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RESEARCH ARTICLE

Predicting Opioid Overdose Deaths Using Prescription Drug Monitoring Program Data

Lindsey M. Ferris, DrPH,[1,2] Brendan Saloner, PhD,[1] Noa Krawczyk, PhD,[3] Kristin E. Schneider, PhD,[3] Molly P. Jarman, PhD,[1,4] Kate Jackson, MPH,[5] B. Casey Lyons, MPH,[5] Matthew D. Eisenberg, PhD,[1] Tom M. Richards, MS,[1,6] Klaus W. Lemke, PhD,[1,6] Jonathan P. Weiner, DrPH[1,6]

Introduction: Prescription Drug Monitoring Program data can provide insights into a patient's likelihood of an opioid overdose, yet clinicians and public health officials lack indicators to identify individuals at highest risk accurately. A predictive model was developed and validated using Prescription Drug Monitoring Program prescription histories to identify those at risk for fatal overdose because of any opioid or illicit opioids.

Methods: From December 2018 to July 2019, a retrospective cohort analysis was performed on Maryland residents aged 18–80 years with a filled opioid prescription (n=565,175) from January to June 2016. Fatal opioid overdoses were identified from the Office of the Chief Medical Examiner and were linked at the person-level with Prescription Drug Monitoring Program data. Split-half technique was used to develop and validate a multivariate logistic regression with a 6-month look-back period and assessed model calibration and discrimination.

Results: Predictors of any opioid-related fatal overdose included male sex, age 65–80 years, Medicaid, Medicare, 1 or more long-acting opioid fills, 1 or more buprenorphine fills, 2 to 3 and 4 or more short-acting schedule II opioid fills, opioid days' supply ≥91 days, average morphine milligram equivalent daily dose, 2 or more benzodiazepine fills, and 1 or more muscle relaxant fills. Model discrimination for the validation cohort was good (area under the curve: any, 0.81; illicit, 0.77).

Conclusions: A model for predicting fatal opioid overdoses was developed using Prescription Drug Monitoring Program data. Given the recent national epidemic of deaths involving heroin and fentanyl, it is noteworthy that the model performed equally well in identifying those at risk for overdose deaths from both illicit and prescription opioids.

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INTRODUCTION

The U.S. is in the midst of an historic drug overdose crisis. In 2017, 67.8% of overdose deaths involved opioids.[1] The rise of opioid overdose deaths has spurred increased efforts to improve the safety and quality of care for patients prescribed opioids. Deaths linked to prescription opioids (obtained legally or otherwise) have leveled off in recent years owing to concerted efforts to curb opioid prescribing; however, deaths related to illicit opioids (e.g., heroin and fentanyl) surged for most of the past decade.[2] States have mobilized a range of interventions, programs, and tools to combat the epidemic.

From the [1]Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; [2]Chesapeake Regional Information System for our Patients, Baltimore, Maryland; [3]Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; [4]Center for Surgery and Public Health, Brigham and Women's Hospital, Boston, Massachusetts; [5]Maryland Department of Health, Behavioral Health Administration, Office of PDMP and Overdose Prevention Applied Data Programs, Baltimore, Maryland; and [6]Johns Hopkins Center for Population Health Information Technology, Baltimore, Maryland

Address correspondence to: Brendan Saloner, PhD, Johns Hopkins Bloomberg School of Public Health, 624 N Broadway, Room 344, Baltimore MD 21205. E-mail: bsaloner@jhu.edu.

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One increasingly common tool used to monitor opioid prescribing behavior and provide clinical insight into an individual's controlled substance history is a Prescription Drug Monitoring Program (PDMP), which collects data on all scheduled drugs dispensed from pharmacies and other dispensers within the state. Authorized PDMP users often include physicians, pharmacists, law enforcement, and public health officials. These parties can query PDMPs to gain greater insight into patterns of potentially harmful or unlawful prescription drug use.[3] For clinicians, PDMPs can provide insights into whether a patient may be at greater risk of an adverse event, including a fatal overdose. However, forming this judgment is generally a subjective process of looking through the patient's entire PDMP history and weighing a range of factors during a brief patient visit.[4,5] Decision aids need to be developed using these data to guide clinicians wishing to identify patients at risk for adverse events.

Risk factors associated with negative opioid-related outcomes include a history of high average daily opioid dosage, prolonged duration of use, concurrent opioid and benzodiazepine use, opioid stockpiling (i.e., accumulating more opioids while medication is still on hand), and visits to multiple prescribers.[6–9] Relatively few studies have linked prescription histories to fatality data, and most of these studies examine the strength of the association of risk factors to overdose, rather than developing and analyzing the performance of predictive models using these factors.[8–12] One prior study developed and validated a predictive model for chronic opioid users but leveraged an integrated health system's pharmacy claims database that did not encompass all payer prescription data.[13] Another study developed a predictive model for fatal overdose on a statewide population using the Oregon PDMP linked to fatality data from 2011 to 2014.[8] That study was able to derive a well-performing model to predict fatal overdose with an area under the curve (AUC) statistic of 0.82.[8] However, there is a need for updated models from states that are hardest hit by the opioid crisis, as well as models that separately evaluate risk of illicit opioid death as the opioid epidemic shifts away from prescribed to illicit opioids.

Although there is likely a high degree of overlap between illicit and prescription opioid use, it is unclear whether prescription histories can predict opioid overdose deaths well, especially deaths that primarily or solely involve illicit opioids.[14] For this study, a predictive model was developed and internally validated using Maryland PDMP data linked to a database of overdose fatalities. Maryland has one of the highest opioid overdose death rates in the U.S. (ranking 8th in 2017)[1] and has a robust PDMP and health information exchange capable of linking the prescription data to a variety of other state databases, including opioid fatalities.

METHODS

Study population

The Maryland PDMP collects information on controlled substance prescriptions (Schedule II–V) dispensed within the state, including mail order pharmacies dispensing into Maryland and pharmaceuticals dispensed in physician offices. Any controlled substances administered with assistance, such as inpatient hospital, assisted living, or hospice, are exempt from reporting to the PDMP. Additionally, opioid treatment programs (e.g., methadone maintenance) are exempt from reporting to the PDMP owing to the complexities of the 42 CFR Part 2 federal statute governing confidentiality of substance use disorder patient records. Human subjects approval for the study was provided by IRBs at the Johns Hopkins University and the Maryland Department of Health.

The cohort of patients was identified retrospectively to develop and internally validate a predictive model. Maryland residents aged 18–80 years who had at least 1 opioid prescription filled between January 1 and June 30, 2016 were included. The 2016 death data used for the outcome measure originated from the Office of Chief Medical Examiner, a statewide agency that investigates all deaths in which a physician was not in attendance or were due to a homicide, suicide, injury, or unusual circumstances,[15] were linked to the PDMP data using a probabilistic algorithm applied to the demographic data (name, date of birth, address, sex, phone number, and Social Security number) before de-identification of the data sets. This matching was performed by the State's Health Information Exchange, which regularly links patient data from many sources without a common patient identifier (Appendix Text 1, available online, provides more detail on the matching algorithm).

Measures

Measures of controlled substance prescribing patterns were created using PDMP data in the first 6 months of 2016 (January 1 to June 30), following measures previously used in the literature.[8,13,16,17] First, total unique opioid prescribers and dispensers (pharmacies or prescribers that dispense take-home medications) were identified during the study period. Second, counts of opioid prescriptions filled were identified in 5 major categories: methadone fills, other long-acting opioids (e.g., oxycodone), short-acting opioids in Schedule II (e.g., hydrocodone–ibuprofen), opioids used for treatment of opioid use disorder (e.g., buprenorphine), and short-acting opioids in Schedules III–IV (e.g., butorphanol). Other prescription drugs were muscle relaxants, benzodiazepines, and other nonbenzodiazepine sedative fills. Third, individuals were identified with ≥91 days' supply of opioids, individuals with concomitant opioid and benzodiazepine prescriptions, and a categorical variable for average morphine milligram equivalents daily dose.[18] Demographic data (age and sex) were extracted from the individuals' most recent prescription during the study period.

The following 2 dependent variables were identified for 2 models using 2016 Office of Chief Medical Examiner data: (1) any opioid-related overdose deaths (ORODs), defined as all deaths where opioids were indicated as a cause of death, even if other substances were present; and (2) illicit ORODs, defined as any death involving heroin or fentanyl not in combination with prescription opioids. Determination of cause of death was performed by the medical examiner using toxicology data and other evidence

collected during the forensic investigation. Outcome variables used were agnostic to suicidal death.

Statistical analysis

Model selection was intended to derive a reliable model with predictors that would be readily interpretable by end users (e.g., PDMP administrators). Thus, the model fitting process considered several competing considerations: the performance of each individual predictor, the fit statistics for the overall model (e.g., the AUC), and parsimony (all else equal, fewer predictors are likely to be more useful to end users). Univariate ORs were examined for any and illicit ORODs associated with each of the predictor variables. Cut points for continuous variables, including number of opioid prescribers, number of opioid dispensers, and each type of prescription drug fill (e.g., buprenorphine, methadone, and long-acting opioids), were determined using classification and regression tree analyses.[19] Patients with missing ZIP codes or age were excluded at the start of the analysis. A logistic regression model was developed and validated using a split-half validation approach in which half of the patients were selected randomly for the derivation cohort and the other half were used to validate the model. The performance of the model discrimination was quantified using the AUC statistic, a measure of the discriminatory ability of risk classification models that can range from 0.0 to 1.0. Statistical analyses were performed from December 2018 to July 2019 using SAS, version 9.4.

RESULTS

Descriptive statistics for the derivation and validation cohorts are represented in Table 1. The full cohort consisted of 565,175 individuals with a total of 1,926,390

Table 1. Characteristics of the Study Population and Overdose Fatality Outcome Cohorts

Characteristic	Full cohort	Illicit opioid overdose death	Any opioid overdose death
Age/sex			
Female, *n* (%)	330,996 (58.6)	105 (33.3)	204 (39.6)
Male, *n* (%)	234,179 (41.4)	210 (66.7)	311 (60.4)
Age 18–34 years, *n* (%)	116,289 (20.6)	89 (28.2)	122 (23.7)
Age 35–49 years, *n* (%)	123,647 (24.5)	103 (32.7)	186 (36.1)
Age 50–64 years, *n* (%)	194,820 (34.5)	113 (35.9)	189 (36.7)
Age 65–80 years, *n* (%)	115,392 (20.4)	10 (3.2)	18 (3.5)
Age, years, mean (SD)	50.1 (15.8)	44.6 (12.4)	45.2 (11.9)
Opioid use			
Opioid prescribers, mean (SD)	1.4 (0.9)	1.8 (1.3)	1.9 (1.4)
Opioid prescribers ≥3, *n* (%)	52,660 (9.3)	64 (20.3)	114 (22.1)
Opioid dispensers, mean (SD)	1.2 (0.6)	1.5 (1.0)	1.6 (1.1)
Opioid dispensers ≥3, *n* (%)	25,055 (4.4)	37 (11.7)	69 (13.4)
Opioid OUD fills, mean (SD)	0.18 (1.22)	1.03 (3.34)	0.69 (2.68)
Opioid LA fills, mean (SD)	0.29 (1.26)	0.43 (1.72)	0.66 (1.80)
Opioid SA-II fills, mean (SD)	1.57 (2.14)	1.93 (2.46)	2.49 (3.02)
Opioid other SA fills, mean (SD)	0.60 (1.34)	0.41 (0.98)	0.45 (1.01)
Methadone fills, mean (SD)	0.05 (0.55)	0.09 (0.81)	0.10 (0.76)
MMEDD ≤49	399,727 (70.7)	153 (48.6)	234 (45.4)
MMEDD 50–89	89,949 (15.9)	47 (14.9)	88 (17.1)
MMEDD 90–119	24,049 (4.3)	15 (5.8)	30 (5.8)
MMEDD ≥120	51,450 (9.1)	100 (31.7)	163 (31.7)
Other controlled substance use			
Benzo fills, mean (SD)	0.51 (1.59)	1.06 (2.34)	1.53 (2.60)
Sedative fills, mean (SD)	0.16 (0.81)	0.21 (0.88)	0.35 (1.17)
Muscle relaxant fills, mean (SD)	0.04 (0.43)	0.09 (0.55)	0.14 (0.70)
Descriptive			
Patients with opioid fills, *n*	565,175	315	515
Death rate per 100,000 patients	n/a	55.7	91.1
Opioid prescriptions, *n*	1,523,371	1,228	2,257
Opioid prescriptions, mean (SD)	2.7 (3.2)	3.9 (4.5)	4.4 (4.6)
CS prescriptions, *n*	1,926,390	1,655	3,297
CS prescriptions, mean (SD)	3.4 (4.3)	5.3 (6.2)	6.4 (6.7)

Note: Illicit opioid overdose deaths were defined as any death involving heroin or fentanyl but not prescription opioids.
Benzo, benzodiazepine; CS, controlled substance; LA, long-acting; MMEDD, morphine milligram equivalent daily dose; OUD, opioid use disorder; SA, short-acting.

controlled substance prescriptions, of which 79.1% (1,523,371) were opioids. The population was predominantly female (*n*=330,996, 58.6%) with an average age of 50.1 (SD=15.8) years. A total of 515 experienced an any OROD and 315, an illicit OROD. Individuals who experienced an illicit OROD were younger on average (44.6 years, SD=12.4 years), as were individuals who experienced any OROD (44.2 years, SD=11.9 years) compared with the full population. A higher proportion of the population who experienced an OROD had seen 3 or more prescribers (illicit, 20.3%; any, 22.1%) or 3 or more pharmacies (illicit, 11.7%; any, 13.4%) compared with the full population (3 or more prescribers, 9.3%; 3 or more pharmacies, 4.4%).

Reference categories used in the logistic regression models (Table 2) included female sex, age 35–50 years, 1 opioid prescriber, 1 dispenser, no methadone fill, no opioid use disorder prescriptions, no long-acting opioid prescriptions, no short-acting schedule II opioid prescriptions, total opioid days' supply of up to 90 days, <50 morphine milligram equivalents daily dose, no concomitant opioid and benzodiazepine prescriptions, and no other controlled substance prescriptions.

The any OROD model found age 65–80 years to be a protective factor (OR=0.15, 95% CI=0.07, 0.30). The variable that indicated the highest risk was prescriptions related to opioid use disorder (OR=4.47, 95% CI=2.46, 8.12). Individuals with 2 or more benzodiazepine prescriptions (OR=3.31, 95% CI=2.24, 4.87) or who had at least 4 short-acting, Schedule II opioid prescriptions (OR=3.09, 95% CI=1.71, 5.60) were also at significantly higher risk. AUC calculations indicated that the model

Table 2. Multivariate Models of Risk Factors for Illicit Opioid Overdose and Any Opioid Overdose Deaths, 2016 (January–December)

PDMP data risk factor, 2016 (January–June)	Any opioid fatal overdose model		Illicit opioid fatal overdose model	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Sex/age				
Male	**2.22 (1.72, 2.87)**	**<0.0001**	**3.02 (2.14, 4.28)**	**<0.0001**
Age 18–34 years	1.22 (0.88, 1.70)	0.236	1.29 (0.86, 1.93)	0.217
Age 50–64 years	0.87 (0.65, 1.17)	0.369	0.83 (0.56, 1.22)	0.341
Age 65–80 years	**0.15 (0.07, 0.30)**	**<0.0001**	**0.16 (0.06, 0.40)**	**0.0001**
Opioid use				
Opioid prescribers 2	1.14 (0.80, 1.63)	0.470	1.15 (0.72, 1.84)	0.541
Opioid prescribers ≥3	1.42 (0.92, 2.17)	0.111	1.48 (0.82, 2.66)	0.190
Opioid dispensers 2	1.09 (0.78, 1.54)	0.612	1.04 (0.65, 1.64)	0.883
Opioid dispensers ≥3	1.37 (0.89, 2.11)	0.147	1.36 (0.75, 2.45)	0.308
Methadone fills ≥1	1.01 (0.43, 2.38)	0.976	1.76 (0.61, 5.10)	0.295
Opioid LA fills ≥1	**1.68 (1.11, 2.53)**	**0.013**	1.51 (0.84, 2.73)	0.170
Opioid OUD fills ≥1	**4.47 (2.46, 8.12)**	**<0.0001**	**8.61 (3.86, 19.20)**	**<0.0001**
Opioid SA-II fills 1	1.17 (0.74, 1.85)	0.505	1.04 (0.59, 1.84)	0.885
Opioid SA-II fills 2–3	**2.39 (1.71, 4.02)**	**0.0010**	1.78 (0.90, 3.52)	0.099
Opioid SA-II fills ≥4	**3.09 (1.71, 5.60)**	**0.0002**	**2.71 (1.25, 5.87)**	**0.012**
Opioid SA-III,IV fills ≥1	1.13 (0.79, 1.62)	0.492	0.97 (0.60, 1.58)	0.917
Opioid supply ≥91 days	**0.37 (0.25, 0.54)**	**<0.0001**	**0.39 (0.24, 0.63)**	**0.0001**
MMEDD 50–89	1.38 (0.97, 1.97)	0.071	1.18 (0.74, 1.88)	0.481
MMEDD 90–119	1.37 (0.77, 2.44)	0.285	1.31 (0.63, 2.76)	0.472
MMEDD ≥120	**1.92 (1.18, 3.11)**	**0.008**	1.12 (0.56, 2.24)	0.758
Concomitant opioid/benzo	0.90 (0.57, 1.43)	0.657	0.73 (0.37, 1.44)	0.357
Nonopioid				
Benzodiazepine fills 1	1.48 (0.92, 2.38)	0.103	1.30 (0.70, 2.44)	0.407
Benzodiazepine fills ≥2	**3.31 (2.25, 4.87)**	**<0.0001**	**2.62 (1.53, 4.49)**	**0.0004**
Muscle relaxant fills ≥1	**2.40 (1.44, 4.03)**	**0.0008**	1.61 (0.64, 4.01)	0.311
Sedative fills ≥1	1.31 (0.86, 1.98)	0.207	0.79 (0.38, 1.63)	0.516

Note: Boldface indicates statistical significance (p<.05). Reference categories: female; age 35–49 years; 1 opioid prescriber; 1 opioid dispensing pharmacy; no methadone fill; no OUD fill; no LA fill; no SA fill; 1–90 days of opioid supply; <50 MMEDD; no concomitant opioid/benzodiazepines; and no fills for benzodiazepines, muscle relaxants, and sedatives. Illicit opioid overdose deaths were defined as any death involving heroin or fentanyl but not prescription opioids.

Benzo, benzodiazepine; LA, long-acting; MMEDD, morphine milligram equivalent daily dose; OUD, opioid use disorder; PDMP, prescription drug monitoring programs; SA, short-acting.

accurately predicted any OROD (derivation, AUC=0.81; validation, AUC=0.77).[20] The selected risk model cut off was 0.0010, which balanced sensitivity and specificity. At this cut off, sensitivity was 67.6%, specificity was 78.0%, positive predictive value (proportion of individuals truly at risk correctly predicted as being at risk) was 0.28, and negative predictive value (proportion of individuals not at risk correctly predicted as not being at risk) was 99.96 (Appendix Table 1, available online).[21]

The illicit OROD model demonstrated similar associations to the model calibrated on any opioid overdose death, although 1 or more long-acting opioid fills, 2 to 3 short-acting schedule II opioid fills, ≥120 morphine milligram equivalents daily dose, and 1 or more muscle relaxant fills were not found to be significant predictors. Consistent with any OROD, age 65–80 years (OR=0.16, 95% CI=0.06, 0.40) was found to be protective. Prescriptions related to opioid use disorder (OR=8.61, 95% CI=3.86, 19.20) similarly indicated the highest risk of the outcome and was an even stronger predictor for illicit OROD. Individuals who were male (OR=3.02, 95% CI=2.14, 4.28) and had 4 or more short-acting schedule II opioid prescriptions (OR=2.71, 95% CI=1.25, 5.87) were also at significantly higher risk. The AUC indicated that the model accurately predicted illicit OROD as well as the any OROD model, (derivation, AUC=0.80; validation, AUC=0.76).[20] The selected risk score cut off was 0.0005, with sensitivity of 70.9%, specificity of 71.4%, positive predictive value of 0.14, and negative predictive value of 99.98 (Appendix Table 2, available online).

DISCUSSION

The performance of predictive models for OROD among Maryland adults with a prescription for at least 1 opioid medication within the study period were evaluated. The models predicting risk of any OROD and those predicting illicit OROD had very similar performance characteristics, indicating that prescription records are reasonably predictive of illicit OROD among patients with recent opioid prescription activity in the PDMP. Risk of overdose was especially high among male patients in both models, those using opioid use disorder medication, those with 4 or more short-acting schedule II opioid prescriptions, or those having 2 or more benzodiazepine prescriptions. These results are congruent with many of the risk factors that have been previously identified in the literature.[8,16,22] A model incorporating a wide set of prescription-related risk factors demonstrated moderate predictive ability in both the derivation and validation cohorts.

This study demonstrates the potential of a predictive model to identify high-risk patients prescribed opioids in a PDMP whether the fatality is due to prescription or illicit opioids. To date, most studies have leveraged self-reported data to predict illicit ORODs[23] or used PDMP data for descriptive analyses only.[24] Using the PDMP as a source of risk information to help predict illicit ORODs is thus a novel approach. Given that the model was validated for a rare outcome and resulted in a low positive predictive value, the model may best serve as a broad public health tool focused on stratifying levels of risk, but more detailed assessments of risk will depend on clinicians applying further screening to those who are identified as high-risk. Indeed, given the high risk of false positives, this risk model used on its own could cause unintended harm and thus requires a careful implementation strategy. However, applying a risk score universally within a state's PDMP could provide important input to those designing public health programs, and could ultimately help improve quality of care and directed interventions. For example, a numerical risk score or a high-risk flag could be added to the PDMP data to identify subpopulations of risk to which limited resources, such as naloxone distribution, could be applied, or a secondary validated tool could be applied to the subpopulation for more fine-grained differentiation of risk. Given that the risk model assigns a risk score to every individual within the population, representing a spectrum of risk from highest to lowest, the implementer of the predictive model must decide what the appropriate tolerance is for false positives versus false negatives when attempting to capture populations at risk. Consideration must also be made on what risk factors included in the model may represent proxies for other vulnerabilities that would need to be considered carefully. For example, prescriptions for medications for opioid use disorder (i.e., buprenorphine) were found to be predictive of higher overdose risk; however, rather than leading to overdose risk, these drugs can be protective against overdose. More likely, patients who take these medications have a history of addiction that independently predisposes them to overdose risk.[25]

Should a risk model be used for broader population identification and paired with a tool that can appropriately identify individuals truly at risk of an OROD, greater clinician training on pain management and addiction medicine to adequately interpret risk information should be provided. Further research is needed to determine the most effective approach for deploying population-level risk tools using PDMP-derived quantitative markers of opioid overdose risk, as applied here.

Limitations

Although this study makes important contributions, several limitations should be noted. These findings are

based on individuals who received at least 1 controlled opioid prescription and therefore are likely only to be generalizable to similar populations. For this study, diagnostic codes were not accessible and therefore could not be factored into certain conditions of interest, such as those patients with end-stage cancer. The PDMP data also are limited by the fact that only prescriptions dispensed within or into Maryland are available and therefore may not represent a complete PDMP prescription history of the patients included in the study. Prescriptions filled in other states by Maryland residents would be reported to the respective dispenser's state PDMP and not to the state of residence. As stated in the Discussion, the low positive predictive value limits the utility of the model such that it is best used only as a method to identify subpopulations at risk. The positive predictive value of the model is likely to be improved through greater integration of patient-level predictors from outside the PDMP, such as prior history of nonfatal opioid overdose. This is an important area for further research. Finally, although it is promising that a viable model can be developed using only 6 months of risk factor data, the use of a relatively small window of time in this study may not adequately evaluate longer-term risk factors for overdose. Given that addiction and overdose often have extended histories and do not follow a calendar timeframe, there may be benefit in assessing longer lookback and follow-up periods as part of future research.

CONCLUSIONS

This study occurred during a period where many overdose fatalities involved illicit fentanyl and heroin. This study provides one of the first demonstrations of developing a predictive model for illicit ORODs that was similar in performance to any ORODs using only prescription data available in 1 statewide PDMP. Though the models had acceptable AUCs, the low positive predictive value indicates that the models are better suited for population-based risk stratification, rather than identifying specific individuals for interventions at the point of care. Information similar to what was used to identify at-risk individuals in Maryland in this study is available currently in every state and the District of Columbia. Given the large number of individuals impacted by the opioid epidemic, it is essential that further work be rapidly undertaken to implement and evaluate wide-scale interventions that use risk identification models like the one described here. Such population-level analytic decision support tools would assist public health agencies to effectively identify and help those persons who are at risk of opioid overdose death.

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Author contributions: LF contributed to the conception of the study, drafted the manuscript, identified key study variables, and facilitated data linkage. JW and BS led and oversaw the research project, conceptualized the study question and variables, and revised the manuscript. KWL developed variables, created and performed model analysis, and revised the manuscript. TR generated the study variables and analytic database. BCL and KJ contributed to the conception of the study, secured databases for analysis and linkage, helped develop study variables, and revised the manuscript. NK, KS, MJ, and ME contributed to the conception of the study and revised the manuscript.

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SUPPLEMENTAL MATERIAL

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