MODELING THE IMPACT OF HOSPITAL-BASED ADDICTION CONSULT SERVICES ON POST-DISCHARGE MORTALITY

By

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A DISSERTATION

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List of Abbreviations

ACO	Accountable Care Organization
ACS	Addiction Consult Service
CCO	Coordinated Care Organization
CDPS	Chronic Illness and Disability Payment System
IMF	Illicitly Manufactured Fentanyl
IMPACT	IMProving Addiction Care Team
ISPOR-SMDM	International Society for Pharmacoeconomics and Outcomes Research and the Society for Medical Decision Making's Good Research Practices Model Validation
HEDIS	Healthcare Effectiveness Data and Information Set
MOUD	Medication for Opioid Use Disorder
OR-HOPE	Oregon HIV/Hepatitis and Opioid Prevention and Engagement
OTP	Opioid Treatment Program
OUD	Opioid Use Disorder
OHSU	Oregon Health & Science University
REDUCE	Reducing Infections Related to Drug Use Cost-Effectiveness
SUD	Substance Use Disorder

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Abstract

Introduction: Hospitalizations for patients diagnosed with Opioid Use Disorder (OUD) are rising. Hospitalization is a touchpoint to connect with patients with OUD, initiate evidence-based treatment, and link patients to community treatment programs. Addiction Consult Services (ACS) facilitate care for patients with OUD in the hospital, build connections to community treatment programs and are an emerging gold-standard of care for hospitalized patients with OUD. There are few formal ACS in the United States, and little research has explored how ACS expansion might impact health outcomes at the population level. The objectives of this study were to evaluate how ACS expansion might impact post-discharge OUD treatment engagement and 12-month drug-related mortality, among patients hospitalized with OUD.

Methods: This work uses Oregon Medicaid claims data to model trajectories of care for 8,450 patients hospitalized with OUD from April 2015 through September 2018. In Chapter 2, we describe a Markov model built to reflect patient transitions through care systems following hospitalization for OUD. In Chapter 3, we describe causes of 12-month mortality within our cohort. In Chapter 4, we apply our Markov model to estimate the impact of ACS expansion through Coordinated Care Organizations for Medicaid enrollees in Oregon. Finally, in Chapter 5, we again apply our Markov model to estimate the toll of increasing drug supply contamination with illicitly-manufactured fentanyl (IMF) on post-discharge drug-related mortality, and to what degree ACS expansion might mitigate drug-related deaths.

Results: We successfully built and validated a Markov model that mirrors patient trajectories of care through healthcare systems among patients with OUD, hospitalized in Oregon. Within 12-months of hospital discharge, 522 patients died (7.8%); 307

patients died from a drug or substance related cause (4.6%), and 71 died from a drug overdose (1.1%). We estimate that ACS expansion in Oregon could increase post-discharge OUD treatment from 20% to 47% across the state. Additionally, in the context of increasing IMF contamination, of the next 10,000 hospital admissions, we estimate that 913 (Low, High = (252, 1616)) may die from drug-related causes. ACS expansion across the state could potentially avert 138 of those drug-related deaths.

Conclusions: ACS expansion could help engage patients hospitalized with OUD in post-discharge OUD treatment and, particularly in the context of increasing IMF contamination, reduce drug-related deaths. Future work should support expansion and evaluation of new ACS.

Chapter 1: Introduction

Adapted in part from:

King, C. A., Englander, H., Korthuis, P. T., Barocas, J. A., McConnell, K. J., Morris, C. D., Cook, R. *Designing and validating a Markov model for hospital-based addiction consult service impact on 12-month drug and non-drug related mortality.* Under Review. Preprint available on MedRxiv at 10.1101/2020/12/01/20242164

Drug overdose is the leading cause of unintentional injury death in the United States (1). Among people with opioid use disorder (OUD), 20% eventually die of drug overdose (2), but cardiovascular diseases, cancer, and infectious diseases also contribute. Patients with OUD who are hospitalized for OUD-related and other diagnoses are often medically complex and face life-threatening illnesses. These patients experience higher mortality rates than hospitalized patients with similar conditions (2).

Hospitalization is a vulnerable time for patients with OUD. People with OUD may leave the hospital before completing recommended medical therapy if withdrawal symptoms are untreated (3). People who withdraw from opioids have lower drug tolerance and increased risk of drug overdose after discharge in the absence of treatment for OUD (4-6). Medications for opioid use disorder (MOUD) delivered in the hospital can treat withdrawal symptoms and reduce overdose risk (7), and are often necessary, but not sufficient, to help keep patients engaged in inpatient care. Despite this, most hospitalized patients with OUD are not started on MOUD (8, 9), though, when offered, nearly three-quarters of patients with OUD choose

to start MOUD (10). Interventions to improve initiation of MOUD among hospitalized patients are urgently needed (11).

Addiction consult services (ACS) are an emerging intervention to engage hospitalized patients in care and meet patient-driven goals for substance use treatment (12). Evaluation of ACS demonstrates improved engagement in post-hospitalization treatment and decreased substance use (11, 12). However, assessing the effect of ACS using gold-standard study designs is challenging because of the costs and logistical challenges associated with multi-site, cluster-randomized trials. Additionally, it is rarely feasible to assess distal, rare outcomes like drug-related mortality in the context of a hospital-based intervention. We consequently do not know how ACS affect post-discharge drug-related mortality or non-drug related mortality for patients with OUD.

This dissertation describes the use of modeling with cohort simulation to help understand how ACS impact post-discharge OUD treatment engagement and mortality, including in the context of ACS scale up. Chapter 2 describes the model construction and validation, including population of the model with Oregon Medicaid claims data. Chapter 3 describes trends in mortality, by cause, among Oregon Medicaid patients hospitalized with OUD from 2015 to 2017. Chapter 4 describes a mechanism to scale up ACS in Oregon (through Coordinated Care Organizations) and achievable gains in post-discharge treatment engagement from successful scale-up. Finally, for people with OUD who purchase non-prescribed opioids, the drug supply in Oregon is increasingly contaminated with fentanyl (13). Chapter 5 adapts the Markov model to mirror recent trends in Oregon of increased fentanyl-related overdose deaths, and then models ACS expansion to understand how ACS might decrease drug-related deaths.

Chapter 2: Designing and validating a Markov model for hospital-based addiction consult service impact on 12-month drug and non-drug related mortality

Adapted in part from:

King, C. A., Englander, H., Korthuis, P. T., Barocas, J. A., McConnell, K. J., Morris, C. D., Cook, R. *Designing and validating a Markov model for hospital-based addiction consult service impact on 12-month drug and non-drug related mortality.* Under Review. Preprint available on MedRxiv at 10.1101/2020/12/01/20242164

2.1 Introduction

Hospitalizations are rising for people with OUD (14). Within hospitals, Addiction Consult Services (ACS) can help improve care for people with OUD (15). To date, ACS have been shown to decrease post-discharge substance use and substance use disorder severity (12), increase engagement in post-discharge OUD treatment (11), and improve patient trust in healthcare providers (16). Healthcare systems are considering how to improve hospital-based care for people with OUD (17). And yet, little is known about how scaling up ACS care might impact post-discharge OUD treatment engagement or drug and non-drug related mortality outside of a single hospital setting.

Modeling can help answer this question. Broadly, modeling healthcare systems can allow researchers to rapidly test different care delivery scenarios

and capture robust estimates of study outcomes, which can support healthcare system decision-making and answer salient clinical questions. Modeling inpatient care scenarios for patients with OUD can guide healthcare systems on how best to address a rapidly evolving epidemic more quickly and adaptively than randomized trials. Simulation modeling has previously been used to estimate prevented overdose deaths from the expansion of naloxone distribution (18-20), and the implementation of safe-injection sites (21). The objective of Chapter 2 was to design and validate a Markov model that estimates the impact of ACS care on 30-day post-discharge OUD treatment engagement and 12-month mortality among hospitalized patients with OUD.

2.2 Methods

2.2.1 Model Structure

We used a Markov model to estimate the impact of ACS care on 12-month mortality among hospitalized patients with OUD (Figure 1). Our model has the following components: ACS consult, post-discharge OUD treatment engagement, and 12-month post-discharge drug related death, non-drug related death, and survival.

The Oregon Health & Science University's Institutional Review Board approved this study (#00010846).

2.2.1.1 ACS Referral

Once patients are admitted to the hospital, they can be referred to ACS care. ACSs exist across a growing number of North American hospitals. Typically, they include care from an interprofessional team that may include of

medical providers, social workers, nurses, and alcohol and drug counselors (22). Some intentionally include people with lived experience in recovery (23-25). ACSs typically address needs of people use any substance (for example, stimulant, alcohol, and opioids) and care includes comprehensive assessments, withdrawal management, medication treatment, psychosocial and harm reduction interventions, and efforts to support patient engagement and linkage to care across settings. ACSs commonly also provide staff education and patient advocacy (15, 22, 26). For this model, we used an intention-to-treat approach; all patients referred to ACS were included regardless of level of care engagement or specific services received.

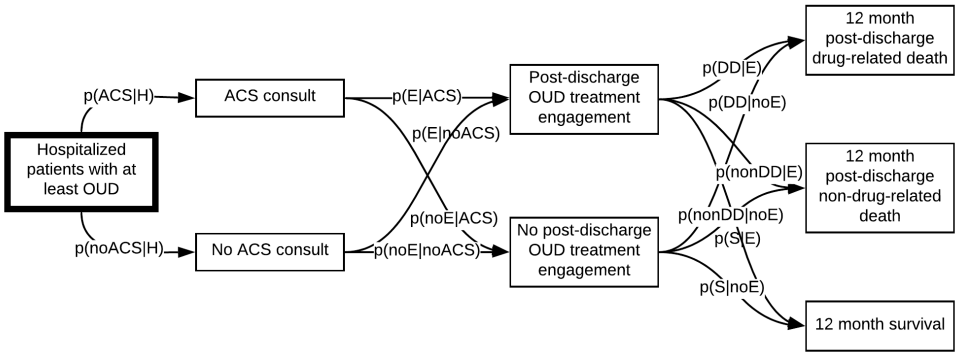
2.2.1.2 Post-discharge OUD treatment engagement

We used a modified Healthcare Effectiveness Data and Information Set (HEDIS) measure of engagement to stratify for post-discharge OUD treatment engagement. The original measure requires that patients initiate treatment and have two or more additional alcohol or drug services or medication for OUD within 34 days of initiation (27). Recent research has shown that evidence-based MOUD has superior outcomes in preventing mortality and decreasing opioid use (7). For this reason, we defined post-discharge OUD treatment engagement as: 1) at least two filled prescriptions for buprenorphine, extended-release naltrexone, or methadone from an Opioid Treatment Program in the 30 days following hospital discharge, or 2) a prescription for extended-release naltrexone or buprenorphine that covered 28 of the 30 days post-hospital discharge (28).

2.2.1.3 12-month mortality

At twelve months, deaths are classified as drug related versus non-drug related (including as circulatory, neoplasm, infectious, digestive (including alcohol-related liver disease), external (including suicide and unintentional injury), respiratory, endocrine, and other) by ICD-10 mortality codes described by Hser et al (2).

Figure 1. Markov model of hospital-based addiction care in Oregon, 2015-2018



2.2.2 Model data

Where data exists for recalibration, our Markov model could be used in any setting with patients hospitalized with OUD. We populated our model with data from Oregon Medicaid claims data and expert opinion, described below, to reflect care from an addiction consult service in Portland, Oregon, and its impact on post-discharge drug and non-drug related mortality.

2.2.3 Setting and study design

Oregon Health & Science University in Portland, Oregon is home to an inpatient ACS, the Improving Addiction Care Team (IMPACT). IMPACT is a

hospital-based service that utilizes an interdisciplinary team of physicians, advanced practice providers, social workers, and peers with lived experience in recovery to support non-treatment seeking adults with substance use disorder. Patients are eligible to be referred if they have known or suspected substance use disorder (SUD), other than tobacco use disorder alone. IMPACT conducts substance use assessments, initiates medication-based treatment (including buprenorphine, methadone and extended release naltrexone for OUD) and behavioral treatment where appropriate, and connects patients to post-discharge SUD treatment. IMPACT utilizes a harm reduction approach and integrates principles of trauma-informed care. Previous research describes IMPACT's design and evaluation (10, 11, 15, 24, 25, 29, 30). Notably, IMPACT is the only comprehensive ACS in Oregon, though a few hospitals offer MOUD initiation during hospitalization.

2.2.4 Participants

We used Oregon Medicaid claims data to identify patients hospitalized at least once with OUD from April 2015 through August 2018, including IMPACT patients. For mortality analyses only, we also utilized mortality data from Oregon Vital Statistics through December 31, 2018; thus, patients admitted through January 1, 2018 were included to allow 12 months of follow-up time. Patients were eligible for inclusion if they were over 18 years old and had an ICD-9 (304.*) or ICD-10 (F11*) diagnosis of OUD during a hospital admission.

2.2.4.1 Cohorts for transition points

We defined three cohorts for our analyses utilizing Oregon Medicaid data. First, we included all patients who met eligibility criteria in analysis for our first

transition, referral to ACS. Then, we used a matched cohort of three controls to one IMPACT patient for our post-discharge OUD care engagement and mortality analyses. We matched without replacement on hospital admission quarter and admission number, including one admission per person.

2.2.5 Transition data

For ACS referral, we identified all hospitalized patients with OUD in Oregon during the study period, and then identified the subset who were referred to the ACS. For post-discharge OUD treatment engagement, we used Oregon Medicaid claims data to identify if patients met the modified HEDIS engagement measure in the 30 days following hospital discharge. For 12-month mortality, we used Oregon Vital Statistics data to identify deaths in our cohort during the study period through December 31, 2018. For mortality models, the cohort was limited to include only participants seen before January 1, 2018 to allow for 12 months of follow-up time for all participants. We classified deaths as drug related versus non-drug related as indicated above. We manually reviewed deaths that were not captured by these codes and reclassified to fit into drug versus non-drug related categories.

2.2.6 Transition probabilities

We used a Bayesian approach to obtain transition probabilities for our Markov model using Oregon data. First, we obtained prior information from experts in addiction (described below). After surveying expert participants, we calculated the mean and identified the minimum and maximum ratings. We then numerically fit beta distributions to those quantities using differing “confidence levels” (31). Then, we updated our priors with the information from data about our

cohort described above. We estimated marginal probabilities over observed cases using fitted Bayesian logistic regression models at each transition point (32).

2.2.6.1 Bayesian priors via expert elicitation

We used expert elicitation to capture prior information for our models. We identified important covariates at each transition point, including age (in years), gender (female/male), race (White/not White/unknown), ethnicity (Hispanic/Not Hispanic), concurrent alcohol use disorder (yes/no), concurrent stimulant use disorder (yes/no), hospital length of stay (in days), rural residence (yes/no), filled at least one prescription for medication for OUD in the month before hospital admission (yes/no), previously admitted to the hospital (yes/no), and Chronic Illness and Disability Payment System (CDPS) Score (continuous). The engagement model also included referral to an ACS (yes/no). The mortality models included engagement in care after discharge (yes/no) and filled a naloxone prescription in the 30 days after hospital discharge (yes/no).

We used a clinical-vignette design to ask providers about the relevance of covariates on patient outcomes. To do this, participants provided a probability estimate for different events: referral to an ACS, post-discharge engagement, and mortality.

For example, a vignette could read:

"The patient is a young White man with OUD and AUD. He was in the hospital for several days. He was on medication for OUD at admission. He had never previously been admitted to the hospital. He has many comorbidities. He is

not from a rural area. What is the probability he engaged in post-discharge treatment for OUD within 30 days of discharge?"

Experts evaluated 16 (referral to ACS), 17 (engagement) and 18 (mortality) vignettes selected from an optimal experimental design generated for each model (33). From the optimal design, we chose a subset of the vignettes that were substantially different from one other for ease of interpretability and to maximize the information gathered about each covariate.

As part of our IRB-approved research, study authors (HE, PTK) generated lists of experts in addiction consult services and hospital-based addiction treatment in general in the United States. Each participant took only one survey. We aimed to recruit at least five participants for each survey, with a goal of at least three responses per survey. For the referral to ACS survey, we also asked participants to refer hospitalists at their institutions to complete the survey, as hospitalists are frequently providers who refer patients to ACS. Ultimately, six participants took the ACS survey (6 of 11, 54.5%), four took the engagement survey (4 of 5, 80%), and three took the mortality survey (3 of 8, 37.5%).

2.2.6.2 Bayesian logistic regression models

We used the transformed prior information from expert surveys and Oregon Medicaid cohort data to fit Bayesian logistic regression models at each transition point. Models were fit using Markov Chain Monte Carlo methods (34). We sampled each parameter 10,000 times with 2000 burn-in chains. We used multiple metrics to assess model convergence. First, we used Gelman and Rubin's potential scale reduction factor; all values in all models equal 1.0. Values close to 1.0 are suggestive of convergence. Effective sample sizes all

approximated the number of posterior draws requested. All model trace plots appear to have a caterpillar-like distribution, and there were no divergent transitions. Autocorrelation plots for all parameters suggest low autocorrelation. We used the package Shiny Stan to evaluate Bayesian model fit (35).

We tested different prior information strengths: first, using a cohort sample size method, where the prior information equivalates a percent of the study sample size (0.1%, 1%, 5% and 10%); second, using a confidence interval method, where we fit beta distributions to the range of survey responses, and then used the maximum and minimum values as borders for 80%, 85%, 90%, and 95% confidence intervals. We picked the best-fit model using Pareto smoothed importance-sampling leave-one-out cross validation using the loo package in R where lower expected log predictive density values indicate a better model fit (36). We also prioritized models where Pareto k diagnostic values had at least good reliability for all estimates.

We used mcmcObsProb in the BayesPostEst package (37) to estimate marginal transition probabilities over observed cases with the fitted Bayesian logistic regression models. We created prior-posterior plots using ggplot2 (38).

2.2.7 Model validation

We validated our model using the frameworks suggested by the International Society for Pharmacoeconomics and Outcomes Research and the Society for Medical Decision Making's Good Research Practices Model Validation guidelines (ISPOR-SMDM) (39). We explored five components of validity: face validity, internal validity, cross validity, predictive validity, and

external validity. As suggested, we provide a non-technical description of our model in Appendix 3.

2.2.8 Role of the funding source

The funding sources had no part in designing the study, interpreting the data, writing, and publishing the report.

2.3 Results

There were 8,450 patients admitted at least once with OUD in Oregon from April 2015 through August 2018. Among the 6,654 patients seen by January 1st, 2018, at twelve months, 114 (1.7%) participants died from drug-related causes and 408 (6.1%) died from non-drug related causes. Participant demographics are included in Table 1.

Table 1. Participant demographics for Chapter 1

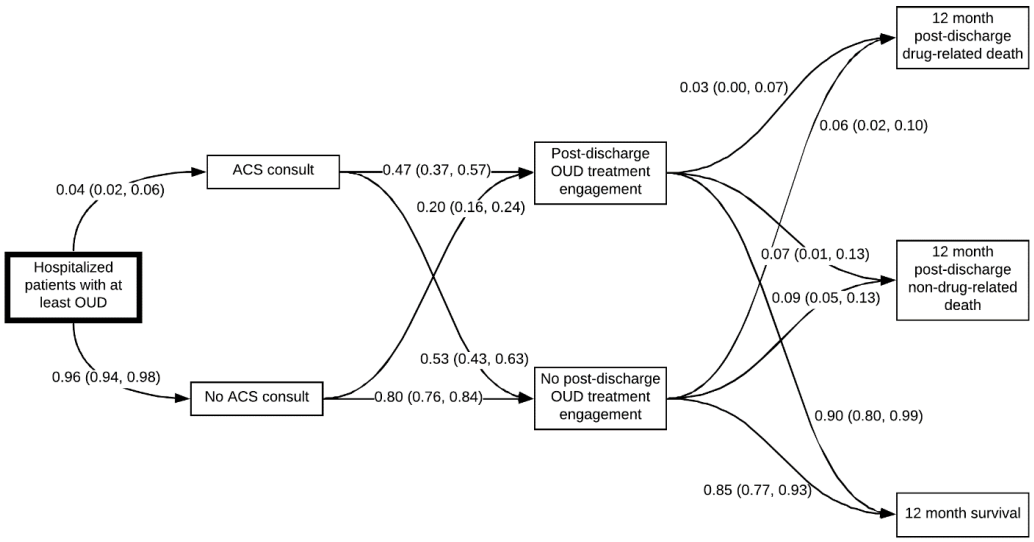
	All patients n=8,450	**Seen by ACS** n=265	**Not Seen by ACS** n=8,185	**p-value**
Age Years	44.5 (15.4)	39.5 (0.77)	44.6 (0.17)	<0.001
Gender Male	3,632 (43.0%)	159 (60.0%)	3,473 (42.4%)	<0.001
Race White	5,919 (70.1%)	169 (63.8%)	5,750 (70.3%)	0.034
Not White	543 (6.4%)	16 (6.0%)	527 (6.4%)	
Unknown race	1,988 (23.5%)	80 (30.2%)	1,908 (23.3%)	
Ethnicity Hispanic	299 (3.5%)	10 (3.8%)	289 (3.5%)	0.002
Alcohol use disorder	306 (3.6%)	14 (5.3%)	322 (3.9%)	0.269

Stimulant use disorder	689 (8.2%)	41 (15.5%)	642 (7.8%)	<0.001
Length of stay (days)	6.6 (11.2)	14.9 (0.97)	6.4 (0.12)	<0.001
Rural residence	2,234 (26.4%)	32 (12.1%)	2,202 (26.9%)	<0.001
Medication for OUD at hospital admission	1,508 (17.8%)	48 (18.1%)	1,460 (17.8%)	0.908
Previously admitted to hospital	1,891(22.4%)	116 (43.8%)	1,775 (21.7%)	<0.001
CDPS Score	2.5 (1.6)	3.11 (0.11)	2.48 (0.02)	<0.001

Transition probabilities derived from Bayesian logistic regression models are depicted in Figure 2. In our study, 4% (95% CI= 2%, 6%) of patients admitted at least once for OUD were referred to an ACS in Oregon. Of those, 47% (95% CI= 37%, 57%) engaged in post-discharge OUD care. Of the 96% not seen by an ACS, 20% (95% CI= 16%, 24%) engaged in post-discharge OUD care. The risk of drug-related death at 12 months among patients who engaged in post-discharge OUD care was 3% (95% CI= 0%, 7%) versus 6% (95% CI = 2%, 10%) in patients who did not engage in care. The risk of non-drug related death was 7% (95% CI =1%, 13%) among patients who engaged in OUD treatment, versus 9% (95% CI= 5%, 13%) for those who did not. For referral to ACS care, the best-fit Bayesian logistic regression model used an 80% confidence interval; for all other models, a sample size of 0.1% fit best (Appendix 1). All estimates had

acceptable Pareto k-diagnostic values. We report posterior intervals for each covariate from Bayesian logistic regression models in Appendix 2.

Figure 2. Markov model with estimated transition probabilities for hospital-based addiction care in Oregon, 2015-2018



2.3.1 Model validation

2.3.1.1 Face validity

To assess face validity, one researcher (CK) designed the model and received feedback from experts in addiction medicine outside of the study team about the model's face validity. Experts agreed that the model reflected the path of care for patients admitted to hospitals in Oregon with OUD (*structure)*. Further, the use of Oregon Medicaid data, versus data from the literature, was considered a strength in deriving *evidence* for the model by outside experts. ACS and their

impact on care for patients with OUD is of immense interest to healthcare systems and policymakers, and experts also agreed that the question was timely and important (*problem formation).* Finally, after data analysis, the model results were presented to researchers who agreed that estimates from the model matched their expectations (*results).*

2.3.1.2 Internal validity

We conducted additional checks and analyses to ensure internal validity of our Bayesian approach (also referred to as technical validity, (40)). First, a recent paper used a similar approach and data structure to evaluate the impact of prenatal maternal factors on nonadherence to infant HIV medication in South Africa. After building our Bayesian model, we used the deidentified data from the South Africa analysis to attempt to replicate identical results as were published. The built model exactly replicated the results of the South African analysis. Second, we conducted classic logistic regression models for each transition point in addition to the Bayesian models. We placed a 1/3, 1/3 noninformative prior (Kerman's prior) on all covariates, which should be roughly approximate to the classic logistic regression results. Our results with non-informative priors were sufficiently similar to classical logistic regression results. Finally, we conducted code "walk throughs" as suggested, where the analyst (CK) walked through code with an expert in these methods (RC).

In addition to the above steps, because we used Bayesian analyses for our transition probabilities, we needed to ensure that our final estimates of confidence intervals around engagement and mortality estimates actually

encompassed the observed number of people who engaged, and people who died from drug-related and non-drug related deaths. We simulated estimates, generating “Low” and “High” modeled estimates based on “best” and “worst” cases of model dynamics (e.g. lower confidence bound of estimate for ACS referral, lower confidence bound for post-discharge OUD treatment engagement, upper confidence bound for drug-related mortality generates an estimate for “High” death). Of the 6,654 patients with 12 months follow-up time, the model estimates that 1,330.8 patients engage in care (Low, High =(1,064.6, 1,597.0)). We observed 1,318 patients who engaged in care in the cohort. Additionally, the model estimated 357.2 drug related deaths (Low, High =(98.5, 632.6)); there were 114 observed drug related deaths in the dataset. Similarly, the model predicted 570.8 non-drug related deaths (Low, High =(263.6, 865.0)); there were 408 observed non-drug related deaths in the dataset. Mortality analyses rarely account for all sources of follow-up which may mean that reported mortality estimates in the literature are lower than in reality. Thus, it was not surprising that modeled transition probabilities from Bayesian logistic regression for 12-month mortality may be higher than raw observed proportions.

2.3.1.3 Cross-validation

Researchers at a separate academic medical center have developed, validated and calibrated the Reducing Infections Related to Drug Use Cost-Effectiveness (REDUCE) model, a Monte Carlo microsimulation model (41). This model has the capacity to answer similar questions to what we post here, using estimates derived from published data and from expert sources. In contrast to our model which uses a cohort defined by opioid use disorder, the REDUCE model simulates data for people who inject drugs. Because model estimates for

the REDUCE model are derived from a variety of sources in different parts of the county, we expected outcomes from the REDUCE model to be different from our model; we felt these differences are important to understand.

To support cross-validation of our model, the research team that developed the REDUCE model generated 4,153 simulated patients admitted to the hospital for the first time. Of those, 36 died while in the hospital (0.9%). Of the 4117 still alive at hospital discharge, 96 (2.3%) died within 12 months of hospital discharge (95% CI = 1.9%, 2.8%). This is lower than our estimated 928 (13.9%) deaths from our Markov model (Low, High =(5.4%, 22.5%)).

There are several important differences between the REDUCE model and our model. First, as previously mentioned, the REDUCE model simulates data from patients who inject drugs, while ours models patients who have OUD more generally. There are important demographic differences between these two groups, including that our model also includes patients with a primary diagnosis of cancer. Next, the percentage of people seen by an ACS in the REDUCE model was higher than in our model: 25% of patients in REDUCE were seen by an ACS versus 4% in our model. The REDUCE model uses data from Boston, where higher numbers of patients are seen by ACS. This makes it challenging to understand REDUCE estimates in the context of Oregon specifically. Additionally, patients had a higher post-discharge treatment engagement rate in the REDUCE model. In REDUCE, approximately 25.2% of patients receive medication for OUD for at least one week in the month following discharge, versus our model, where 20% of patients not seen by an ACS receive MOUD after discharge. Finally, data from the first simulated admission was used to estimate 12-month mortality from REDUCE; because we matched our cohort controls on the number of previous admissions among patients seen by an ACS,

it is possible that our patients were older and sicker than patients who had never previously been admitted to the hospital. While the base model structures are similar, our model is populated with data that provides a focused understanding of addiction consult services in Oregon. Populating our model with different data, including Boston estimates, could provide tailored explorations of ACS in different settings.

2.3.1.4 External validity

To examine external validity, we used large, high-quality, recent studies of representative populations in independent cohorts of participants to separately validate post-discharge OUD treatment engagement and 12-month drug related and non-drug related mortality. We simulated a cohort of size determined from outside research and looked to see if our simulated confidence interval (cohort simulation/matrix multiplication method, (40)) was different from observed values or confidence intervals from the published estimates (Table 2). Where there was disagreement, we describe potential causes.

Table 2. Table of results for external validation of Markov model

Data Source	Justification of selection	Dependent, partially dependent, independent data source	Part of model evaluated	Comparison of differences and results in data sources	Evaluation of cohort simulation results versus observed data
Naeger et al. (42)	Testing in national dataset	Independent	Post-discharge OUD	Data from 36,719 patients with	Cohort simulation showed

			treatment engagement	an inpatient admission for opioid abuse, dependence, or overdose, 2010 to 2014 -Data from time period just prior to Oregon Medicaid cohort; engagement may have been lower -Included any prescription for post-discharge MOUD	7343.8 (Low, High =(5875, 8812)) people predicted to engage versus 6132 people observed -Modeled range of estimates contains point estimate of observed engagement
LaRochelle et al 2018 (43)	Testing in large cohort study	Independent	12-month drug and non-drug related mortality	17,568 Massachusetts adults without cancer from 2012 to 2014 -Dataset mortality may be lower because of exclusion of patients with cancer	Cohort simulation showed 8.6 non-drug related deaths per 100 person-years (95% CI=1.5, 13.0), and 5.4 opioid-related deaths per 100 person-

				-Post-discharge treatment engagement for OUD included all time, to 12 months, of post-discharge engagement, which may further decrease drug-related deaths	years (95% CI=4.0, 9.5) -Observed all-cause mortality was 4.7 deaths (4.4, 5.0) per 100 person-years; opioid-related mortality was 2.1 deaths (1.9 to 2.4) per 100-person years -There is no difference in non-drug related deaths between the simulated cohort and observed data -Opioid-related deaths may be higher in

					our model because of a more liberal definition of opioid-related deaths
Ashman et al. (CDC) (44)	Testing in large cohort study	Independent	12-month all-cause mortality	-24,340 patients with an opioid hospitalization across 94 National Hospital Care Survey hospitals -Analysis included patients with cancer	Cohort simulation showed 3,394 all-cause deaths (95% CI = 1324, 5478) versus 1,879 (2,295*0.819) all-cause deaths observed -Modeled confidence interval contains point estimate of observed all-cause mortality

2.3.1.5 Predictive validity

All relevant data was included in building the Markov model described in this paper. We have planned analyses to evaluate our model predictions versus Medicaid claims data for the same cohort of patients seen in through December of 2020, once data is released.

2.4 Discussion

We built and validated a Markov model that reflects trajectories of care and survival at twelve months for patients hospitalized with OUD in Oregon. We used a Bayesian framework to integrate clinical expertise with data from Oregon Medicaid claims to estimate transition probabilities in our model. After development, we validated our model using ISPOR-SMDM standards, evaluating face validity, internal validity, cross validity, predictive validity and external validity.

The single other model that evaluates ACS care delivery is the REDUCE model, used in model cross validation in this analysis (41). Versus the REDUCE model, our model estimates are more context-relevant estimates of post-discharge OUD treatment engagement and 12-month drug and non-drug related mortality in Oregon. Our overall mortality estimate is higher than the REDUCE model, which may reflect severity of illness of people who are older, sicker, with more previous inpatient hospitalizations and limited linkage to post-discharge OUD care in Oregon. This is important as one potential use of our populated model is to predict the impact of expanding inpatient ACS care in Oregon; a model populated with Oregon data may better reflects the local care setting at

baseline may provide more accurate results following intervention. Additionally, populating our model with different data in different ACS context may similarly provide tailored results.

This study had several limitations. First, because we sought to build a model that reflected addiction care in Oregon, the model may not be generalizable to other settings. Still, the Oregon experience may help inform modeling in other states with limited ACS uptake, and we used Bayesian estimates from national experts to inform transition probabilities. Second, claims data is often inaccurate in classifying patient race and ethnicity; our study estimates may not correctly capture the experience of people of color in Oregon. Third, we originally planned to use 30-day mortality as an outcome for this study, but we were unable to do so because of limited drug-related mortality in the 30-day post-discharge period; we used 12-month mortality data instead. Finally, Medicaid claims data does not separate costs for inpatient delivery of medication for OUD, so it was not possible to tell if patients received OUD inpatient outside of an ACS.

This model can be used to evaluate changing scenarios of care in spaces where healthcare providers, healthcare systems, or policymakers are considering implementing or changing ACS coverage in their applicable system. The strength of the model comes from the estimates used to populate it, and with recalibration, the model can be adapted to different settings of ACS care delivery. In this paper, we describe data that reflects ACS care in Oregon. Using this data, we can model changing scenarios of care in Oregon, from increasing ACS care delivery to implementing drug-policy related changes, potentially including

reducing barriers to naloxone access, implementing safe consumption sites or safe supply interventions, and others. Future research should use this model to evaluate changes in care delivery in Oregon to understand how these changes may impact survival among patients with OUD.

2.5 Conclusion

Hospitalization is a critical time for patients with OUD, and addiction consult services can help support patients during hospitalization and connect them to post-discharge care. Markov modeling can help researchers, clinical teams and policy makers understand how changes in care systems might impact patient outcomes. Additionally, our model allows healthcare systems and policymakers to evaluate the impact of ACS on mortality. In this work, we built and validated a Markov model that reflects the trajectories of care and survival for patients hospitalized with OUD in Oregon. Future research should use this work to evaluate state-wide clinical and policy changes that may impact patient survival.

2.6 Acknowledgements

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2.7 Declarations of Competing Interests

Dr. Korthuis serves as principal investigator for NIH-funded studies that accept donated study medication from Alkermes (extended-release naltrexone) and Indivior (buprenorphine).

2.8 Funding

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Chapter 3: Causes of death in the 12 months after hospital discharge among patients with opioid use disorder

Adapted in part from:

King, C. A., Cook, R., Korthuis, P. T., Morris, C. D., Englander, H. *Causes of death in the 12 months after hospital discharge among patients with opioid use disorder.* In preparation.

3.1 Introduction

Hospitalizations are increasing among people with opioid use disorder (OUD) (14). Many patients with OUD who are hospitalized want access to medications for OUD (MOUD) (10), but MOUD is underutilized in inpatient settings (45). Hospitalization represents an important touchpoint for patients with OUD. Among patients who died from a drug overdose in one study, nearly half had been seen in healthcare settings, including hospitals, in the previous year (46) and patients with substance use disorders are seven times more likely to be admitted to the hospital than the general population (47). Increased mortality has been attributed to lower tolerance among patients who withdraw from opioids and do not start MOUD in the immediate post-discharge period. In this group, subsequent return to use is associated with increased overdose risk in drug and alcohol treatment centers (5, 48), and among people leaving incarceration (49). The subsequent risk of overdose death for patients with OUD who are hospitalized to 12 months post-discharge is not well described, nor are the causes of death in this population beyond the immediate post-discharge period. The objective of this study was to describe causes of death in the year post-discharge among patients hospitalized with OUD.

3.2 Methods

3.2.1 Study setting and design

This analysis is part of a larger project modeling care trajectories for hospitalized patients with OUD in Oregon (50). We used data from all Oregon Medicaid patients who were hospitalized at least once between April 2015 and December 2017. Data were linked to Oregon Vital Statistics mortality data through December 2018. The Oregon Health & Science University's Institutional Review Board approved this study (#00010846).

3.2.2 Participants

This study included patients age 18 years old and older and had an ICD-9 (304.*) or ICD-10 (F11*) diagnosis code of OUD during a general hospital admission during the study window.

3.2.3 Measures

We extracted the following variables from Oregon Medicaid claims data: age (years), sex (male/female), race (White/Black or Person of Color/Unknown), ethnicity (Hispanic/Not Hispanic), length of stay (days), and rural residence (yes/no).

3.2.4 Outcome

We classified deaths using categories defined by ICD-10 codes from the National Center for Health Statistics (51). We categorized drug-related deaths as all unintentional, intentional, and undetermined intent deaths from drug poisoning (ICD-10 codes X40-X49; X60-X69; Y10-Y19) and deaths attributed to mental and behavioral disorders because of substance use (F10-F19) (51). We describe mortality categories in Table 3.

Participants were classified in each category of death for which they had codes; for example, a person with a code for drug-related death and for respiratory death was counted in both categories. A patient who died from endocarditis would be included as a drug-related death if a code for mental and behavioral disorders because of substance use (F10-F19) was also listed on their death certificate.

3.2.5 Data analysis

We calculated the cumulative monthly mortality rate and overall percentage of patients who died from each cause described in Table 3 within 12-months of hospital discharge.

Table 3. Death classifications and causes of death (n) at 12 months post-hospital discharge among patients with OUD in Oregon, 2015-2018

Type of Death	Example diagnoses	Number of deaths at 12 months post-discharge (n=552)
Drug-Related*	-Mental and behavioral disorders due to psychoactive substance use (F10-F19) -Intentional self-poisoning (suicide) by and exposure to drugs and other biological substances (X60-X64) -Intentional self-poisoning (suicide) by and exposure to other unspecified solid or liquid substance and their vapors (X65-X66, X68-X69) -Intentional self-poisoning (suicide) by and exposure to other gases and vapors (X67)	301 (54.5%)

	-Accidental poisoning and exposure to noxious substances (X40-X49) -Poisoning by and exposure to drugs and biological substances, undetermined intent (Y10-Y14) -Poisoning by and exposure to other and unspecified solid or liquid substance, undetermined intent (Y15-Y16, Y18-Y19) -Poisoning by and exposure to other gases and vapors, undetermined intent (Y17)	
Diseases of the circulatory system	Hypertensive disease, Ischemic heart disease, Stroke	218 (39.5%)
Diseases of the respiratory system	Influenza, Pneumonia	185 (33.5%)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	Senility, ill-defined and unknown causes of mortality	134 (24.3%)
Neoplasms	Pancreatic cancer, Colon cancer	102 (18.5%)
Endocrine, nutritional and metabolic diseases	Diabetes mellitus, Malnutrition, Metabolic disorders	100 (18.1%)
Certain infectious and parasitic diseases	HIV, Viral hepatitis, Septicemia	98 (17.8%)

Diseases of the digestive system	Crohn's disease, Alcoholic liver disease	91 (16.5%)
Drug Overdose (Unintentional, Intentional, Undetermined)	As in Drug-Related, other than F10 to F19	71 (12.9%)
Diseases of the genitourinary system	Glomerular diseases, renal failure	71 (12.9%)
Diseases of the nervous system	Meningitis, Parkinson's disease, Epilepsy	55 (10.0%)
External causes of mortality	Car accident, homicide	47 (8.5%)
Mental and behavioral disorders (other than F10-F19)	Schizophrenia, Mood disorders	45 (8.2%)
Diseases of blood and blood-forming organs	Anemias, Coagulation defects	20 (3.6%)
Diseases of musculoskeletal system and connective tissue	Rheumatoid arthritis, Systemic lupus erythematosus	19 (3.4%)
Diseases of the skin and subcutaneous tissue	Infections of skin and subcutaneous tissue	14 (2.5%)
Congenital malformations, deformations and chromosomal abnormalities	Congenital malformations of nervous system, Congenital malformations of heart	<10**

*Because patients can be counted in more than one category, a patient with endocarditis could have a code for opioid use disorder (F11) and a code for endocarditis (I39); this patient would be counted in categories for death from both Drug-related and Diseases of the circulatory system.

**Suppressed; less than 10 patients

3.3 Results

From April 2015 to December 2017, 6,654 Oregon Medicaid patients with an OUD diagnosis were admitted to the hospital. Patients were predominately female (56.7%) and White (72.2%), with an average age of 44.2 years (SD=15.4 years) and average length of stay of 6.5 days in the hospital (SD=10.9 days). Approximately one-quarter of patients (26.5%) were from rural areas. In the 12 months post-discharge, 522 patients died (7.8%) in Oregon; 307 patients died from a drug or substance related cause (4.6%), and 71 died from a drug overdose (1.1%).

Of the 522 patients who died within 12 months, 58.8% had a drug-related cause included in their death certificate; this was the most frequent cause of mortality. Diseases of the circulatory system (39.5%), diseases of the respiratory system (33.5%), other causes of death (24.3%), neoplasms (18.5%), endocrine, nutritional, and metabolic diseases (18.1%), and certain infectious and parasitic diseases (17.8%) were the next most frequently identified causes of death in the cohort (Table 3). Figure 3 displays cumulative mortality, by cause.

Table 4 shows cumulative drug and non-drug related mortality over the study period. In the month after hospital discharge, 130 (2%) of patients in the cohort died.

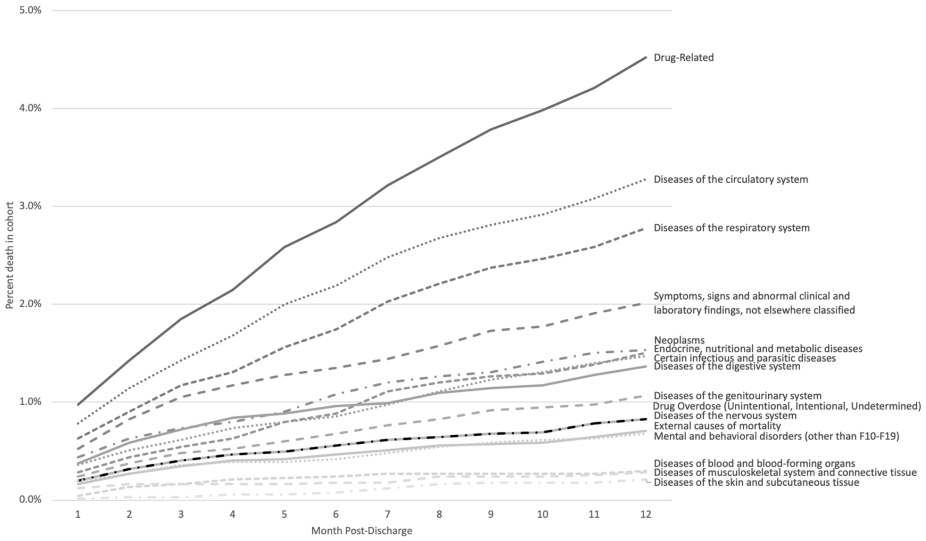
Sixty-five (1%) died from drug-related causes and 0.2% died from drug overdose. At twelve-months, 301 (5%) of patients died from drug-related causes and 0.8% died from a drug overdose. There were no overdose deaths in the first two months post-discharge among patients who engaged in OUD treatment in the first month after discharge.

Table 4. Cumulative drug and non-drug related mortality at 12 months post-hospital discharge among patients with OUD in Oregon, 2015-2018

	Month 1		Month 2		Month 3		Month 4		Month 5		Month 6		Month 7		Month 8		Month 9		Month 10		Month 11		Month 12	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Total number of deaths (of 6,654 patients)	130	2.0%	190	2.9%	234	3.5%	264	4.0%	306	4.6%	342	5.1%	385	5.8%	416	6.3%	446	6.7%	468	7.0%	493	7.4%	522	7.8%
Drug-Related	65	50.0%	95	50.0%	123	52.6%	143	54.2%	172	56.2%	189	55.3%	214	55.6%	233	56.0%	252	56.5%	265	56.6%	280	56.8%	301	57.7%
All other causes	65	50.0%	95	50.0%	111	47.4%	121	45.8%	134	43.8%	153	44.7%	171	44.4%	183	44.0%	194	43.5%	203	43.4%	213	43.2%	221	42.3%

Among patients who died from drug-related causes, the most common ICD-10 codes listed on their death certificates were F17.9 (Nicotine Dependence), J44.9 (Chronic obstructive pulmonary disease, unspecified), X42 (Accidental poisoning by and exposure to narcotics or hallucinogens), B182 (Chronic viral hepatitis C), and T401 (Opioid overdose). Among patients who were classified as not dying from drug-related causes, the most common ICD-10 codes listed on their death certificates were A419 (Sepsis, unspecified organism), I50 (Heart failure), I10 (Essential primary hypertension), B18.2 (Hepatitis C), and J44.9 (Chronic obstructive pulmonary disease, unspecified).

Figure 3. Cumulative mortality by cause among people hospitalized with OUD in Oregon, 2015-2018



3.4 Discussion

Patients with OUD are at high-risk of death from a myriad of causes in the year after hospital discharge. In this study, at 12-months following hospitalization, nearly 5% of patients died from a drug-related cause. Importantly, causes of death spanned nearly every medical specialty, reflecting the burden of comorbid medical conditions among people with OUD. And yet, patients with OUD frequently have stigmatizing experiences seeking healthcare from a variety of different care specialties (3, 52). This underscores two key needs: first, healthcare providers in many disciplines should learn about and offer treatment for OUD, regardless of whether the patient's illness is attributable to their substance use. Second, healthcare systems and policymakers must create healthcare systems that destigmatize OUD and better care for patients at risk of death. Inpatient addiction consult services are one way that hospital systems can better care for patients with OUD (10, 11, 15, 29).

There are some limitations to this work. First, Oregon has low racial and ethnic diversity, and may not be generalizable to other populations. Second, OUD may be underassessed in patient data; we may be missing patients who do have OUD but do not have a diagnosis. Third, our study only uses death data from Oregon Vital Statistics; we may have missed deaths that happened outside of the state.

Hospitalized patients with OUD are at high risk of death, from both drug and non-drug related causes, in the year after discharge. Future research should consider not only overdose, but a more comprehensive definition of drug-related death in understanding post-discharge mortality among hospitalized patients with OUD, and care systems should work to mitigate the risk of death in this population.

3.5 Conflicts of Interest

No authors have financial conflicts of interest. Dr. Korthuis serves as principal investigator for NIH-funded trials that accept donated study medications from Alkermes (extended-release naltrexone) and Indivior (buprenorphine-naloxone).

3.6 Funding

This research was supported through grants from the National Institutes of Health, National Institute on Drug Abuse (UG1DA015815, UG3DA044831). Grant UL1TR002369 provided support of REDCap, the web application this study used for data collection.

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Chapter 4: Expanding inpatient Addiction Consult Services through Accountable Care Organizations for Medicaid enrollees: A modeling study

Adapted in part from:

King, C. A., Cook, R., Korthuis, P. T., McCarty, D., Morris, C. D., Englander, H. *Expanding inpatient Addiction Consult Services through Accountable Care Organizations for Medicaid enrollees: A modeling study.* Under Review.

4.1 Introduction

Hospitalizations for patients diagnosed with Opioid Use Disorder (OUD) are rising (14). Admissions for patients with OUD total over $15 billion dollars annually in the United States, including $700 million for related infections (53). Hospitalization is a touchpoint to connect with patients with OUD, initiate evidence-based treatment, and link patients to community treatment programs, including Opioid Treatment Programs and X-waivered buprenorphine providers (46). Initiating medication for OUD (MOUD) in the hospital can reduce post-discharge mortality from OUD when MOUD treatment continues (54-56), but robust hospital-community partnerships must exist to link and retain patients in care (57-59).

Addiction Consult Services (ACS) facilitate care for patients with OUD in the hospital, build connections to community treatment programs and are an emerging gold-standard of care for hospitalized patients with OUD (12). ACS are often interprofessional teams of providers who provide comprehensive care for OUD in the hospital (22). ACS also have ancillary benefits, including broadly improved treatment environments for patients with OUD (60) and facilitation of hospital-community partnerships to smoothly

transition patients from hospital-based care to community-based treatment (59). ACS patients have less substance use post-discharge (12), greater trust in healthcare providers (16), and higher rates of post-discharge OUD treatment engagement (11) compared to OUD patients hospitalized without ACS services. ACS may work best in areas with existing outpatient treatment resources; in some areas, limited opportunities to engage in outpatient treatment could be a barrier to ACS implementation (61, 62).

Little research explores how to best increase adoption of inpatient ACS for patients with OUD. One potential strategy is through Medicaid Accountable Care Organizations (ACOs). As of 2019, at least fourteen states had Medicaid ACOs (63). ACOs typically have local leadership, and focus on improving care coordination, cost-efficiency, and care quality for enrollees, and many aim to integrate physical and behavioral healthcare and reduce disparities (64). ACOs can help better integrate inpatient and outpatient care for patients with OUD, and could support ACS expansion in ways that make sense for stakeholders regionally, from directly funding hospital-based ACS, to hiring ACS teams to deploy to hospitals. Because Medicaid programs bear the highest financial costs among payers for OUD admissions (53), have rising numbers of patients hospitalized with OUD (14), and are invested in creating medical homes for patients in strong primary care systems (64), ACOs are a natural home for ACS expansion. ACS, moreover, can help ACOs better meet meaningful benchmarks for care for patients with OUD.

In 2012, Oregon implemented Coordinated Care Organizations (CCOs), a type of ACO. Since implementation, Oregon has a cost-effective track record of care delivery (65). In 2020, Oregon launched CCO 2.0, new goals to further improve and integrate behavioral health systems, increase care value, and address social determinants of

health and health equity (66). Oregon's current ACS (29), formed in 2015, helps reach these goals; this ACS has initiated medication for OUD (MOUD) in the hospital for over 70% of OUD patients (including for patients who are underserved by traditional care systems, and patients who are homeless) (10), improved outpatient treatment engagement (11), improved care settings for patients with SUD (60), and increased patient trust in healthcare teams (16). To expand ACS care, however, hospitals need strong referral pathways that require improved community treatment access, particularly in rural areas (67). Oregon's CCOs could help engage healthcare systems and outpatient treatment providers to scale up ACS and improve community treatment access. The objectives of this study were to estimate the effects of 1) expanding ACS care through CCOs in Oregon on post-discharge OUD treatment engagement, and separately, 2) increasing community treatment access within CCOs on post-discharge OUD treatment engagement.

4.2 Methods

4.2.1 Model structure and data

We built and validated a Markov model that described trajectories of care for hospitalized patients with OUD, which we describe in detail elsewhere (Figure 2, Chapter 2) (50). In our model, patients are hospitalized and have a diagnosis of OUD. In the hospital, patients can be seen by an ACS; engage in post-discharge OUD treatment within 30 days; and die from a drug-related cause or die from a non-drug related cause, within 12 months after discharge. We populated our model with Oregon Medicaid data using Bayesian analyses. Cohort simulation uses data from Medicaid admissions from April 2015 through December 2017.

The Oregon Health & Science University's Institutional Review Board approved this study (#00010846).

4.2.2 Addiction Consult Service in Oregon

In this model, we used data from Oregon Health & Science University's ACS, the Improving Addiction Care Team (IMPACT). IMPACT is an interdisciplinary team (i.e., physicians, advanced practice providers, social workers, and peers with lived experience in recovery) that meets adults with substance use during hospitalization for acute medical and surgical conditions. Most are not engaged in treatment before hospitalization and are not seeking treatment at time of admission. Any hospital provider or social worker can refer patients with known or suspected substance use disorder (SUD), other than tobacco use disorder alone. IMPACT evaluates substance use, initiates medication-based treatment and psychological services as appropriate, and connects patients to post-discharge SUD care. Previous research describes IMPACT's development and outcomes (10, 11, 15, 24, 25, 29, 30). IMPACT at OHSU is the only ACS among 62 hospitals in Oregon, although some hospitals also provide MOUD for hospitalized patients.

4.2.3 Outcome measure

The primary outcome in this analysis is post-discharge OUD treatment engagement. We used a modified Healthcare Effectiveness Data and Information Set (HEDIS) measure of engagement to measure post-discharge OUD treatment engagement (27, 28). Because of the superiority of MOUD in reducing harms for people with OUD versus other treatments (7), patients were considered engaged in post-

discharge OUD care if, within 30 days of hospital discharge, they had 1) at least two filled prescriptions for buprenorphine or extended-release naltrexone, 2) enrolled in an Opioid Treatment Program (OTP) for at least two days, or 3) a prescription for extended-release naltrexone or buprenorphine that covered 28 of the 30 days post-hospital discharge (28, 50).

4.2.4 Coordinated Care Organizations (CCOs)

CCOs convene regional stakeholders to coordinate high-quality care for patients that are part of their system (68). In Oregon, nearly 90% of patients on Medicaid are assigned to a CCO (65). The remaining individuals have open card Medicaid, meaning that any provider that accepts Oregon Medicaid insurance can treat them; these patients may also have more complex health conditions (69). CCOs in Oregon are generally organized at the regional level (70). We assigned patients to the CCO that billed for the hospital encounter included in the analysis (each patient had one admission selected (50)).

4.2.5 Analyses

4.2.5.1 Observed data

We report the number of patients hospitalized with OUD from 2015 to 2017 among each CCO and the number and percent of patients who engaged in OUD treatment in the 30 days after discharge.

4.2.5.2 Expanding ACS care

After excluding patients seen by IMPACT, we used cohort simulation (40) to estimate the change in post-discharge treatment engagement for OUD if all admitting hospitals within the CCO had access to addiction consult service care and all eligible patients were referred to ACS.

4.2.5.3 Assessing community treatment access

In the absence of hospital-based addiction care (including ACS), there are some patients who will connect to outpatient treatment for OUD on their own or through other outreach efforts. For some patients, this may be a continuation of treatment that they initiated prior to hospitalization. In our base model, the average rate of post-discharge treatment engagement for OUD among patients not seen by an ACS was 20% (16%, 24%), with an observed ceiling effect of nearly 30% in the CCO that contains the Portland-metro area. We considered 20% to reflect average saturation of treatment opportunities (increased outreach, accessible MOUD) such that 20% of patients would engage in post-discharge care for OUD in the absence of an ACS.

For this analysis, we estimated the number of patients in each CCO that might engage in care if outpatient treatment systems were sufficiently available, in the absence of an ACS consult during hospitalization. To do this, for CCOs with observed engagement below 20%, we also used cohort simulation to report the number of additional patients that might engage in care with saturated outpatient treatment and no ACS, by CCO and across the state. To contextualize differences in outpatient treatment systems, we also report the number of Opioid Treatment Programs and X-waivered buprenorphine providers in each CCO region (71, 72).

4.2.6 Changes in CCOs over time

We used Medicaid data from 2015 to 2017 to populate our model. Over time, some CCOs have ended or merged with others, while others have replaced them. There was also one new CCO created after 2017. During the study window, patients in this county were covered by a different CCO that still exists in 2020. We included this new CCO in our results table but do not attribute patients to it. Finally, one CCO ended in 2018, and patients were transitioned to four existing CCOs. Because we could not identify which CCOs these patients were transitioned to, we omitted them from this analysis.

4.3 Results

4.3.1 Observed data

From 2015 to 2017, 5,878 Oregon Medicaid patients were hospitalized with OUD, and their care was billed to a CCO. Of those, 1,298 (22.1%) patients engaged in post-discharge OUD treatment after hospital discharge.

4.3.2 Expanding ACS care

In the study window, 5,711 of 5,878 patients (97.2%) were not seen by an ACS. Simulation of referral of these patients to ACS while hospitalized increased post-discharge OUD treatment engagement to 47.0% (95% CI 45.7%, 48.3%), or 2,684 patients (95% CI 2610, 2758). The gains in post-discharge OUD treatment with ACS

expansion by CCO are described in Table 1. CCO-specific increases in engagement range from 14.9% to 50.0% with ACS expansion. To achieve these estimates, post-discharge OUD treatment systems must be expanded to accommodate linkage-to-care for at least 47% of patients hospitalized within each CCO.

Table 5. Observed and simulated post-discharge treatment engagement by CCO, Oregon, 2015-2017

					With ACS expansion (excluding previous ACS patients)		With average treatment (increased to 20%) and no ACS expansion			
CCO	Number of Patients (n)	Observed engagement (n)	Observed engagement (%)	Number of non-ACS patients (n)	Simulated patients (n, 95% CI)	Difference in engagement (%)	Simulated patients (n, 95% CI)	Difference in engagement (to 20%) (%)	Number of Opioid Treatment Programs in counties (n)	Number of X- waivered providers in counties (n)
A	14	0	0.00%	14	7 (3,11)	50.00%	3 (1, 7)	21.40%	0	17
B	202	10	5.00%	201	94 (78, 108)	41.60%	40 (29, 53)	14.90%	1	57
C	51	*	<10%	51	24 (17, 31)	*	10 (5, 17)	*	1	12
D	214	22	10.30%	211	99 (84, 114)	36.00%	42 (31, 55)	9.30%	1	118
E	904	100	11.10%	899	423 (393, 453)	35.70%	180 (157, 205)	8.80%	10	526
F	97	14	14.40%	96	45 (35, 55)	32.00%	19 (12, 28)	5.20%	1	30
G	451	82	18.20%	450	212 (191, 233)	28.80%	90 (74, 108)	1.80%	2	74
H	173	32	18.50%	172	81 (68, 94)	28.30%	34 (24, 46)	1.20%	0	33
I	143	28	19.60%	140	66 (54, 78)	26.60%	28 (19, 39)	0.00%	0	20
J	35	*	<20%	32	15 (9,21)	25.70%	6 (2, 12)	0.00%	0	27
K	370	78	21.10%	370	174 (155, 194)	25.90%	-	-	1	52
L	176	42	23.90%	169	79 (66, 92)	21.00%	-	-	1	17
M	392	95	24.20%	387	182 (163, 201)	22.20%	-	-	2	43
N	2,656	787	29.60%	2,519	1184 (1134, 1232)	14.90%	-	-	9	461
O	0	-	-	0	-		-	-	1	65

*Suppressed; fewer than 10 patients

4.3.3 Increasing community treatment access

Ten of fifteen (66.7%) CCOs had fewer than 20% of patients engage in post-discharge OUD care (range: 0% to 19.6%). Twenty-three of 30 counties (76.7%) covered by these 10 CCOs are designated as non-metro (rural) counties by the Office of Management and Budget (73). We simulated increases in post-discharge treatment engagement to levels of 20% to estimate the number of people who might engage in post-discharge OUD care, in the context of expanded treatment systems in areas with current limited engagement and no ACS expansion. In these 10 CCOs, increasing outpatient treatment such that 20% of patients engage without ACS linkage increased the patients engaging in post-discharge OUD care from 12.9% or 296 patients in care at baseline to 20% (95% CI 18.1%, 21.4%) or 453 (95% CI 416, 491) in simulated analyses. See Table 1 for changes by each CCO, and number of Opioid Treatment Programs and X-waivered buprenorphine providers by CCO.

4.4 Discussion

Our model suggests that expanding addiction consult services can improve post-discharge OUD treatment engagement for hospitalized patients with OUD. To realize gains, hospitals must develop and support ways to connect patients to community treatment when they leave the hospital, which in some settings requires expanded community treatment access (e.g. additional providers who prescribe buprenorphine). In this study, expanding ACS care can approximately double post-discharge OUD treatment engagement (from 22% to 47%). Some CCOs may not have the infrastructure to immediately accept 47% of linked patients from healthcare systems into community treatment programs, or treatment systems that exist may be inflexible or not meet the needs of patients in those regions. This is reflected in low levels of post-discharge

engagement in some CCOs. It is possible to make some gains in engaging patients in post-discharge OUD treatment without ACS, but the average engagement if all CCOs meet the sample average is still 25% lower than in the context of ACS expansion.

The analysis builds on existing work demonstrating hospitalization as a critical touchpoint for patients with severe medical comorbidities who are at high risk for overdose and death (46). Many of these patients are not engaged in treatment before hospitalization (11) and many may want treatment (10), may benefit from harm reduction interventions, or both. CCOs seek to create systems where primary care providers are the foundation of an integrated system of care (64). When patients are not engaged in care for OUD, hospitalization can be a stabilizing moment to engage and prepare to reconnect with primary care teams after discharge. A key component of ACS is supported handoffs from the hospital to community treatment programs (through OTPs or to outpatient providers prescribing buprenorphine) (59). Treatment gaps exist in Oregon, particularly in rural counties. CCOs could help support ACS expansion with linkage to in-person or telemedicine outpatient buprenorphine providers where OTPs are unlikely to meet most patients needs because of distance. Importantly, for IMPACT (the ACS in Oregon), patients experiencing higher degrees of marginalization (e.g., homeless, with a partner who uses substances) were more likely to initiate medication in the hospital for OUD than other patients (10). This suggests that ACS may also be a route to engage more vulnerable patients in the state whose needs for treatment have not been address by outpatient systems.

Outside of ACS expansion, other interventions support engaging people with OUD in outpatient treatment; Oregon's CCOs and healthcare systems are trying different interventions to prevent drug-related deaths and engage patients in care (74-76). For

example, the Oregon HIV/HCV and Opioid Prevention and Engagement (OR-HOPE) and PRIME Plus Peer Programs provide two examples of harm minimization services and use of peers to facilitate relationship-building, particularly in rural communities (77, 78). Further, House Bill 4143 initiated a pilot program in Oregon to place peer recovery workers in hospital emergency departments to help connect patients to treatment (79). CCOs are uniquely poised to understand how programs such as these contribute to goals of integrated care for people with OUD in their regions, what has worked well and what has failed in the past, and how to best expand care now to meet the needs of patients. CCOs must work closely with stakeholders, including with people who use drugs, to design treatment systems that work for patients and within local healthcare systems. Further, CCOs may be prepared to expand ACS care, but hospital systems and outpatient treatment environments may not be ready, or may not have the bandwidth, to expand addiction care. Support from existing ACS to hospital systems considering expansion, including through interprofessional telemedicine mentoring programs, may help close this readiness gap (80).

Oregon is in the middle of an opioid overdose epidemic, which is worsening in the context of increasing fentanyl on the West Coast (13) and potentially the COVID-19 pandemic (81). CCOs span the state, and have important contextual understandings of local hospitals and outpatient treatment environments, and understand community needs. CCOs are uniquely situated to coordinate life-saving care for patients with OUD, particularly those who are hospitalized and need integrated care across multiple settings.

This context for CCOs is not unique to Oregon. Common features of ACOs nationally are goals for locally run, cost-saving, high quality care for Medicaid enrollees

(64, 68). As the opioid overdose epidemic continues across the United States, ACOs can serve as coordinating hubs for patients hospitalized with OUD who want to subsequently transition to outpatient care for OUD. ACS are one way to improve care environments for patients hospitalized with OUD and smooth transitions to outpatient care, where such outpatient systems exist.

This research has several limitations. First, our base model was populated with Oregon Medicaid data, which lags behind real-time trends; trends in outpatient treatment, ACS referral, or mortality may have changed since 2017. Oregon Medicaid claims data may also not include all treatment received if patients changed insurance post-discharge. Second, our analysis does not include cost data, which may be useful in exploring ACS expansion. Third, OTP and buprenorphine provider lists may underestimate the number of OTPs and X-waivered buprenorphine providers at the time of publication; not all providers who are X-waivered are listed online. Finally, Oregon is a state with limited racial and ethnic diversity, and ACS may impact populations differently in other states.

There are implications from this work for policymakers and healthcare leaders. First, healthcare systems must find ways to better care for patients with OUD who are hospitalized. ACSs are the emerging gold-standard of treatment for patients with OUD who are hospitalized; ACS can initiate or continue treatment for OUD, offer harm reduction tools, and connect patients to care, while potentially broadly improving inpatient treatment settings for patients (12, 22, 59, 60). To realize this, hospitals should identify and support clinical and administrative champions to develop programs, and work with other ACSs regionally or nationally to help support growth. In Oregon, for example, hospitals preparing to expand inpatient addiction treatment can participate in

interprofessional telemedicine mentoring, which can provide support as programs develop (80). As previously mentioned, ACS also link patients to care after discharge. To do this, post-discharge care systems must exist to connect patients. Policies resulting from the SARS-COV-2 pandemic have made it possible to connect patients to care virtually; for example, patients can access buprenorphine via tele-prescribing (82). However, it is unclear if these changes will last past the end of the pandemic; either way, treatment systems must be sufficiently prepared to accept an increased number of patients discharging from healthcare settings in the context of improved inpatient addiction care.

To ease this transition, policymakers at the state level should consider creating financial incentives for ACOs to link and engage hospitalized patients to treatment for OUD. Further, there will always be patients who need access to hospital-based care. This is reason to expand ACS across the state. However, some hospitals are small, or critical access hospitals; for these hospitals, ACOs may provide a unique opportunity to expand ACS care without requiring each hospital to implement an ACS. ACO leadership should work with healthcare systems to identify how to expand inpatient addiction care for patients hospitalized with OUD, including through ACS.

4.5 Conclusion

ACOs are uniquely positioned to improve care and coordination for patients hospitalized with OUD. Implementing ACS in ACO networks can improve post-discharge OUD treatment engagement, but community treatment systems must be prepared to accept more patients as inpatient addiction care improves. Policymakers and ACO

leadership should work to integrate incentives for OUD care systems with meaningful outcomes for patient care.

4.6 Acknowledgements

We would like to thank Jill Archer, Danielle Meyer, and Katie Harris for their guidance in developing this work.

4.7 Declarations of Competing Interests

Dr. Korthuis serves as principal investigator for NIH-funded studies that accept donated study medication from Alkermes (extended-release naltrexone) and Indivior (buprenorphine).

4.8 Funding

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Chapter 5: Drug supply contamination, hospitalizations, and 12-month post-discharge drug-related mortality among patients with opioid use disorder: modeling the role of Addiction Consult Services

Adapted in part from:

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5.1 Introduction

Illicitly manufactured fentanyl (IMF) is increasing in international drug supply chains (83), and IMF-related opioid overdose deaths are rising in the United States (US) (84). Through 2018, increases in IMF-related mortality primarily occurred in states in the Eastern half of the US, but emerging data suggests that IMF and fentanyl-analogues are newly permeating the drug markets among Western states (13). This has led to a nearly 400% increase in the contribution to national opioid overdose deaths involving synthetic opioids (fentanyl and fentanyl-analogues, excluding methadone) from Western states since 2017, a trend that does not appear to be slowing (13). The SARS-CoV-2 pandemic may further exacerbate IMF related deaths as people return to opioid use because of pandemic-related stress and changed access to recovery supports, use opioids without others nearby because of fears of SARS-COV-2, and use drugs from an unstable illicit drug supply chain (81, 83, 85, 86).

Hospitalizations are also rising for people with opioid use disorder (OUD) (14, 87), and hospitalization is a key opportunity to engage patients with OUD and work to define and meet their substance use treatment and harm reduction goals (88). In one study, nearly half of patients who had an opioid overdose had come in contact with a healthcare provider in the year prior to overdose, including while hospitalized (46). In general, the risk of opioid overdose increases after periods of withdrawal from opioids (5), making hospitalization a critical, and reachable, moment to connect with patients (10). As IMF-related overdoses continue to increase, hospitals must find ways to decrease harms from a contaminated drug supply in the context of already heightened risk post-discharge of opioid overdose and death. This may include initiating medication for OUD (MOUD) in the hospital, connecting patients to outpatient care, prescribing naloxone, providing fentanyl test strips, and having conversations about overdose prevention strategies.

Addiction consult services (ACS) can improve treatment for patients hospitalized with OUD. ACS are interprofessional teams of healthcare providers, including physicians, nurses, advanced practice providers, social workers, and alcohol and drug counselors (22, 29, 50). Some ACS include peers with lived experience with substance use disorders who are in recovery (23-25). ACS typically meet patients with known or suspected substance use disorders for the first time while hospitalized. They provide addiction-specific care, including substance use assessments, management, and treatment. Typically, ACS incorporate harm reduction interventions into care, including counseling about safer use practices (22, 89). ACS decrease post-discharge substance use and lessen the severity of substance use disorders (12), increase post-discharge substance use disorder treatment engagement (11) and improve patient trust in healthcare providers and the healthcare system (16). Importantly, ACS also change the

treatment environment at hospitals where they exist, modeling patient-centered, non-stigmatizing standards of care for of non-ACS clinicians, and in turn improving treatment received by patients with substance use disorders and hospital policies to support care for people with SUD (15).

In this context, one important part of ACS care is facilitating conversations about overdose risk and steps to mitigate that risk. This can include connecting patients to treatment for OUD, or in cases where patients plan to continue using opioids, supporting patients to access harm reduction tools like safe drug supply (90), safe consumption sites (91, 92), drug checking (where people can test a sample of substances they are using to see if it contains IMF) (93) and naloxone (18, 94, 95) that may help reduce overdose risk. ACS can create spaces to discuss harm reduction interventions, including training family members and friends to administer naloxone if there is a suspected opioid overdose.

Previous work has used modeling to estimate the impact of interventions on synthetic opioid deaths in Canada (21). In this paper, we first estimate the effect of increasing IMF contamination on drug-related death in Oregon among patients hospitalized with OUD. We then estimate how expanding hospital-based addiction consult services may impact post-discharge drug-related death, assuming IMF has increased in the drug supply. This work offers a roadmap to proactively mitigate the risk of death from IMF-related opioid overdose among patients hospitalized with OUD through ACS expansion.

5.2 Methods

5.2.1 Model structure and data

We previously built and validated a Markov model that maps progression through care systems for patients hospitalized with OUD, from the time of hospital admission through 12-months post-discharge (Figure 2, (50)). In our model, patients can be referred to an addition consult service (ACS), engage in post-discharge OUD care, and survive, die from a drug-related cause (predominately overdose) or die from a non-drug related cause at 12 months post-discharge. We used Oregon Medicaid data from 2015 to 2018, and Bayesian techniques, to populate our model.

The Oregon Health & Science University's Institutional Review Board approved this study (#00010846).

5.2.2 Addiction Consult Services

5.2.2.1 ACS in Oregon

The transition probability for ACS is populated with data from patients referred to Oregon Health & Science University's ACS, the Improving Addiction Care Team (IMPACT). IMPACT is similar to ACS described above, and previous research describes IMPACT implementation and outcomes (10, 11, 15, 24, 25, 29, 30). Any hospital provider or social worker can refer patients with known or suspected substance use disorder (SUD), other than only tobacco use disorder. IMPACT is the only ACS in Oregon, though some of the state's 62 hospitals provide MOUD for patients hospitalized with OUD. Importantly, over time, IMPACT has come to prescribe naloxone to nearly every patient with opioid use, and recently also for people who use methamphetamines

given risk of IMF contamination of methamphetamine (96) and high rates of polysubstance use in Oregon (30).

5.2.3 Outcome measure

The primary outcome in this analysis is 12-month drug related mortality. We defined drug-related mortality by definitions from Hser et al (2) which include ICD-10 mortality codes for accidental, intentional, and undetermined overdose with additional codes for drug-related mental and behavioral disease.

5.2.4 Analyses

5.2.4.1 Increasing hospitalization of people with OUD

Hospitalizations among people with OUD are increasing (14). This may be because of increased toxicity in the context of a contaminated drug supply, because more people are using opioids, because of other environmental stressors, or combinations of these. However, it also means that more patients with OUD come in contact with a system that could initiate and refer patients to care, provide them with harm reduction options, or both. Our cohort from April 2015 to September 2018 (3.5 years) included 8,450 patients admitted at least once with OUD in Oregon (50). For this analysis, we simulate 10,000 patients hospitalized with OUD through our Markov model (described above). We anticipate that this would reflect rises in both the number of people with OUD in the state and the number of people who are hospitalized because of their OUD. Results describe changes in drug-related death, in the context of expanded ACS, for the next 10,000 patients hospitalized with OUD in Oregon.

5.2.4.2 Modeling increased risk of drug-related death

For our cohort, we model baseline drug-related deaths, and estimated drug related deaths in the context of rising fentanyl contamination in Oregon. In 2018, Oregon reported 2.8 deaths per 100,000 people from synthetic opioids other than methadone, totaling 339 opioid-involved deaths (97), which the CDC predominately attributes to IMF and fentanyl analogues (98). A recent paper describing 2019 trends in fentanyl-related deaths west of the Mississippi River found a 63% increase in fentanyl-related deaths in 2019 (13). In late 2020, the Oregon Health Authority published a press release that describes a 70% increase in drug overdose in Oregon from 2019 to 2020, primarily driven by an increase in fentanyl and fentanyl analogues in the drug supply (81). After increasing the cohort size, we then increased our transition to drug-related death by 70% at 12 months (see columns 5 and 6 in Table 1) (81). We report the modeled number of deaths, with high and low estimates estimated by simulating “worst case” and “best case” scenarios in our model. To calculate the “worst” and “best” case scenarios, we adjusted transition probabilities to the ends of 95% confidence intervals calculated around each transition probability point estimate that would qualitatively make the system “worst” or “best.” For example, a “worst” case scenario would be the lower end of the confidence intervals around ACS referral and post-discharge engagement and higher end of the confidence interval around drug-related death, whereas “best” case would be the opposite.

5.2.4.3 Modeling hospital-based interventions’ impact on drug-related deaths

In the context of increased IMF deaths, we estimated the impact of expanding addiction consult services in the state on post-discharge drug-related mortality. Currently, 4% of Medicaid enrollees hospitalized with OUD are referred to an ACS in

Oregon. We simulated increases from 10% to 100% (in 10% intervals) in referral, to estimate how expansion might affect drug-related mortality. As with our increased risk of drug-related death, we simulate high and low estimates by simulating “worst case” and “best case” scenarios in the model.

5.3 Results

In our cohort of 6,654 hospitalized patients with OUD and 12 months follow-up time, we previously estimated 357 (Low, High = (99, 633)) drug-related deaths (50). In a simulated cohort of 10,000 patients with no change in the drug supply, we estimate that 537 (148, 951) patients would die from drug-related causes within 12-months of hospital discharge. In the context of increased IMF in the drug supply, this estimate increased to 913 (252, 1616). ACS referral at baseline was 4%; increasing ACS referral to accommodate 10%, 50%, or 100% of patients in the state reduces drug-related deaths to 904 (248, 1608), 849 (202.7, 1565), and 780 (147, 1511), respectively. The number of patients needed to treat to avoid one drug-related death in the context of increased IMF was 72.6 (estimated by simulating all patients without referral to ACS, and then all patients with referral to ACS). Results for all simulations are included in Table 6.

Table 6. Observed and simulated changes in drug and non-drug related death in the context of increasing IMF and ACS expansion in Oregon

				Risk of drug-related death		**Simulated number of drug-related deaths**		
Qualitative Description	**Cohort**	**Number of patients**	**Average % referred to ACS**	**Engaged in OUD treatment in month**	**Did not engage in OUD treatment**	**Avg.**	**Low**	**High**

				after discharge	in month after discharge			
-	Observed 2015-2017	6,654		3% (0.01%, 7%)	6% (2%, 10%)	357	99	633
No change in drug supply, no change in ACS	Simulated	10,000	4%	3% (0.01%, 7%)	6% (2%, 10%)	537	148	951
Increased risk of IMF contamination, no change in ACS						913	252	1616
Increased risk of IMF contamination, increased referral to ACS			10%	5.1% (0.01%, 11.9%)	10.2% (3.4%, 17%)	904	248	1608
			20%			891	236	1597
			30%			877	225	1586
			40%			863	214	1576
			50%			849	203	1565
			60%			835	192	1554
			70%			822	180	1543
			80%			808	169	1533
			90%			794	158	1552
			100%			780	147	1511

5.4 Discussion

In a simulated cohort that represents the next 10,000 Medicaid patients admitted with OUD to hospitals in Oregon, if in-hospital treatment systems and the drug supply remain as they were in 2018, we estimate that 537 patients would die from drug-related

causes within 12-months of discharge. Published data suggests that the illicit drug supply is increasingly contaminated with IMF, and that this (and other contaminants) have led to increased illicit drug-related deaths in Oregon since 2018 (13, 81). In the context of rising IMF in the drug supply, we estimate that nearly 913 patients would die if in-patient treatment systems do not change. Expanding ACS across the state for the next 10,000 admissions may save up to 138 additional lives.

Results suggest that expanding ACS care across the state could improve care systems for patients with OUD, which will be essential in the context of rising IMF in the drug supply, and the subsequent risk of IMF-related overdose death. To accomplish this, outpatient treatment systems must be prepared to accept patients connected to care from hospital-based settings. Limited Opioid Treatment Programs in rural areas (99) may limit the usefulness of ACS. However, changes to access to buprenorphine during the SARS-COV-2 pandemic have made it possible for patients to initiate treatment on buprenorphine via telemedicine (82), and recent changes to eliminate the X-waiver requirement for physicians prescribing buprenorphine may expand treatment access (100). Congress is considering ongoing extended use of telehealth for buprenorphine beyond the SARS-COV-2. These regulatory changes could make it easier for patients to initiate and stay on medication for OUD after hospital discharge (101).

Expanding ACS will require multifaceted commitment from stakeholders across the state, including healthcare providers, hospital-system leadership, outpatient treatment providers, and people who use drugs. In some healthcare systems, providers who can serve as “champions” for ACS expansion could be instrumental in realizing ACS care delivery; interprofessional tele-mentoring may help support providers interested in expanding ACS in their hospitals (80). Oregon’s Accountable Care

Organizations for Medicaid enrollees, called Coordinated Care Organizations (CCOS), are one mechanism to support ACS expansion. Where CCOs are prepared to support ACS expansion, and hospital-based providers who can champion this work exist, partnerships should form to help realize ACS development. Additionally, some hospitals in Oregon are rural or frontier hospitals (102). Other models of ACS expansion that allow referral to an ACS, including telemedicine-based systems or centralized models that live within CCOs where ACS providers could be deployed to smaller hospitals, should be explored in considering how to increase access to ACS.

ACS expansion will take time, resources and capacity building. In the absence of immediate change, hospitalists may play a key role in caring for patients hospitalized with OUD (103), particularly during the SARS-COV-2 pandemic (104), and may be best equipped, in the absence of an ACS, to initiate conversations about overdose risk with patients preparing for discharge. To do this effectively, hospitalists will need additional training in opioid use disorder as a chronic disease (15), and harm reduction and trauma-informed care principles and strategies (80). Existing systems could be strengthened by distributing harm reduction tools and connecting patients to substance use disorder care, including through interprofessional team members (105), but we anticipate that the benefit from this may be less than ACS expansion.

There are some limitations of this work. First, Oregon has limited racial and ethnic diversity, which may limit generalizability from this analysis to states with greater racial/ethnic diversity. Second, ACS estimates are derived from a single ACS in a metropolitan area in Oregon. It is possible that estimates of ACS effectiveness would differ in other regions. Limited work has explored the effectiveness of different ACS in

the United States to date, and future work should evaluate potential geographic variability in ACS acceptability and expansion.

There are implications from this work for policymakers and healthcare systems. First, there needs to be a coordinated response. Policymakers should work with Accountable Care Organizations for Medicaid enrollees, stakeholders, healthcare systems, people with OUD and stimulant use disorder to understand how best to implement strategies to reduce opioid-overdose, particularly in light of rising overdose rates that involve IMF. As IMF-related mortality continues to climb, a robust, coordinated response that prioritizes the needs of people who use opioids, and other substances including methamphetamine, is urgently needed. Second, while this analysis focused on currently legal paths to reduce opioid overdose deaths, state and federal policymakers should continue to consider international models that can decrease opioid overdose rates, including safe supply (90), safe consumption sites (91), improving drug checking technology (creating options for testing for the presence of specific fentanyl analogues and other contaminants (106)) and others.

In the absence of a coordinated response, healthcare systems should seek to understand how best to care for patients with OUD within their care settings. It may not be feasible for all hospitals to implement ACS; however, having team members (healthcare providers, pharmacists) who can initiate non-judgmental conversations with patients about treatment and practical harm reduction strategies is essential. Initiatives to help reduce stigma around OUD may improve staff attitudes among those who care for people with OUD (15).

There are implications from this work for policymakers and healthcare systems. First, there needs to be a coordinated response. Policymakers should work with Accountable Care Organizations for Medicaid enrollees, stakeholders, healthcare systems, people with OUD and stimulant use disorder to understand how best to implement strategies to reduce opioid-overdose, particularly in light of rising overdose rates that involve IMF. As IMF-related mortality continues to climb, a robust, coordinated response that prioritizes the needs of people who use opioids, and other substances including methamphetamine, is urgently needed. Second, while this analysis focused on currently legal paths to reduce opioid overdose deaths, state and federal policymakers should continue to consider international models that can decrease opioid overdose rates, including safe supply (90), safe consumption sites (91), improving drug checking technology (creating options for testing for the presence of specific fentanyl analogues and other contaminants (106)) and others.

In the absence of a coordinated response, healthcare systems should seek to understand how best to care for patients with OUD within their care settings. It may not be feasible for all hospitals to implement ACS; however, having team members (healthcare providers, pharmacists) who can initiate conversations with patients about treatment and practical harm reduction strategies is essential. Initiatives to help reduce stigma around OUD may improve staff attitudes among those who care for people with OUD (15).

5.5 Conclusion

IMF-related drug overdoses are increasing rapidly on the West Coast (13). Hospitalized patients with OUD are at high risk for overdose and death following

discharge, and hospitalization is a key time to engage with patients with OUD to discuss treatment opportunities and harm reduction strategies (22, 88). Hospitals should expand interventions to help reduce IMF-related opioid overdoses, including through implementation of ACS. In the context of rising IMF-related deaths, ACS expansion could help connect patients to treatment, offer harm reduction interventions, or both, which can help reduce the risk of opioid-related death.

5.6 Acknowledgements

We would like to thank Jill Archer, Danielle Meyer, and Katie Harris for their guidance in developing this work.

5.7 Declarations of Competing Interests

Dr. Korthuis serves as principal investigator for NIH-funded studies that accept donated study medication from Alkermes (extended-release naltrexone) and Indivior (buprenorphine).

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Chapter 6: Discussion and concluding remarks

Addiction consult services are rapidly becoming a gold-standard for hospital-based care delivery for people with substance use disorders, including opioid use disorder. To date, ACS have been shown to reduce the amount and severity of substance use after hospital discharge, support initiation of medication for OUD in the hospital, improve patient engagement in post-discharge OUD treatment, improve patient trust in healthcare providers, and more broadly, improve the general climate of care for patients with OUD in the hospital (10-12, 15, 16). As research continues, it is likely that other benefits from ACS will be described.

In this dissertation, I describe a model that connects ACS care referral to post-discharge OUD treatment engagement and 12-month post-discharge mortality. While modeling has previously been used to in addiction care to describe the use of other interventions to reduce opioid overdose death (notably naloxone (21)), to our knowledge, this is the first manuscript that uses modeling to describe potential outcomes of ACS care expansion at the state level. The use of the model alone has implications for thinking about expansion of care models for patients with addiction in Oregon and nationally.

In Chapter 3, I describe trends in mortality among patients hospitalized with OUD from 2015 to 2018. While many efforts nationally are focused on reducing opioid overdose deaths, this work demonstrates that opioid overdose deaths are only one of many causes that cause mortality among patients hospitalized with OUD. In fact, in our cohort, nearly every medical specialty was represented among causes of death at 12-months. This affirms the need for healthcare providers in all specialties, and not only those who are part of ACS teams, to work to create caring environments for patients with

OUD that they will see. This is essential as the number of patients with OUD, and hospitalizations among patients with OUD, continue to rise (14).

In Chapters 4 and 5, I describe the potential impact of expanding ACS across Oregon in terms of patients engaged in post-discharge OUD treatment in the month after discharge, and drug-related deaths avoided as 12 months in the context of increasing illicitly-manufactured fentanyl (IMF) contamination. Oregon, and much of the west coast, is in the midst of rapidly increasing deaths from IMF contamination (13). ACS expansion may help mitigate deaths and engage patients in care, but expansion cannot wait to realize these gains. This is challenging, as ACS expansion will require multifaceted support from healthcare system leaders, clinicians, and potentially, payors (e.g. Medicaid Coordinated Care Organizations). Interprofessional opportunities to improve hospital-based addiction care, like Oregon Health & Science University's Project ECHO, may increase readiness to change systems among participants (80). However, it may also be helpful for state leaders, including policymakers and the Oregon Health Authority, to support ACS expansion to help address the opioid overdose epidemic. Coordinated leadership may help partnership necessary for ACS expansion to progress.

There are several unanswered questions that remain for ACS care. First, to date, no research has definitively shown that ACS can reduce post-discharge mortality in the immediate post-discharge period. There are efforts underway to answer this question, which may be critical in clearly demonstrating an immediate benefit to ACS. Additionally, a limitation of this work was a lack of cost data included in the Markov model. Policymakers and healthcare system leaders need to know what it will cost to expand inpatient addiction care and build an ACS. It is essential that future research consider integrating cost estimates into predictions. Finally, future work should also validate the effect of ACS outside of single-hospital settings. Some work is underway to explore this (28).

Historically, care systems have inadequately cared for patients with OUD (45); in the face of increasing drug supply contamination and rising hospitalizations and mortality among people with OUD, ACS can serve as one way to create hospitable care systems for patients and support patients' goals for their substance use. Future research should support initiatives to expand and evaluate ACS in Oregon and nationally.

Appendix 1: Model fit statistics for Chapter 2

Appendix 1, Table 1: Model fit statistics for Chapter 2

	Sample Size or Confidence Interval percentage	Expected log pointwise predictive density	Effective number of parameters	Leave-one-out information criterion	Pareto k diagnostic values (all at least "ok")
Referral to ACS	**0.1% sample size**	-1108.8	10.6	2217.6	Yes
	1% sample size	-1273.0	6.9	2546.1	Yes
	5% sample size	-1614.2	5.6	3228.5	Yes
	10% sample size	-1949.8	7.4	3899.5	Yes
	80% confidence interval	-1103.8	11.2	2207.6	Yes
	85% confidence interval	**-1109.9**	**10.7**	**2219.7**	**Yes**
	90% confidence interval	-1118.6	10.6	2237.2	Yes

	95% confidence interval	-1132.2	10.4	2264.5	Yes
Engagement in post-discharge OUD treatment	**0.1% sample size**	**-397.1**	**12.4**	**794.2**	**Yes**
	1% sample size	-406.6	10	813.3	Yes
	5% sample size	-457.8	7.4	915.7	Yes
	10% sample size	-511.3	7.2	1022.5	Yes
	80% confidence interval	-415.6	9.6	831.3	Yes
	85% confidence interval	-419.2	9.5	838.5	Yes
	90% confidence interval	-424.3	8.9	848.6	Yes
	95% confidence interval	-434.0	8.4	868.0	Yes
Twelve-month drug-related mortality	**0.1% sample size**	**-95.9**	**8.7**	**191.8**	**Yes**
	1% sample size	-98.5	6.3	197.1	No

	5% sample size	-109.1	5	218.2	No
	10% sample size	-116.6	5.1	233.1	No
	80% confidence interval	-104.3	6.6	208.7	No
	85% confidence interval	-104.9	6.3	209.8	No
	90% confidence interval	-106.1	6.2	212.3	No
	95% confidence interval	-107.3	5.8	214.6	No
Twelve-month non-drug-related mortality	**0.1% sample size**	**-189.4**	**14.0**	**378.8**	**Yes**
	1% sample size	-189.9	11.4	379.8	Yes
	5% sample size	-192.8	8.7	385.7	Yes
	10% sample size	-194.3	7.4	388.7	No
	80% confidence interval	-195.2	7.6	390.4	Yes

	85% confidence interval	-195.5	7.2	391.0	Yes
	90% confidence interval	-196.1	7.0	392.2	Yes
	95% confidence interval	-196.9	6.7	393.8	No

Appendix 2: Estimates from classical and Bayesian logistic regression models, and prior-posterior plots from Chapter 2

Appendix 2 Table 1: Estimates from classical and Bayesian logistic regression models, Chapter 2

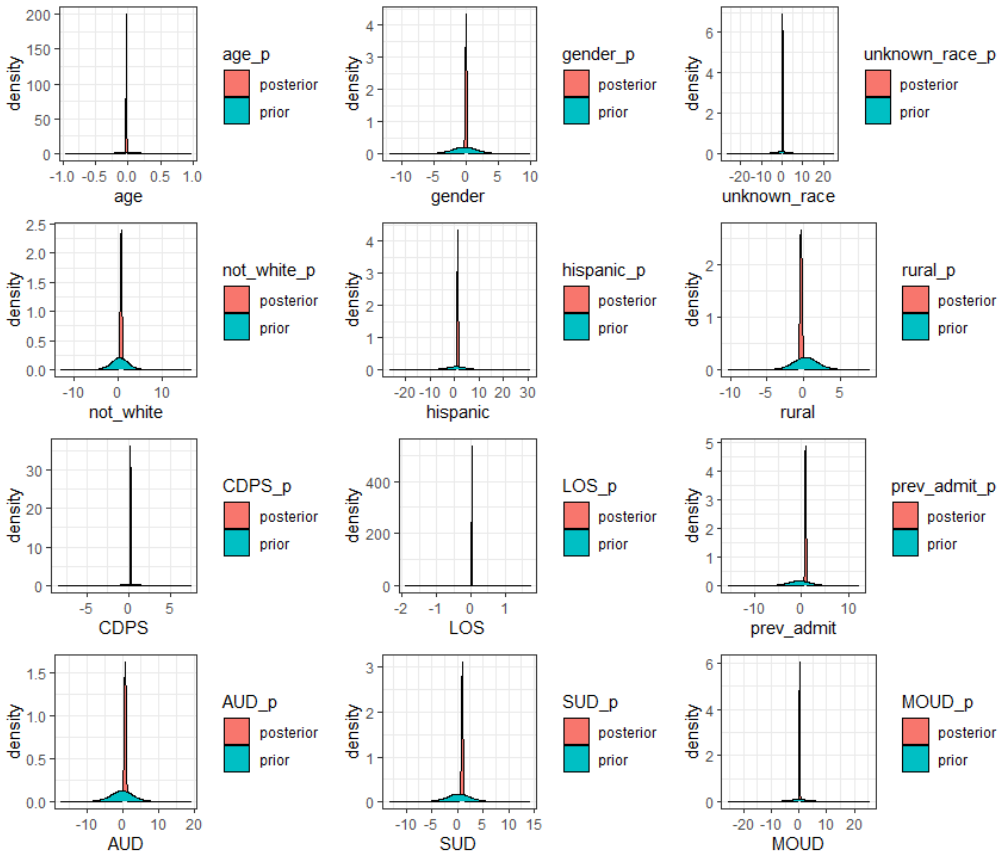
		Adjusted logistic regression output OR (95% CI)	Bayesian logistic regression output OR (95% Posterior Interval)
Referral to ACS	Intercept	0.03 (0.02, 0.05)	0.04 (0.02, 0.06)
	Age	0.97 (0.96, 0.98)	0.97 (0.96, 0.98)
	Gender (ref= female)	1.78 (1.38, 2.31)	0.94 (0.75, 1.18)
	Race: unknown	1.22 (0.91, 1.61)	1.17 (0.89, 1.54)
	Race: Not White	0.90 (0.51, 1.48)	2.04 (1.40, 2.90)
	Ethnicity: Hispanic	0.93 (0.44, 1.74)	3.54 (2.43, 5.06)
	Alcohol Use Disorder	1.26 (0.67, 2.18)	1.90 (1.12, 3.09)
	Stimulant Use Disorder	1.68 (1.15, 2.39)	2.57 (1.88, 3.49)
	Length of stay	1.02 (1.02, 1.03)	1.02 (1.01, 1.03)
	Rural residence	0.39 (0.26, 0.56)	0.69 (0.51, 0.92)
	On medication for OUD at time of hospital admission	1.00 (0.71, 1.37)	1.21 (0.91, 1.61)

	Previously admitted to the hospital	2.19 (1.69, 2.84)	2.25 (1.77, 2.85)
	CDPS Score	1.24 (1.15, 1.32)	1.25 (1.17, 1.33)
Engagement in post-discharge OUD treatment	**Intercept**	0.10 (0.04, 0.20)	0.12 (0.05, 0.28)
	Age	1.00 (0.98, 1.01)	1.00 (0.98, 1.01)
	Gender (ref= female)	0.98 (0.67, 1.44)	0.93 (0.66, 1.31)
	Race: unknown	1.03 (0.67, 1.59)	0.99 (0.64, 1.50)
	Race: Not White	1.98 (1.01, 3.83)	2.08 (1.15, 3.74)
	Ethnicity: Hispanic	0.71 (0.23, 1.96)	0.69 (0.29, 1.61)
	Alcohol Use Disorder	0.71 (0.27, 1.71)	1.20 (0.55, 2.55)
	Stimulant Use Disorder	1.13 (0.63, 1.96)	1.20 (0.71, 2.04)
	Length of stay	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
	Rural residence	0.48 (0.28, 0.81)	0.55 (0.34, 0.88)
	On medication for OUD at time of hospital admission	40.94 (25.55, 67.54)	31.60 (20.27, 50.10)
	Previously admitted to the hospital	0.91 (0.62, 1.33)	0.92 (0.64, 1.33)
	CDPS Score	1.00 (0.88, 1.13)	1.00 (0.89, 1.13)
	Referred to ACS	6.91 (4.56, 10.64)	6.24 (4.21, 9.32)
	Intercept	0.0013 (0.0001, 0.02)	0.01 (0.001, 0.04)
	Age	1.02 (0.99, 1.06)	1.02 (0.99, 1.05)

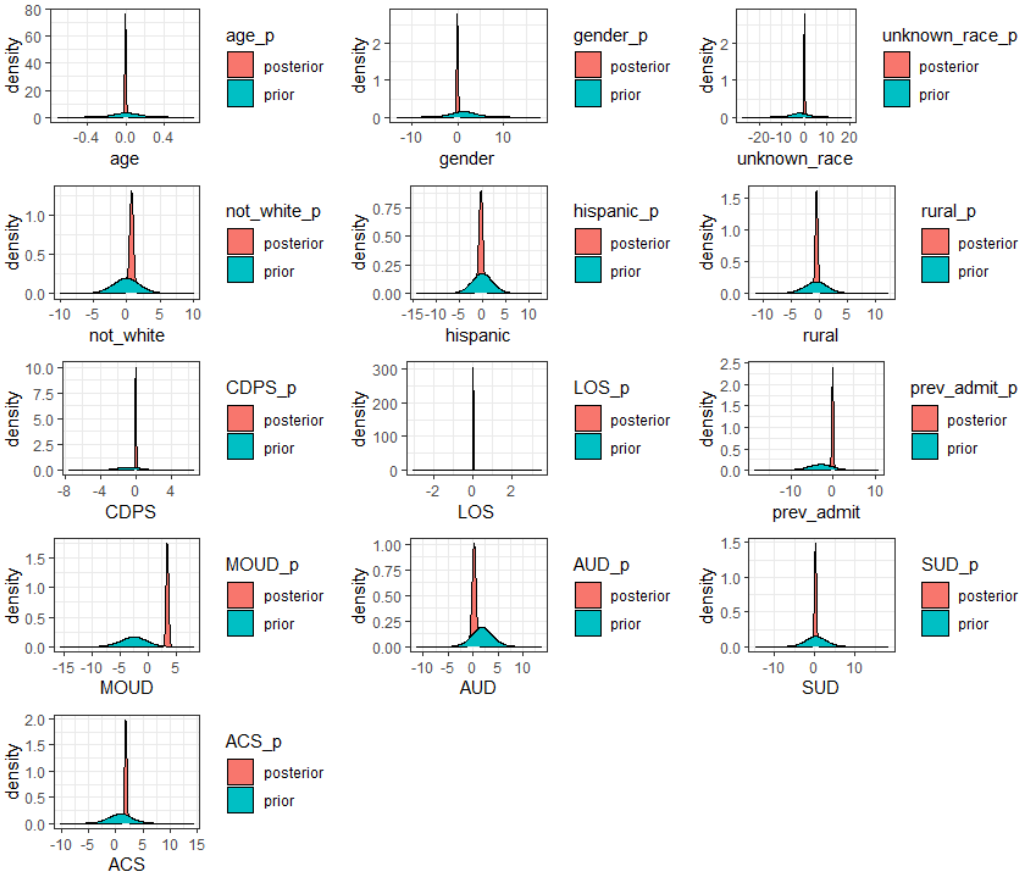
Twelve-month drug-related mortality	**Gender (ref= female)**	1.76 (0.69, 4.49)	0.62 (0.30, 1.25)
	Race: unknown	2.43 (0.85, 6.93)	2.26 (0.84, 5.87)
	Race: Not White	2.22 (0.51, 9.64)	4.28 (1.42, 12.32)
	Ethnicity: Hispanic	0.29 (0.01, 5.86)	1.60 (0.40, 5.36)
	Alcohol Use Disorder	1.98 (0.54, 7.21)	2.97 (0.95, 8.29)
	Stimulant Use Disorder	0.56 (0.10, 3.32)	0.68 (0.14, 2.53)
	Length of stay	1.01 (0.996, 1.03)	1.00 (0.97, 1.02)
	Rural residence	0.86 (0.26, 2.83)	1.20 (0.47, 2.91)
	On medication for OUD at time of hospital admission	2.99 (0.82, 10.96)	1.92 (0.64, 5.50)
	Previously admitted to the hospital	4.41 (1.50, 12.98)	3.45 (1.48, 8.54)
	CDPS Score	1.09 (0.81, 1.45)	1.03 (0.78, 1.33)
	Filled naloxone prescription within 30 days of hospital discharge	1.12 (0.05, 23.52)	3.61 (0.89, 12.96)
	Engaged in post-discharge OUD treatment	0.24 (0.05, 1.11)	0.39 (0.12, 1.16)
	Intercept	0.001 (0.0002, 0.006)	0.002 (0.0003, 0.01)
	Age	1.05 (1.03, 1.07)	1.05 (1.03, 1.07)

Twelve-month non-drug-related mortality	**Gender (ref= female)**	1.27 (0.73, 2.23)	0.99 (0.58, 1.69)
	Race: unknown	1.30 (0.60, 2.84)	1.19 (0.54, 2.51)
	Race: Not White	0.51 (0.15, 1.78)	0.85 (0.28, 2.23)
	Ethnicity: Hispanic	2.98 (1.04, 8.57)	3.43 (1.22, 8.89)
	Alcohol Use Disorder	0.25 (0.04, 1.43)	0.37 (0.07, 1.40)
	Stimulant Use Disorder	0.46 (0.14, 1.57)	0.46 (0.12, 1.40)
	Length of stay	1.00 (0.99, 1.01)	1.00 (0.98, 1.01)
	Rural residence	1.01 (0.52, 1.97)	1.14 (0.59, 2.12)
	On medication for OUD at time of hospital admission	1.15 (0.41, 3.26)	1.23 (0.47, 3.10)
	Previously admitted to the hospital	1.47 (0.84, 2.59)	1.43 (0.82, 2.51)
	CDPS Score	1.57 (1.35, 1.83)	1.57 (1.35, 1.84)
	Filled naloxone prescription within 30 days of hospital discharge	0.32 (0.02, 6.17)	0.81 (0.11, 3.86)
	Engaged in post-discharge OUD treatment	0.76 (0.30, 1.92)	0.68 (0.28, 1.58)

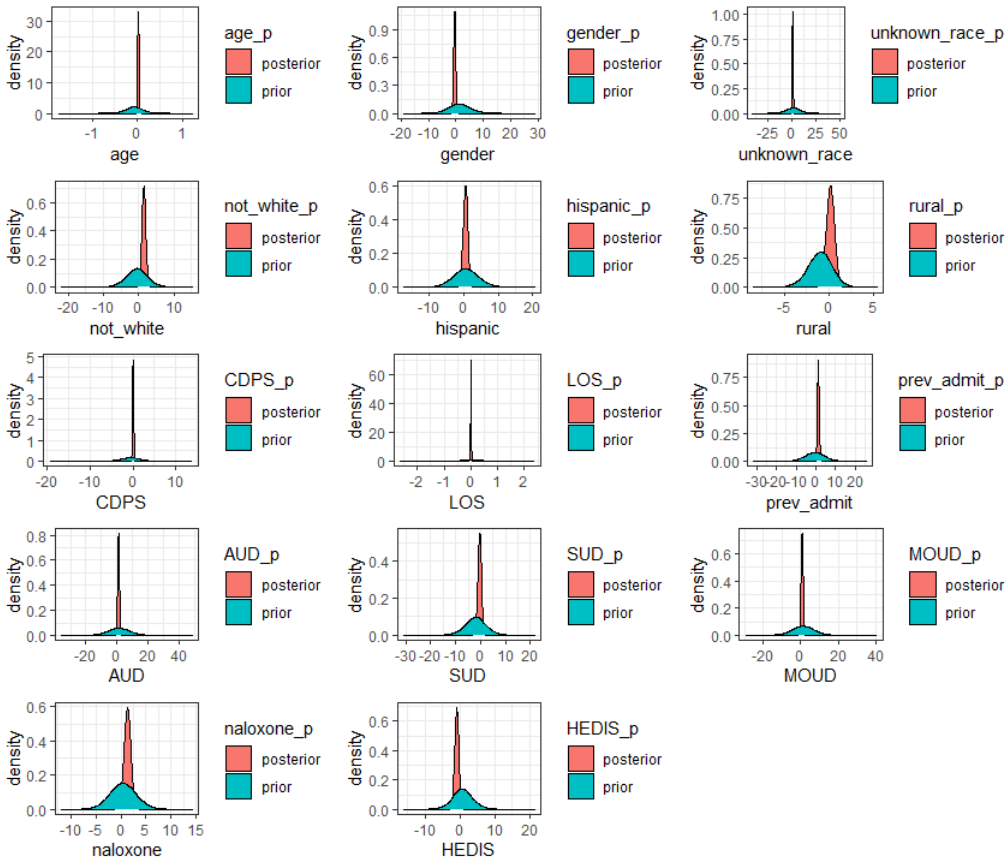
Appendix 2, Figure 1. Prior-posterior plots for referral to addiction consult service



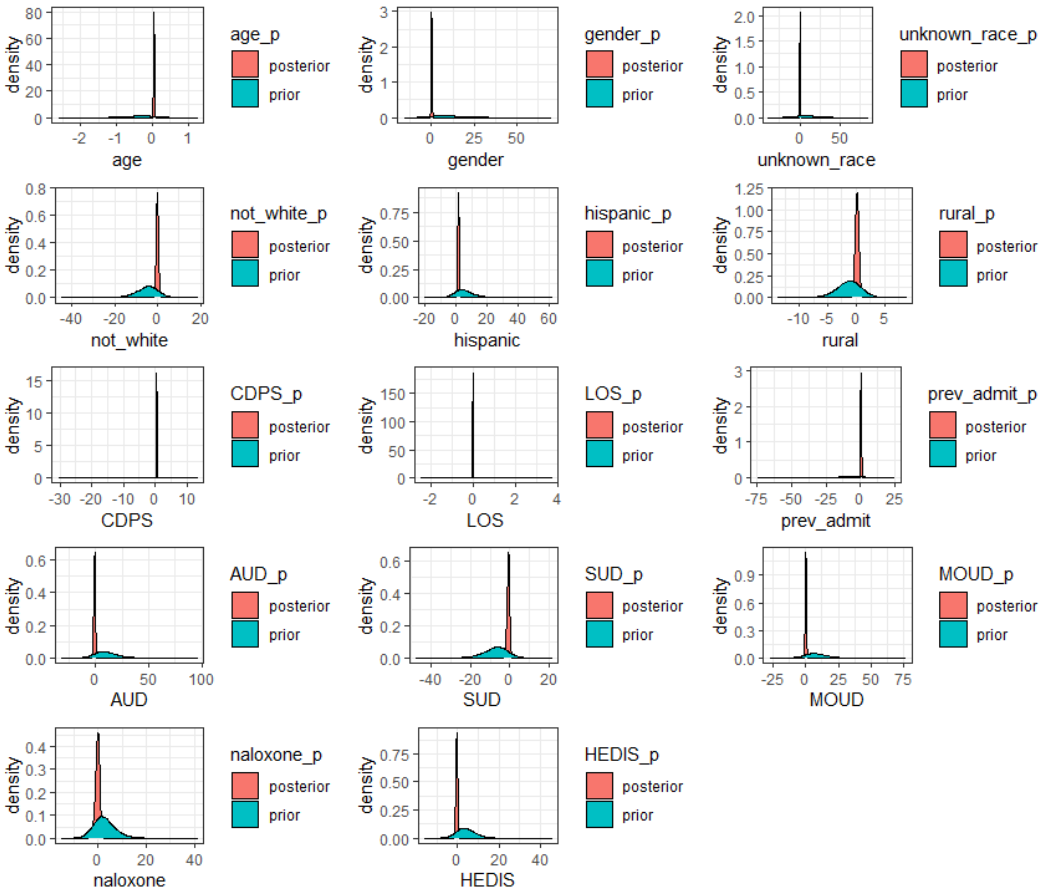
Appendix 2, Figure 2. Prior-posterior plots for engagement in post-discharge OUD treatment



Appendix 2, Figure 3. Prior-posterior plots for drug-related mortality at 12 months



Appendix 2, Figure 4. Prior-posterior plots for non-drug related mortality at 12 months



Appendix 3. Non-technical model description for Chapter 2

9.1 Model and purpose

The purpose of this model is to understand how people who are hospitalized with opioid use disorder progress through care, from the time they are hospitalized through 12 months after they are discharged. We are especially interested in addiction care in Oregon, but the model could be used in states and settings other than ours.

9.2 Types of applications designed to address

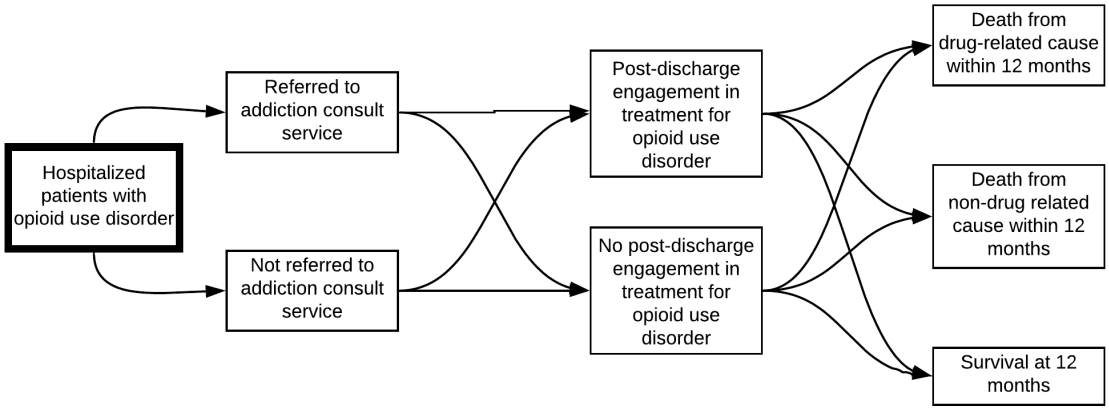
The model is designed to understand mortality, from drug-related causes like overdose, and from non-drug related causes like heart attack, in the twelve-months after discharge from the hospital. We wanted to know how referral to addiction consult services, a specialized team in the hospital that cares for patients admitted with addiction, impact post-discharge engagement in treatment for opioid use disorder and death within twelve months of discharge.

9.3 Sources of funding and their role

This work was funded by the National Institutes of Health. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Dr. Korthuis serves as principal investigator for NIH-funded studies that accept donated study medication from Alkermes (extended-release naltrexone) and Indivior (buprenorphine).

9.4 Structure

Here is our model structure (Figure 1). Once patients were admitted to a hospital in Oregon from 2015 to 2018 and diagnosed with opioid use disorder, they could be referred to see an addiction consult service, or not. After they were discharged, they could engage in post-discharge care for opioid use disorder, or not. At twelve months, we looked to see if they were still alive, or if they had died, if it was from a drug-related, or non-drug related cause. We used Oregon Medicaid claims data to gather information. We also used information from experts in addiction. We combined the Medicaid data with the expert information using a technique called Bayesian analysis.



9.5 Model validation and summary of results

We validated our model a few ways. First, we spoke to experts about what we had planned, and they agreed that this model represented how patients move through care in real life, and that the questions we had about survival were important to answer. Next, once we fit our model, we checked to make sure our actual number of deaths matched the number modeled. Then, we compared our model estimates to another model, built independently by a research team in Boston, to compare results. After that, we used high-quality data from published studies to see if our model could accurately predict what happened to patients in published studies. We found that, in general, our model better matched observed estimates from Oregon than the national model, which suggests that using our model with local data in different contexts may provide more accurate information in those settings.

9.6 Main limitations for its intended applications

The main limitation of this model is that it does not include non-addiction consult service addiction care in hospitals. We are not able to tell how much of a difference there might be from addiction consult services versus standard addiction care provided by other types of doctors. However, we know that there are additional benefits from addiction consult services: they can help transform hospital environments more broadly to better care for patients with addiction. Additionally, very few people receive addiction care while in the hospital in general.

9.7 Reference to the model's technical documentation

For more information, see our paper (50).

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