Study Title:
The Association Between Opioid-Restricting Policies and Pharmacologic Pain Management and Health-Related Quality of Life Among Childhood Cancer Survivors

Working Group: Psychology Working Group

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I. Background and Rationale

Increasing Prevalence of Childhood Cancer Survivors and Pain: An estimated 15,190 children under 19 years old will be diagnosed with cancer in the United States in 2023.[1] While cancer remains the leading cause of death among children, 5-year survival has improved to 85% in recent years.[1] However, this growing survivor population faces significant health challenges; in particular, treatment-related late effects including pain.[2] Pain among these survivors can be long-lasting – approximately 60% of childhood cancer survivors reported pain, and one-third of them reached moderate to severe pain levels during adulthood.[3,4]

Pharmacologic Pain Management Among Survivors and Those Insured With Medicaid: Opioid analgesics are recommended for patients with moderate-to-severe cancer pain.[5] Yet, concerns remain with excessive and prolonged opioid use,[6] especially among children and adolescents who are more susceptible to opioid misuse and addiction as they are going through biological and psychosocial development.[7] Nevertheless, clinical guidelines for opioid use to treat cancer-related pain among childhood cancer survivors are limited. Our prior work based on commercial claims data showed that 23% of privately insured childhood cancer survivors filled opioid prescriptions in the first year after treatment completion, a rate significantly higher than controls without cancer.[8] But little is known about opioid use patterns among Medicaid-insured survivors. Medicaid covers >2 million U.S. cancer survivors and about one-in-three childhood cancer survivors at their diagnosis.[9] Our prior work showed that **17-24% of survivors in the Childhood Cancer Survivor Study (CCSS) were insured with Medicaid in a given year[10], representing a sizable proportion of the CCSS cohort and an economically disadvantaged population who face higher risks for distress and pain** yet with less access to alternative non-pharmacologic pain control strategies than those with private insurance.[9]

Opioid-restricting Policies and Potential Impact on Childhood Cancer Survivors: The United States has experienced an exponential rise in the use of opioids and opioid overdose deaths since 1990.[12] In response, state governments enacted policies that aim to alleviate opioid misuse, primarily by regulating the administrative process for opioid prescription and dispensing.[13] These include **prescription drug monitoring programs (PDMP)** and **laws limiting the opioid quantity that can be prescribed**.[14] PDMPs are state-run electronic databases that track controlled substance prescriptions.[14] Other laws more directly impose legal restrictions on the days of supply, quantity, and/or dosage of opioids prescribed or dispensed by medical professionals.[13] These programs vary in scope across states, including different schedules of controlled substances being regulated, and whether there are “must-query” requirements (i.e., “mandate”) of prescribing providers.[14] For example, Arizona and Kentucky imposed limits to Schedule II substance,[15] which includes the majority of opioids (e.g., hydrocodone, oxycodone, methadone); while Minnesota and New York also apply restrictions to Schedule III-IV drugs with smaller amounts of opioid (e.g., morphine, codeine).[15] States’ PDMP

mandates also vary by covered circumstances (e.g., initial prescription only vs. every prescription; or **whether care related to cancer diagnosis or treatment is exempt [i.e., cancer exempt]**[14]).

By 2019, 38 states had enacted mandated PDMPs (12 states had a cancer exemption) and 39 states implemented laws that limit prescribing or dispensing of opioids.[13] Notably, federal guidelines for opioid prescription and pain management do not specifically address children/adolescents or childhood cancer survivors, given limited evidence on risks and benefits.[16] Our prior work showed sizable reductions in opioid use and potential opioid misuse among childhood cancer survivors following the 2016 CDC opioid prescription guidelines release, which explicitly exclude cancer pain.[17] Our prior work also showed that elderly patients with cancer experienced reductions in opioid prescriptions in states that implemented mandatory PDMPs without a cancer exemption, while states that provided a cancer exemption did not demonstrate declines in patients with cancer. However, evidence on how these opioid-restricting policies affect childhood cancer survivors' pain management and quality of life is lacking.

Conceptual Framework: This study aims to characterize patterns of **pharmacologic pain management (i.e., opioid and non-opioid medication use)** and assess how state opioid-restricting policies affected pain management and downstream outcomes among survivors of childhood cancer. We draw on the Andersen & Davidson's Model of Health Services Use to conceptualize the policy impact.[18] This framework considers state opioid-restricting policies as a contextual factor, along with individual predisposing, need, and enabling characteristics, which can affect cancer survivors' use of pharmacological pain management, other health behaviors (non-pharmacologic pain management, other substance use), and ultimately, their health-related quality of life (**Figure 1**).

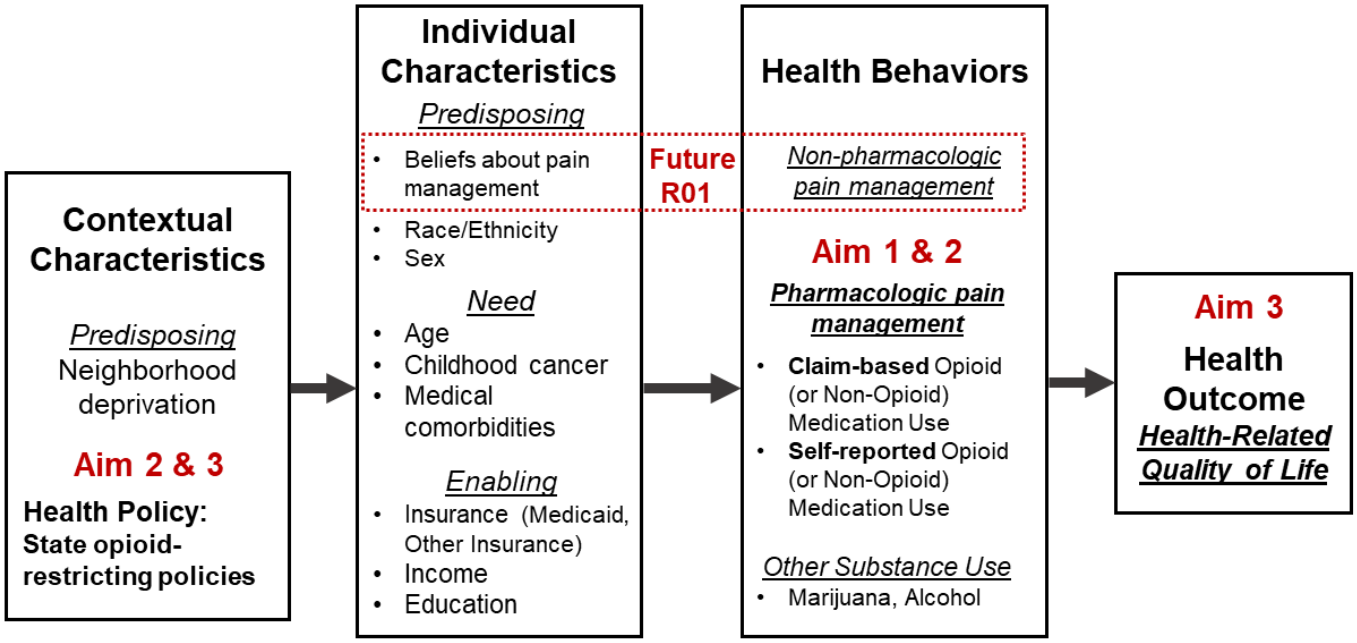


Figure 1. Conceptual Framework Adapted from Andersen & Davidson

II. Specific Aims and Hypotheses

Aim 1: Describe the trend and patterns of utilization of (a) **self-report** utilization of opioid and non-opioid medications, and (b) **claim-based** utilization of opioid and non-opioid medications among Medicaid-insured survivors and siblings in CCSS.

Hypothesis 1a: Self-report utilization will differ between Medicaid-insured survivors/siblings and other (e.g., privately insured, uninsured) survivors/siblings.

Hypothesis 1b: Among Medicaid-insured survivors and siblings, claim-based and self-report utilization will be greater in survivors than in siblings.

Hypothesis 1c: Among Medicaid-insured survivors and siblings, claim-based utilization will differ from self-report utilization due to survey bias (e.g., underreporting, medication misclassification) or measurement errors (e.g., filled vs. written prescription).

Aim 2: Among the full sample of survivors and siblings in CCSS, investigate the association of state opioid-restricting policies (PDMP mandates, opioid prescription limiting laws) with (a) **self-report** utilization of opioid and non-opioid medications and (b) **self-report** health-related quality of life (HRQOL).

Hypothesis 2a: Implementation of PDMP mandates without a cancer exemption and opioid prescription limiting laws will be associated with reductions in self-report opioid medication use, and increases in self-report non-opioid medication use among survivors and siblings, with these changes greater in survivors than siblings.

Hypothesis 2b: Implementation of PDMP mandates without a cancer exemption and opioid prescription limiting laws will be associated with changes in self-report HRQOL among survivors and siblings, with these changes greater in survivors than siblings.

Aim 3: Among Medicaid-insured survivors and siblings in CCSS, investigate the association of state opioid-restricting policies (PDMP mandates, opioid prescription limiting laws) with **claim-based** utilization of opioid and non-opioid medications.

Hypothesis 3: Implementation of PDMP mandates without a cancer exemption and opioid prescription limiting laws will be associated with reductions in claim-based opioid medication use, and increases in claim-based utilization of non-opioid medication, with these changes greater in survivors than siblings.

III. Analysis Framework

Data Sources

- **CCSS survey (FU4/FU5/FU6/FU7):** The *CCSS* consists of a retrospective cohort of 38,036 5-year survivors of childhood cancer diagnosed at 21 years or younger during 1970-1999 and over 5,000 siblings. The 4 waves of CCSS survey administered between 2007-2019 collected rich information on demographics, socioeconomic status, self-report medication use and other substance use, chronic health conditions, HRQOL, and cancer-related factors.

- **National administrative Medicaid claims data (2009-2019):** The *Medicaid claims data* include information on Medicaid enrollment, demographics, and records for services delivered in outpatient/ambulatory, inpatient, and pharmacy settings. They contain diagnosis codes, procedure codes, National Drug Codes, and dates of services.

  Linkage: In an ongoing project (R03CA267456), **our team has established a unique linkage between the CCSS survey FU4/FU5/FU6 and the administrative Medicaid claims data**. Specifically, the linkage was conducted using the following individual-level variables: Social Security Number, date of birth, and sex. A deterministic matching approach based on these individual-level variables were first conducted by statisticians at the Chronic Conditions Warehouse (CCW) contracted by CMS; results on matching were then returned by CCW.[19,20] This study will build upon this existing linkage and add in a more recent survey wave (FU7) to comprehensively measure pharmacologic pain management and HRQOL among CCSS participants.

- **State prescription drug policy data (2009-2019):** We will build upon an existing database for PDMP policies from our prior work, and extract additional policy components related to opioid prescription limiting laws in terms of dosage and days of supply. Policy information has been extracted through existing reports by the Institute for Healthcare Policy and innovation, University of Michigan[21] and public websites[22], as well as peer-reviewed journal articles.[23,24] The final database contains policy implementation date and cancer exemption indicators for each state, which will be merged to the CCSS-Medicaid linkage using CCSS participants' residential zip code and other geographic information when available.

- **Social Deprivation Index County and Zip Code Tabulated Area (ZCTA) files:** We will obtain the social deprivation index (SDI) files from the Robert Graham Center.[25] The SDI index provides composite measures of social determinants of health that incorporate seven demographic characteristics from the American Community Survey (ACS): percent living in poverty, percent with less than 12 years of education, percent single-parent households, percent living in rented housing units, percent living in the overcrowded housing unit, percent of households without a car, and percent of unemployed adults under age 65 years.

Study Population

Full Sample: We will include all CCSS participants from the US who were aged 18-64 years and alive during the study period, and responded to any of the FU4/FU5/FU6/FU7 surveys. We will treat each survey response from the same individual as one record, using appropriate statistical methods to address correlation of the responses from the same individual (see Analytic Approach below). This sample will be used for Aim 1a analyses related to self-report medication use and HRQOL. We estimate that 16,647 unique survivors (43,348 person-years) and 3,483 unique siblings (9,263 person-years) responded to at least one of FU4/FU5/FU6/FU7. To evaluate the impact of opioid-restricting policies in Aim 2, we will extract historic zip codes from CCSS (when available) and Medicaid enrollment files to exclude participants who moved across states during the study period.

CCSS participants with Medicaid coverage ≥6 months in a given year will be included in analyses of claim-based medication use. This sample will be used for Aim 1b analyses. Based on the current linkage, approximately 5,000 unique survivors (32,000 person-years) and 250 unique siblings (1, 200 person-years) had Medicaid ≥6 months in a year during 2009-2019. Similarly, we will further restrict to participants who did not move across states based on available historic zip code from Medicaid enrollment files to evaluate the impact of opioid-restricting policies for Aim 3.

Exploratory Variables

Outcome Variables

Self-report medication use is asked in the CCSS FU4/FU5/FU7 survey: "Please indicate all medicines/drugs you took regularly during the past 2 years… that you took consistently for more than one month, or for 30 days or more in a year." (Table 1) For each of the listed medicines, participants were also asked if he/she was currently taking the medicine. Following previous research, we will use the American Hospital Formulary Service (AHFS) Drug Information database to identify opioid and non-opioid analgesics.[26–28] We will then create two measures of (1) any use of the specific drug in the past 2 years (yes/no) and (2) current use of the specific drug (yes/no) from each survey response. These measures will be evaluated in Aim 1 and 2.

Claim-based medication use: As in our prior claims data-based studies,[17] we will extract all opioid prescription fills from Medicaid Prescription Drug Files using the National Drug Codes compiled by the CDC.[29] We will similarly extract all fills of non-opioid prescription pain management using the National Drug Codes. These will allow us to create, in a given year: 1) an indicator (yes/no) for whether an individual filled any prescription for opioids and non-opioid medication, respectively; 2) an indicator (yes/no) for whether an individual filled any prescription for opioids and non-opioid medication that had at least 30 days of supply, respectively; 2) number of filled prescriptions; 3) days of supply from prescriptions; and 4) daily morphine milligram equivalents (MMEs) for each opioid prescription using medication strength, days of supply, quantity dispensed, and the relevant conversion factor.[29] To allow comparison between self-report and claim-based medication use, we will construct an alternative indicator (yes/no) for whether an individual filled any prescription of opioids and non-opioid medication in a 2-year window (to be compared to the self-reported "any use of the specific drug in the past 2 years"). These measures will be evaluated in Aim 1 and 3.

Claim-based potential opioid misuse and opioid disorder: Following previous studies, we will also create 4 dichotomous variables to indicate potential misuse of opioids[30]: (1) high daily opioid dose (ie, ≥1 opioid prescription with daily dose of ≥100 MMEs), (2) opioid overlap (ie, multiple opioid prescriptions that overlapped for ≥7 days), (3) opioid and benzodiazepine overlap (ie, prescriptions that overlapped for ≥7 days), and (4) opioid dose escalation (ie, ≥50% increase in mean MMEs per month twice consecutively). We will measure opioid use disorder based on the DSM-5-TR.[31] Corresponding ICD-9 and ICD-10 codes that fall under the

category of Opioid Use, Opioid Intoxication, and Opioid Withdrawal will be extracted from Medicaid claims in the year prior to the outcome measures to identify existing opioid disorder. These measures will be evaluated in Aim 1 and 3.

Exhibit 1. Availability of Self-Report Outcome Measures from CCSS Surveys

Variable	CCSS Survey Questions	FU4 (2007)	FU5 (2014)	FU6 (2017)	FU7 (2019)
	Independent Variables				
Age	Date of birth	X	X	X	X
Sex	What is your sex (available from Baseline survey)				
Race/Ethnicity	To which one of the following groups do you belong? Are you Hispanic? (available from Baseline survey)				
Education	"What is the highest grade or level of schooling that you have completed"	X	X		X
Marital Status	Which of the following best describes your current marital status?	X	X		X
Employment Status	What is your current employment status? Include unpaid work in the family business or farm.	X	X		X
Income	Over the last year, what was the total income of the household you live in?	X	X		X
Alcohol	During the last 12 months, how often did you usually have any kind of drink containing alcohol?	X	X		X
Smoking	Have you smoked at least 100 cigarettes since you … / Do you smoke cigarettes now?	X	X		X
Chronic Health Conditions	Please indicate ... if a doctor or other health care professional has told you that you have or have had any of the following conditions. If you answer "yes", please give your age when the condition first occurred.	X	X		X
Second malignancy/ Cancer recurrence	Have you been diagnosed with another cancer, leukemia, tumor, or a recurrence (relapse) since you last provided us information in…	X	X	X	X
Emotional Distress	Please read each one carefully and mark the box that best describes how much that problem has distressed or bothered you during the past 7 days including today.	X	X		X
Cancer-related Anxiety	Do you currently have anxieties/fears as a result of your cancer, leukemia, tumor or similar illness, or its treatment?	X	X		X
	Dependent Variables				
Opioid and Non-Opioid Use	Please indicate all medicines/drugs you took regularly during the two-year period between [] and []/during the PAST 2 YEARS	X	X		X
HRQOL (SF-36)	Multiple questions		X	X	X
SF-36: Bodily Pain	How much bodily pain have you had during the past 4 weeks	X	X	X	X
SF-36: Pain interference	During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	X	X	X	X

Health-related quality of life (HRQOL): HRQOL data are available from CCSS survey data and will be measured by the physical health and mental health composite score from SF-36 items, and 8 subscales – physical function (PF), role limitations-physical (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations-emotional (RE), and mental health (MH) from FU5/FU6/FU7. Physical and mental health composite scores are normalized with a mean of 50 and a standard deviation (SD) of 10, and subscale scores range from 0 to 100, with higher scores corresponding to better well-being.[3] Selected measures from the SF-36, such as bodily pain ("How much bodily pain have you had during the PAST 4 WEEKS?") and pain interference ("During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?") will be available from FU4/FU5/FU6/FU7 (Table 1). We will assess the composite scores as continuous measures, and the bodily pain and pain interference as both continuous and dichotomized measures (e.g., "Severe"/ "Very severe" vs. "None"/ "Very mild"/ "Mild"/ "Moderate"). These measures will be evaluated in Aim 2.

Independent Variables

Opioid-restricting policies: We will examine two types of opioid-restricting policies: **PDMP mandates** with and without cancer exemption, and **opioid limiting laws**.[13] Following our previous work, we will first focus on PDMP mandates that requires licensed prescribers and dispensers to query the state-run PDMP database before prescribing or dispensing opioids (i.e., query mandate) with and without exemption for cancer care.[14] In 2012-2019, the number of states with PDMP query mandate increased from 1 to 37 (**Figure 2**). We will also assess alternative measures that capture PDMP registration mandates (i.e., requiring all opioid prescribers and dispensers to register with the state-run PDMP).[32]

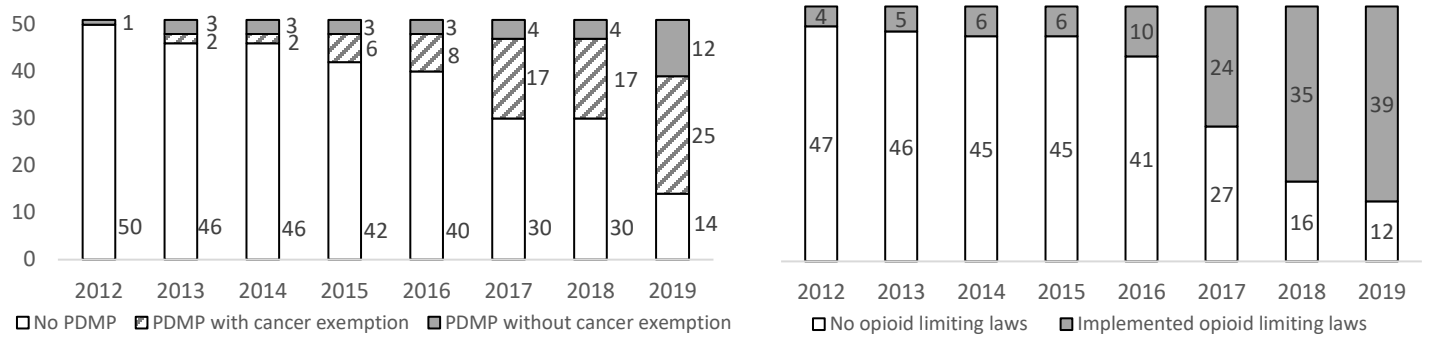
To measure **opioid limiting laws**, we will consider any limits on the initial days of supply or dosage for controlled substance prescriptions as having opioid limits. More stringent measures of shorter days of supply (e.g., 7 days or shorter) or lower dosage (e.g., 90 MME/day or lower[33]) will be applied in sensitivity analyses. Our preliminary policy evaluation suggests that the number of states with any opioid limiting laws during the study period increased from 4 to 39 (**Figure 2**).

In evaluating the impact on claim-based outcomes, each individual will be assigned the implementation status of PDMP mandates and opioid prescription limiting laws, respectively, based on the year of the claim-based measures and individual's state of residence. We will use zip codes available from CCSS and Medicaid data to determine an individual's state of residence and the implementation status for opioid-restricting policies each year. In evaluating the impact on self-report measures including medication use and HRQOL, as the survey collection window spanned more than one year, the assignment of opioid-restricting policies will be based on individuals' survey completion time and time frame of the specific survey question. For example, we will assign the policy implementation status in 2012 for self-report medication use for those who completed FU5 survey in 2014 to capture the policy impact on medication use for the past 2 years.

Covariates: Based on our conceptual framework (**Figure 1**), we will include individual-level predisposing characteristics, enabling characteristics, need characteristics, and other health behaviors. **(Exhibit 1)**

- Predisposing characteristics will include sex and race/ethnicity.
- Enabling characteristics will include education, household income, marital status, employment status, insurance type, and social deprivation index.
- Need characteristics will include age, chronic health conditions, cancer type, cancer treatment (chemotherapy, radiation therapy, surgery), time from cancer diagnosis, second malignancy, cancer recurrence, emotional distress, and cancer-related anxiety.
- Other health behaviors include the use of other substances (e.g., alcohol) and smoking. Alcohol use will be measured using the question about the frequency of having any kind of drink containing alcohol in the past 12 months. Smoking behavior will be assessed using questions including "Have you smoked at least 100 cigarettes since you last provided use information" and "Do you smoke cigarettes now?" and categorized as no smoking, past smoker, and current smoker.

Figure 2. Number of States Implementing PDMP Mandates and Opioid Limit Laws, 2012-2019



Notes: The number of states with PDMP mandates shown in the figure refers to PDMP "query mandate"; the number of states with opioid limiting laws shown in the figure refers to any limit on days of supply or dosage on controlled substance prescription.

Analytic Approach

Aim 1: Among eligible individuals from the CCSS cohort, we will compare (1) the distribution of study covariates by insurance types (e.g., Medicaid, Private, and Other), (2) the self-report medication uses across different insurance type **(Aim 1a)**, (3) the self-report medication use between survivors and siblings and the claim-based medication use between survivors and siblings enrolled in Medicaid **(Aim 1b)**, and (4) the self-report and claim-based medication use among survivors and siblings enrolled in Medicaid separately **(Aim 1c)**.

Given the longitudinal nature of the data (i.e., one individual might have multiple responses), descriptive statistics will be generated on a person-year level, including mean and standard deviation for continuous measures, and frequency and percentages for categorical measures. To account for the clustering of multiple responses from the same individual across different surveys, we will use unadjusted multilevel models to compare the distribution of study covariates by the above-mentioned groups **(Table 1)**. Multivariable logistic regression models will examine the association between insurance type and self-report medication use **(Table 2, Aim 1a),** and examine the differential self-report and claim-based medication use between survivors (vs. siblings, **Table 3, Aim 1b**), both adjusting for other study covariates and clustering on the individual level. For Aim 1c, to compare self-report and claim-based medication use, we will restrict Medicaid records to the years that correspond to CCSS survey questions. For example, we will utilize a participant's 2008-2009 Medicaid records to construct claim-based utilization measures and compare it to the participant's self-report medication use in the past 2 years collected in the 2009 survey. We will then describe the overlap between self-report and claim-based medication use (self-report only or claim-based only, both self-report and claim-based) using frequency and percentage (**Table 4, Aim 1c**) and conduct multilevel logistic regression model to examine the characteristics associated with consistent self-report and claim-based medication use (**Table 5, Aim 1c**). Variation Inflation Factor (VIF) will be calculated to assess potential multicollinearity issues among study covariates.[34]

Aim 2: Among eligible individuals from the CCSS cohort, we will (1) describe sample characteristics by whether the individual's residential state ever implemented any opioid-restricting policy during the study period, (2) examine the association of PDMP mandates and opioid limiting laws with **self-report** utilization of opioid and non-opioid medications **(Aim 2a)**, and (3) examine the association of PDMP mandates and opioid limiting laws with **self-report** health-related quality of life (HRQOL, **Aim 2b**).

Similarly, descriptive statistics will be generated on a person-year level, including mean and standard deviation for continuous measures, and frequency and percentages for categorical measures. To account for the clustering of multiple responses from the same individual across different surveys, we will use unadjusted multilevel models to compare the distribution of study covariates by whether the individual's residential state ever implemented any opioid-restricting policy during the study period. (**Table 6**) The difference-in-differences (DD) approach will be applied to assess the association between states' implementation of each specific opioid-restricting policy (i.e., PDMP mandate, opioid prescription limiting law) and each study outcome (e.g.,

self-report opioid and non-opioid medication use and HRQOL), adjusting for a robust set of covariates as described above, and CCSS survey weight as appropriate.[35] Specifically, using all eligible observation years from 4 survey waves, we will first conduct a Two-Way Fixed Effect Model (TWFE) to regress our outcome measures on an indicator for whether the respondent's residential state implemented PDMP mandate or opioid limiting law in the year of survey completion (or the year before depending on the timeframe of the outcome measures), state- and year-fixed effects, and other study covariates. The coefficient for the policy indicator from the TWFE model captures the average treatment effects of opioid-restricting policies.[36] In other words, this approach will estimate the average adjusted changes in study outcome before and after policy implementation relative to outcome changes in states that never implemented the policy over the study period. Linear probability or logistic model will be used for dichotomized outcomes, generalized linear model will be used for continuous outcomes, and Poisson model will be used for count variables. Standard errors will be clustered at the individual level to address correlation of responses within the same individual. (**Table 7 and 8**) Given the nature of the policy implementation in different years for different states, we will conduct robustness tests using other approaches, including re-estimating the policy effects for each subgroup (i.e., states that implemented opioid-restricting policies in 2017 compared to states never implemented opioid-restricting policies during the study period), and using an event study design.[37,38] An event study approach will also allow us to evaluate varying treatment effects of the policy each year after the implementation and the parallel trend assumption adjusted for other study covariates. We will also conduct sensitivity analyses restricting to individuals who responded to all 4 survey waves.

Aim 3: Among eligible individuals from the CCSS cohort also enrolled in Medicaid in a given year, we will similarly (1) describe sample characteristics (except insurance type as the sample is restricted to Medicaid enrollees) by whether the individual's residential state ever implemented any opioid-restricting policy during the study period, (2) examine the association of PDMP mandates and opioid limiting laws with **claim-based** utilization of opioid and non-opioid medications and potential opioid misuse (**Aim 3**).

Descriptive statistics will be generated on a person-year level including mean and standard deviation for continuous measures, and frequency and percentages for categorical measures. To account for the clustering of multiple responses from the same individual across different surveys, we will use unadjusted multilevel models to compare the distribution of study covariates by whether the individual's residential state ever implemented any opioid-restricting policy during the study period. (**Table 9**) The difference-in-differences (DD) approach will be applied to assess the association between states' implementation of each specific opioid-restricting policy (i.e., PDMP mandate, opioid prescription limiting law) and each study outcome (e.g., claim-based opioid and non-opioid medication use, potential opioid misuse), adjusting for a robust set of covariates as described above, and CCSS survey weight as appropriate.[35] Specifically, using all eligible Medicaid-enrolled individuals with observation years from 2009-2019 Medicaid administrative claims, we will regress our outcome measures on an indicator for whether the respondent's residential state implemented PDMP mandate or opioid limiting law in the year of measurement, state- and year-fixed effects, and other study covariates. (**Table 10 and 11**) Standard errors will be clustered at the individual level to address correlation of responses within the same individual. Sensitivity analyses will also be conducted using event-study design, to evaluate if there is a varying policy effect over time after implementation.[39] (**Table 12**) We will also conduct sensitivity analyses among individuals continuously enrolled throughout the study period.

Sample Size/Power Calculation: Prior CCSS studies suggested 11% and 7% prevalence of opioid use among survivors and siblings.[26] For self-report opioid medication use, a sample of 43,348 person-years for survivors and 9,263 person-years for siblings are sufficient to detect effect sizes of 1% and 2% respectively; and for claim-based opioid medication use, a sample of 32,293 person-years for survivors and 1,325 person-years for siblings are sufficient to detect effect sizes of 2% and 4% respectively with 90% power and the significance level of 0.05. Based on a prevalence of 29% and 24% moderate-to-severe pain among survivors and siblings[4], the same sample size for self-report opioid medication use, will be sufficient to detect effect sizes of 2% and 3% respectively for survivors and siblings with 90% power and the significance level of 0.05. We assumed a SD of 1 with 1:1 ratio for observations in the pre vs post policy groups, and used a two-sided Z-Test with pooled variance to calculate effect sizes.[40] All calculations were done using PASS 2022, v22.0.5.

IV. Special Consideration

Strengths: This is the first attempt to evaluate the impact of opioid-restricting laws on pain medication utilization and HRQOL among childhood cancer survivors. The novel data linkage between the CCSS survey and administrative Medicaid claims will allow us to comprehensively measure and compare self-report and claim-based utilization.

Limitations: First, administrative claims are generated for billing purposes, which could involve coding errors or misdiagnosis.[41] Second, generalizability of the claim-based pain medication use may be limited to survivors enrolled in Medicaid but not those with private insurance. Third, our CCSS-Medicaid linkage is based on participants' social security number (SSN), date of birth, and sex. Therefore, analyses related to Medicaid claim-based measures would be restricted to those with non-missing SSN. The completeness of the SSN variable in the Medicaid data is high (95%) in the states where the CCSS institutions are located. Moreover, as the missing SSN in Medicaid (around 5%) largely concentrates in enrollees aged 20 years or younger[42], the missingness for our cohort who are at least 21 years old would be even smaller. On the other hand, our internal analysis showed that the proportion of the cohort participants with complete SSN is estimated to be 68% within the CCSS cohort (73% among survivors and 40% among siblings, respectively). Based on the current linkage, approximately 5,000 unique survivors (32,000 person-years) and 250 unique siblings (1, 200 person-years) had Medicaid ≥6 months in a year during 2009-2019. To evaluate possible systematic sample selection bias due to SSN missingness, we will compare available sample characteristics between those with and without missing SSN, and ensure that any comparison between self-report and claim-based measures are conducted within the sample cohort of individuals. Furthermore, the mechanisms behind policy impact, including the factors at the survivor-, provider-, and institution-levels that influence pain management, cannot be identified in this proposed study, an area meriting future work to inform policy reforms and clinical guidelines. (**Figure 1**)

Table Shells

Table 1. Sample characteristics among childhood cancer survivors and siblings by insurance type [Aim 1]

	Survivors			*p*-value	Siblings			*p*-value
	Medicaid	Private	Other		Medicaid	Private	Other	
Total Person-Year Observations								
Age in the survey year								
21-29								
30-39								
40 and older								
Sex								
Male								
Female								
Race/ethnicity								
Non-Hispanic white								
Non-Hispanic black								
Hispanic/Latino								
Other								
Education[1]								
High school or less								
Some college or more								
Marital status[1]								
Married								
Unmarried								
Employment status[1]								
Unemployed								
Employed, student, and caring for home								
Alcohol consumption[1]								
5+ times a week								
Less than 5 times a week								
Smoking status[1]								
Never smoke (<100 cigarettes)								
Past smoker								
Current smoker								
Household income[1]								
Less than $40K								
$40K - $79K								
Over $80K								
Chronic medical conditions[1]								
Grade 0, 1, 2								
Grade 3, 4								
Emotional distress[1]								
No								
Yes								
Cancer-related anxiety[1]								

	Survivors			*p*-value	Siblings			*p*-value
	Medicaid	Private	Other		Medicaid	Private	Other	
None, a small amount								
Moderate, a lot, extreme								
Secondary cancers[1]								
No								
Yes								
Recurrence of primary malignancy[1]								
No								
Yes								
Type of cancer								
Leukemia								
Hodgkin's lymphoma								
Non-Hodgkin's lymphoma								
Central nervous system								
Neuroblastoma								
Wilms (kidney) tumor								
Soft tissue sarcoma								
Bone								
Age at diagnosis								
0 – 4								
5 – 10								
11 – 15								
16 – 20								
Years since diagnosis								
≤20								
21 – 30								
>30								
Received chemotherapy								
Any								
None								
Received radiation								
Any								
None								
Received Surgery								
Any								
None								
Social Deprivation Index								
State PDMP Implementation								
No								
Yes, with cancer exemption								
Yes, without cancer exemption								
State Initial Limit Implementation								
No								
Yes								

[1] Measured in the year of survey completion.

Table 2. Comparison of Self-Reported Opioid Use and Non-Opioid Use Across Insurance Type Among childhood cancer survivors and siblings [Aim 1a]

Outcome variables	Survivors			Siblings		
	Unadjusted Percent With Any Use	Adjusted Percent Differences[1] (95% CI)	P-value	Unadjusted Percent With Any Use	Adjusted Percent Differences[1] (95% CI)	P-value
Self-report Opioid Use						
Private		Ref			Ref	
Medicaid						
Other						
Self-report Non-Opioid Use						
Private		Ref			Ref	
Medicaid						
Other						

[1] Adjusted Percent Differences (i.e., marginal effect) generated from logistic models adjust for patient's age in survey year, sex, race/ethnicity, education, marital status, employment status, alcohol consumption, smoking status, household income, chronic medical conditions, emotional distress, cancer-related anxiety, cancer types, cancer treatments, age at diagnosis.

Table 3. Comparison of Opioid Use and Non-Opioid Use Between childhood cancer survivors and siblings [Aim 1b]

Outcome variables	Self-Report			Claim-Based		
	Unadjusted Percent With Any Use	Adjusted Percent Differences[1] (95% CI)	P-value	Unadjusted Percent With Any Use	Adjusted Percent Differences[1] (95% CI)	P-value
Opioid Use						
Siblings		Ref			Ref	
Survivors						
Non-Opioid Use						
Siblings		Ref			Ref	
Survivors						

[1] Adjusted Percent Differences (i.e., marginal effect) generated from logistic models adjust for patient's age in survey year, sex, race/ethnicity, education, marital status, employment status, alcohol consumption, smoking status, household income, chronic medical conditions, emotional distress, cancer-related anxiety, cancer types, cancer treatments, age at diagnosis.

Table 4. Distribution of Self-Report and/or Claim-Based Opioid Use and Non-Opioid Use Among childhood cancer survivors and siblings enrolled in Medicaid [Aim 1c]

Outcome variables	Survivors		Survivors	
	N	Percent	N	Percent
Opioid Use				
Self-report or Claim-based only				
Self-report and Claim-based				
Non-Opioid Use				
Self-report or Claim-based only				
Self-report and Claim-based				

Table 5. Factors Associated with Consistent Self-Report and Claim-Based Opioid Use and Non-Opioid Use Among childhood cancer survivors and siblings enrolled in Medicaid [Aim 1c]

Outcome variables	Survivors			Siblings		
	Unadjusted Percent With Consistent Self-Report and Claim-Based Medication Use	Adjusted Percent Differences[1] (95% CI)	P-value	Unadjusted Percent With Consistent Self-Report and Claim-Based Medication Use	Adjusted Percent Differences[1] (95% CI)	P-value
Age in the observation period						
21-29						
30-39						
40 and older						
Sex						
Male						
Female						
Race/ethnicity						
Non-Hispanic white						
Non-Hispanic black						
Hispanic/Latino						
Other						
Education						
High school or less						
Some college or more						
Marital status						
Married						
Unmarried						
Employment status						
Unemployed						
Employed, student, and caring for home						
Household income						
Less than $40K						
$40K - $79K						
Over $80K						
Alcohol consumption						
5+ times a week						
Less than 5 times a week						
Smoking status						
Never smoke						
Past smoker						
Current smoker						
Chronic medical conditions						
Grade 0, 1, 2						
Grade 3, 4						
Emotional distress						
No						
Yes						
Cancer-related anxiety						
None, a small amount						
Moderate, a lot, extreme						
Secondary cancers						
No						
Yes						
Recurrence of primary malignancy						
No						
Yes						
Type of cancer						
Leukemia						
Hodgkin’s lymphoma						
Non-Hodgkin’s lymphoma						
Central nervous system						
Neuroblastoma						

Outcome variables	Survivors			Siblings		
	Unadjusted Percent With Consistent Self-Report and Claim-Based Medication Use	Adjusted Percent Differences[1] (95% CI)	P-value	Unadjusted Percent With Consistent Self-Report and Claim-Based Medication Use	Adjusted Percent Differences[1] (95% CI)	P-value
Wilms (kidney) tumor						
Soft tissue sarcoma						
Bone						
Age at diagnosis						
0 – 4						
5 – 10						
11 – 15						
16 – 20						
Received chemotherapy						
Any						
None						
Received radiation						
Any						
None						
Received Surgery						
Any						
None						
Social Deprivation Index						

[1] Marginal effect generated from logistic models.

Table 6. Sample characteristics among childhood cancer survivors and siblings by PDMP mandates/Opioid limiting laws implementation [Aim 2]

	Survivors			Siblings		
	In States With PDMP mandates / opioid limiting laws	In States Without PDMP mandates / opioid limiting laws	*p*-value	In States With PDMP mandates / opioid limiting laws	In States Without PDMP mandates / opioid limiting laws	*p*-value
Total Person-Year Observations						
Age in the survey year						
21-29						
30-39						
40 and older						
Sex						
Male						
Female						
Race/ethnicity						
Non-Hispanic white						
Non-Hispanic black						
Hispanic/Latino						
Other						
Education[1]						
High school or less						
Some college or more						
Marital status[1]						
Married						
Unmarried						
Employment status[1]						
Unemployed						
Employed, student, and caring for home						
Household income[1]						
Less than $40K						
$40K - $79K						
Over $80K						
Insurance Type						
Medicaid						
Private						
Other						
Alcohol consumption[1]						
5+ times a week						
Less than 5 times a week						
Smoking status[1]						
Never smoke						
Past smoker						
Current smoker						
Chronic medical conditions[1]						
Grade 0, 1, 2						

	Survivors		*p*-value	Siblings		*p*-value
	In States With PDMP mandates / opioid limiting laws	In States Without PDMP mandates / opioid limiting laws		In States With PDMP mandates / opioid limiting laws	In States Without PDMP mandates / opioid limiting laws	
Grade 3, 4						
Emotional distress[1]						
No						
Yes						
Cancer-related anxiety[1]						
None, a small amount						
Moderate, a lot, extreme						
Secondary cancers[1]						
No						
Yes						
Recurrence of primary malignancy[1]						
No						
Yes						
Type of cancer						
Leukemia						
Hodgkin's lymphoma						
Non-Hodgkin's lymphoma						
Central nervous system						
Neuroblastoma						
Wilms (kidney) tumor						
Soft tissue sarcoma						
Bone						
Age at diagnosis						
0 – 4						
5 – 10						
11 – 15						
16 – 20						
Years since diagnosis						
≤20						
21 – 30						
>30						
Received chemotherapy						
Any						
None						
Received radiation						
Any						
None						
Received Surgery						
Any						
None						
Social Deprivation Index						

[1] Measured in the year of survey completion.

Table 7. PDMP and Other Patient and Contextual Factors Associated with **Self-Report** Opioid Use, Non-Opioid Use, and Health-Related Quality of Life Among Childhood Cancer Survivors and Siblings [Aim 2]

Variables	Survivor		Siblings	
	Marginal Effects (95% CI)	*P-value*	*Marginal Effects (95% CI)*	*P-value*
PDMP				
No				
Yes, with cancer exemption				
Yes, without cancer exemption				
Age in the observation period				
21-29				
30-39				
40 and older				
Sex				
Male				
Female				
Race/ethnicity				
Non-Hispanic white				
Non-Hispanic black				
Hispanic/Latino				
Other				
Education				
High school or less				
Some college or more				
Marital status				
Married				
Unmarried				
Employment status				
Unemployed				
Employed, student, and caring for home				
Household income				
Less than $40K				
$40K - $79K				
Over $80K				
Alcohol consumption				
5+ times a week				
Less than 5 times a week				
Smoking status				
Never smoke				
Past smoker				
Current smoker				
Chronic medical conditions				
Grade 0, 1, 2				
Grade 3, 4				
Emotional distress				
No				
Yes				
Cancer-related anxiety				
None, a small amount				
Moderate, a lot, extreme				
Secondary cancers				
No				
Yes				
Recurrence of primary malignancy				
No				
Yes				

Variables	Survivor		Siblings	
	Marginal Effects (95% CI)	*P-value*	*Marginal Effects (95% CI)*	*P-value*
Type of cancer				
Leukemia				
Hodgkin's lymphoma				
Non-Hodgkin's lymphoma				
Central nervous system				
Neuroblastoma				
Wilms (kidney) tumor				
Soft tissue sarcoma				
Bone				
Age at diagnosis				
0 – 4				
5 – 10				
11 – 15				
16 – 20				
Received chemotherapy				
Any				
None				
Received radiation				
Any				
None				
Received Surgery				
Any				
None				
Social Deprivation Index				

**Notes*: One table will be generated for each outcome.

Table 8. Opioid Limiting Laws and Other Patient and Contextual Factors Associated with **Self-Report** Opioid Use, Non-Opioid Use, and Health-Related Quality of Life Among Childhood Cancer Survivors and Siblings [Aim 2]

Variables	Survivor		Siblings	
	Marginal Effects (95% CI)	*P-value*	*Marginal Effects (95% CI)*	*P-value*
Opioid Limiting Laws				
No				
Yes				
Age in the observation period				
21-29				
30-39				
40 and older				
Sex				
Male				
Female				
Race/ethnicity				
Non-Hispanic white				
Non-Hispanic black				
Hispanic/Latino				
Other				
Education				
High school or less				
Some college or more				
Marital status				
Married				
Unmarried				
Employment status				
Unemployed				
Employed, student, and caring for home				
Household income				
Less than $40K				
$40K - $79K				
Over $80K				
Alcohol consumption				
5+ times a week				
Less than 5 times a week				
Smoking status				
Never smoke				
Past smoker				
Current smoker				
Chronic medical conditions				
Grade 0, 1, 2				
Grade 3, 4				
Emotional distress				
No				
Yes				
Cancer-related anxiety				
None, a small amount				
Moderate, a lot, extreme				
Secondary cancers				
No				
Yes				
Recurrence of primary malignancy				
No				
Yes				
Type of cancer				

Variables	Survivor		Siblings	
	Marginal Effects (95% CI)	*P-value*	*Marginal Effects (95% CI)*	*P-value*
Leukemia				
Hodgkin's lymphoma				
Non-Hodgkin's lymphoma				
Central nervous system				
Neuroblastoma				
Wilms (kidney) tumor				
Soft tissue sarcoma				
Bone				
Age at diagnosis				
0 – 4				
5 – 10				
11 – 15				
16 – 20				
Received chemotherapy				
Any				
None				
Received radiation				
Any				
None				
Received Surgery				
Any				
None				
Social Deprivation Index				

**Notes*: One table will be generated for each outcome.

Table 9. Sample characteristics among childhood cancer survivors and siblings enrolled in Medicaid by PDMP mandates/Opioid limiting laws implementation [Aim 3]

	Survivors			Siblings		
	In States With PDMP mandates / opioid limiting laws	In States Without PDMP mandates / opioid limiting laws	*p*-value	In States With PDMP mandates / opioid limiting laws	In States Without PDMP mandates / opioid limiting laws	*p*-value
Total Person-Year Observations						
Age in year of measurement						
21-29						
30-39						
40 and older						
Sex						
Male						
Female						
Race/ethnicity						
Non-Hispanic white						
Non-Hispanic black						
Hispanic/Latino						
Other						
Education[1]						
High school or less						
Some college or more						
Marital status[1]						
Married						
Unmarried						
Employment status[1]						
Unemployed						
Employed, student, and caring for home						
Household income[1]						
Less than $40K						
$40K - $79K						
Over $80K						
Alcohol consumption[1]						
5+ times a week						
Less than 5 times a week						
Smoking status[1]						
Never smoke						
Past smoker						
Current smoker						
Chronic medical conditions[1]						
Grade 0, 1, 2						
Grade 3, 4						
Emotional distress[1]						
No						
Yes						

	Survivors		*p*-value	Siblings		*p*-value
	In States With PDMP mandates / opioid limiting laws	In States Without PDMP mandates / opioid limiting laws		In States With PDMP mandates / opioid limiting laws	In States Without PDMP mandates / opioid limiting laws	
Cancer-related anxiety[1]						
None, a small amount						
Moderate, a lot, extreme						
Secondary cancers[1]						
No						
Yes						
Recurrence of primary malignancy[1]						
No						
Yes						
Type of cancer						
Leukemia						
Hodgkin's lymphoma						
Non-Hodgkin's lymphoma						
Central nervous system						
Neuroblastoma						
Wilms (kidney) tumor						
Soft tissue sarcoma						
Bone						
Age at diagnosis						
0 – 4						
5 – 10						
11 – 15						
16 – 20						
Years since diagnosis						
≤20						
21 – 30						
>30						
Received chemotherapy						
Any						
None						
Received radiation						
Any						
None						
Received Surgery						
Any						
None						
Social Deprivation Index						

[1] Measured using values from the closest survey to the claim-based measurement year. For example, we will assign the marital status from FU4 (started in 2007) to measurement year 2009-2013.

Table 10. PDMP and Other Patient and Contextual Factors Associated with **Claim-Based** Opioid Use and Potential Misuse, and Non-Opioid Use Among Childhood Cancer Survivors and Siblings **Enrolled in Medicaid** [Aim 3]

Variables	Survivor		Siblings	
	Marginal Effects (95% CI)	*P-value*	*Marginal Effects (95% CI)*	*P-value*
PDMP				
No				
Yes, with cancer exemption				
Yes, without cancer exemption				
Age in the observation period				
21-29				
30-39				
40 and older				
Sex				
Male				
Female				
Race/ethnicity				
Non-Hispanic white				
Non-Hispanic black				
Hispanic/Latino				
Other				
Education				
High school or less				
Some college or more				
Marital status				
Married				
Unmarried				
Employment status				
Unemployed				
Employed, student, and caring for home				
Household income				
Less than $40K				
$40K - $79K				
Over $80K				
Alcohol consumption				
5+ times a week				
Less than 5 times a week				
Smoking status				
Never smoke				
Past smoker				
Current smoker				
Chronic medical conditions				
Grade 0, 1, 2				
Grade 3, 4				
Emotional distress				
No				
Yes				
Cancer-related anxiety				
None, a small amount				
Moderate, a lot, extreme				
Secondary cancers				
No				
Yes				
Recurrence of primary malignancy				
No				
Yes				

Variables	Survivor		Siblings	
	Marginal Effects (95% CI)	*P-value*	*Marginal Effects (95% CI)*	*P-value*
Type of cancer				
Leukemia				
Hodgkin's lymphoma				
Non-Hodgkin's lymphoma				
Central nervous system				
Neuroblastoma				
Wilms (kidney) tumor				
Soft tissue sarcoma				
Bone				
Age at diagnosis				
0 – 4				
5 – 10				
11 – 15				
16 – 20				
Received chemotherapy				
Any				
None				
Received radiation				
Any				
None				
Received Surgery				
Any				
None				
Social Deprivation Index				

**Notes*: One table will be generated for each outcome.

Table 11. Opioid Limiting Laws and Other Patient and Contextual Factors Associated with **Claim-Based** Opioid Use and Potential Misuse, and Non-Opioid Use Among Childhood Cancer Survivors and Siblings **Enrolled in Medicaid** [Aim 3]

Variables	Survivor		Siblings	
	Marginal Effects (95% CI)	*P-value*	*Marginal Effects (95% CI)*	*P-value*
Opioid Limiting Laws				
No				
Yes				
Age in the observation period				
21-29				
30-39				
40 and older				
Sex				
Male				
Female				
Race/ethnicity				
Non-Hispanic white				
Non-Hispanic black				
Hispanic/Latino				
Other				
Education				
High school or less				
Some college or more				
Marital status				
Married				
Unmarried				
Employment status				
Unemployed				
Employed, student, and caring for home				
Household income				
Less than $40K				
$40K - $79K				
Over $80K				
Alcohol consumption				
5+ times a week				
Less than 5 times a week				
Smoking status				
Never smoke				
Past smoker				
Current smoker				
Chronic medical conditions				
Grade 0, 1, 2				
Grade 3, 4				
Emotional distress				
No				
Yes				
Cancer-related anxiety				
None, a small amount				
Moderate, a lot, extreme				
Secondary cancers				
No				
Yes				
Recurrence of primary malignancy				
No				
Yes				
Type of cancer				

Variables	Survivor		Siblings	
	Marginal Effects (95% CI)	*P-value*	*Marginal Effects (95% CI)*	*P-value*
Leukemia				
Hodgkin's lymphoma				
Non-Hodgkin's lymphoma				
Central nervous system				
Neuroblastoma				
Wilms (kidney) tumor				
Soft tissue sarcoma				
Bone				
Age at diagnosis				
0 – 4				
5 – 10				
11 – 15				
16 – 20				
Received chemotherapy				
Any				
None				
Received radiation				
Any				
None				
Received Surgery				
Any				
None				
Social Deprivation Index				

**Notes*: One table will be generated for each outcome.

Table 12. Event Study of PDMP mandates / Opioid Limiting Laws and **Claim-Based** Opioid Use and Potential Misuse, and Non-Opioid Use Among Childhood Cancer Survivors and Siblings **Enrolled in Medicaid** [Aim 3]

Variables	Survivor		Siblings	
	Marginal Effects (95% CI)	*P-value*	*Marginal Effects (95% CI)*	*P-value*
Years to Policy Implementation[1]				
4+ years before				
3 years before				
2 years before				
1 year before				
1st year of implementation				
2nd year of implementation				
3rd year of implementation				
4th + year of implementation				
Age in the observation period				
21-29				
30-39				
40 and older				
Sex				
Male				
Female				
Race/ethnicity				
Non-Hispanic white				
Non-Hispanic black				
Hispanic/Latino				
Other				
Education				
High school or less				
Some college or more				
Marital status				
Married				
Unmarried				
Employment status				
Unemployed				
Employed, student, and caring for home				
Household income				
Less than $40K				
$40K - $79K				
Over $80K				
Alcohol consumption				
5+ times a week				
Less than 5 times a week				
Smoking status				
Never smoke				
Past smoker				
Current smoker				
Chronic medical conditions				
Grade 0, 1, 2				
Grade 3, 4				
Emotional distress				
No				
Yes				
Cancer-related anxiety				
None, a small amount				
Moderate, a lot, extreme				
Secondary cancers				

Variables	Survivor		Siblings	
	Marginal Effects (95% CI)	*P-value*	*Marginal Effects (95% CI)*	*P-value*
No				
Yes				
Recurrence of primary malignancy				
No				
Yes				
Type of cancer				
Leukemia				
Hodgkin's lymphoma				
Non-Hodgkin's lymphoma				
Central nervous system				
Neuroblastoma				
Wilms (kidney) tumor				
Soft tissue sarcoma				
Bone				
Age at diagnosis				
0 – 4				
5 – 10				
11 – 15				
16 – 20				
Received chemotherapy				
Any				
None				
Received radiation				
Any				
None				
Received Surgery				
Any				
None				
Social Deprivation Index				

[1] One table will be generated for each policy.

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