topic 29 (low colposcopy gladnular lgsil lesion squamous intraepithelial dysplasia smear papanicolaou)	0.968	(0.918 - 1.021)	0.228	93%
Topic 3 (microalbumin hemoglobin strip manifestations juvenile glycated complication mellitus ii uncontrolled)	0.967	(0.917 - 1.020)	0.219	98%
Topic 106 (rn minimum mental social evaluation periodic oral bitewings films prophylaxis)	0.965	(0.902 - 1.033)	0.306	93%
Topic 144 (pleurisy rubella mumps bcg examination test screening skin intradermal pulmionary)	0.965	(0.908 - 1.025)	0.249	91%
Topic 192 (heterophile conjunctivitis strep bacterial culture source definitive bronchitis tonsillitus acute)	0.964	(0.913 - 1.018)	0.187	99%
Topic 155 (specimen nursing home laboratory necessary medical connection way allowance drawn)	0.960	(0.897 - 1.028)	0.243	100%
Average quarterly hours worked	0.958	(0.880 - 1.044)	0.326	99%
Topic 137 (phalanges metatarsil cellulitis pain valgus hallux toe minimum limb toes)	0.955	(0.908 - 1.005)	0.075	93%
Topic 7 (therapy modality physical activities provider procedure strength develop exercises areas)	0.953	(0.905 - 1.003)	0.065	100%

Topic 1 (complicating complications current premature classifiable labor mother threatened pregnancy complication)	0.952	(0.898 - 1.009)	0.097	96%
Topic 9 (cholesterol lipoprotein ldl creatine hyperglyceridemia cpk kinase ck measurement hypercholesterolemia)	0.950	(0.897 - 1.006)	0.080	92%
Topic 28 (technique infectious acid nucleic rna gonorrhoeae trachomatis chlamydia dna probe)	0.940	(0.897 - 1.005)	0.072	93%
Topic 72 (vaccination inoculation injection intramuscular jet above dosage split vaccine influenza)	0.948	(0.889 - 1.010)	0.099	99%
Topic 145 (excludes mental palsy lung infantile bronchus special problem functions care)	0.945	(0.866 - 1.031)	0.205	99%
Topic 132 (blood secondary folic cyanocobalamin capacity binding ferritin vitamin deficiency iron)	0.945	(0.891 - 1.002)	0.059	99%
Topic 97 (acute spontaneous otalgia serous nonsuppurative infective rupture supparative eardrum media)	0.942	(0.883 - 1.006)	0.073	94%
Topic 53 (bone breast liver radiation chemotherapy female secondary bronchus lung malignant)	0.941	(0.889 - 0.995)	0.033	100%
Topic 21 (alpha estriol fetoprotein single organisms screening dose post glucose pregnant)	0.938	(0.876 - 1.003)	0.063	96%
Topic 84 (aklaline phosphatase serum alt alanine sgpt ast sgot aspartate amino)	0.931	(0.878 - 0.987)	0.016	100%
Topic 66 (full marrow infusion myeloid chemotherapy myeloma lymphoid leukemia achieved having)	0.930	(0.870 - 0.994)	0.032	100%
Topic 38 (product palsy infantile disposable incontinence procedures temporary mhrh offline disabilities)	0.927	(0.845 - 1.017)	0.110	100%
Topic 141 (diseases precription transmitted sexually measures contraceptives management general contraceptive advise)	0.927	(0.869 - 0.988)	0.020	99%
Topic 36 (community cedarrs incontinence assertive adult monthly program dd mr intellectual)	0.924	(0.836 - 1.021)	0.121	100%
Topic 14 (detection interpretation digitization physician bilateral further aided computer mammogram screening)	0.910	(0.846 - 0.980)	0.012	100%
Sex is male	0.861	(0.778 - 0.954)	0.004	100%
Topic 11 (examination myopia routine gynecological coinsurance deductible office visits copay share)	0.859	(0.800 - 0.922)	0.000	99%
Body mass index	0.851	(0.806 - 0.899)	0.000	100%
Age	0.704	(0.650 - 0.761)	0.000	99%
Primary language is Spanish	0.450	(0.347 - 0.585)	0.000	100%
Race is African American	0.400	(0.337 - 0.474)	0.000	100%
Enrolled in Medicaid managed care	0.386	(0.341 - 0.437)	0.000	100%
Race is Asian, Native American, or other	0.374	(0.276 - 0.507)	0.000	100%
Married is missing	0.350	(0.300 - 0.407)	0.000	100%
Race is missing	0.305	(0.250 - 0.372)	0.000	100%
Ethnicity is Hispanic	0.245	(0.190 - 0.318)	0.000	100%
Eligible for Medicaid as categorically needy	0.136	(0.123 - 0.150)	0.000	100%
Enrolled in RI Pharmaceutical Assistance to the Elderly	0.008	(0.001 - 0.061)	0.000	100%

Note: This is a logistic regression of variables selected by BOLASSO as occurring with a non-zero coefficient in more than 90% of LASSO bootstrap replicates.

Table S7. Area under the receiver-operating characteristic curve (AUC) of neural network models using different subsets of administrative data and outcome definitions.

	Any Poisoning	Dependence	Abuse	Prescription-Opioid	Heroin Poisoning	Treatment
DHS	0.695 (0.684-0.712)	0.705 (0.686-0.728)	0.692 (0.662-0.720)	0.665 (0.623-0.709)	0.554 (0.442-0.646)	0.728 (0.709-0.749)
DLT	0.563 (0.545-0.579)	0.548 (0.527-0.569)	0.513 (0.479-0.549)	0.486 (0.434-0.532)	0.431 (0.363-0.522)	0.535 (0.518-0.558)
DOC	0.694 (0.678-0.712)	0.718 (0.700-0.738)	0.716 (0.687-0.753)	0.626 (0.584-0.673)	0.766 (0.628-0.896)	0.724 (0.697-0.748)
Medicaid	0.763 (0.750-0.779)	0.771 (0.753-0.787)	0.741 (0.702-0.764)	0.675 (0.632-0.720)	0.697 (0.560-0.831)	0.772 (0.757-0.792)
Police	0.637 (0.619-0.651)	0.643 (0.616-0.662)	0.622 (0.595-0.660)	0.598 (0.554-0.642)	0.478 (0.364-0.607)	0.656 (0.632-0.679)
Integrated	0.793 (0.780-0.808)	0.801 (0.780-0.818)	0.773 (0.736-0.807)	0.707 (0.659-0.748)	0.708 (0.566-0.837)	0.810 (0.795-0.829)

Note: Confidence intervals are calculated from 100 bootstrap replicates.