Supplementary Online Content

Ramsey LB, Ong HH, Schildcrout JS, et al; IGNITE Pharmacogenetics Working Group. Prescribing prevalence of medications with potential genotype-guided dosing in pediatric patients. *JAMA Netw Open*. 2020;3(12):e2029411. doi:10.1001/jamanetworkopen.2020.29411

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Statistical Analysis Details

Prescribing patterns over time

We examine prescribing prevalences from 2011 to 2017, separately, for a) any CPIC level A medication, b) at least one, two, three and four CPIC level A medications, c) distinct classes of CPIC level A medications (e.g., analgesic, statins, anticoagulants), d) for individual CPIC level A medications, and e) for medications combined with associated metabolizing genes. For each model, we conducted the logistic regression analysis for binomial data of the form,

$$\log\left(\frac{p_s(t)}{1-p_s(t)}\right) \equiv lo_s(t) = \alpha_0 + f_1(t)\alpha_t + I(Site = s)\alpha_s + f_2(t)I(Site = s)\alpha_{st}.$$

where $p_s(t)$ is the prescription prevalence at site s during year t, $lo_s(t)$ is the corresponding log-odds, and $I(Site = s)$ is an indicator variable that is set to 1 if $Site = s$ and is 0 otherwise. With 16 sites, we included 15 indicator variables. Functions $f_1(t)$ and $f_2(t)$ are flexible spline functions of the year variable (t=2011, 2012, … 2017) that together allow the log-odds to change over time in a non-linear fashion at each site separately. From this model, we were able to estimate the site-specific medication prescription prevalences for each year which we combined across sites to obtain overall, annual prescription prevalences. Because there was dramatic site-to-site variability in sample sizes (see Table 1) we considered two distinct weighting procedures to combine site-year prevalences across sites to estimate overall prevalences each year (t): 1) by site weighting and 2) by patient weighting, the latter as a sensitivity analysis. With by site weighting, we combined site-year estimates across sites by using a simple average. Thus, for S=16 total sites, the equal site weighted average log-odds is given by,

$$\widehat{lo}^{SW}(t) = \frac{1}{S}\sum_{s=1}^{S} \widehat{lo}_s(t)$$

and the estimated variance is given by,

$$\widehat{Var}[\widehat{lo}^{SW}(t)] = \frac{1}{S^2}\sum_{s=1}^{S}\widehat{Var}[\widehat{lo}_s(t)].$$

The log-odds and associated confidence intervals are converted to risks using the inverse of the logistic function. By giving each site equal weight, we assume the perspective that there exists a population of sites from which 16 were sampled and contributed data to this analysis. The risks reported in the main text are based on by site weights. With by patient weighting, we combined site-year estimates using weights that are proportional to sites' sample sizes. With $N_s(t)$ patients at site s in year t and $N_{tot}(t) = \sum_{s=1}^{S} N_s(t)$ total patients observed in year t, the by patient weighted estimated log-odds of medication prescription at year t is given by,

$$\widehat{lo}^{PW}(t) = \sum_{s=1}^{S}\frac{N_s(t)}{N_{tot}(t)}\widehat{lo}_s(t)$$

With an estimated variance,

$$\widehat{Var}[\widehat{lo}^{PW}(t)] = \sum_{s=1}^{S}\left(\frac{N_s(t)}{N_{tot}(t)}\right)^2\widehat{Var}\left[\widehat{lo}_s(t)\right].$$

Intuitively, by patient weighting gives equal weight to each patient in the analysis, and so in contrast to by site weighting, larger sites are more heavily weighted than smaller sites when calculating annual prevalences across sites.

To capture the overall prescribing prevalences during each year, we sought to include all sites in the calculation of the by site weighted and by patient weighted averages; however, several sites were missing annual prescribing data (see Table S2). Because the availability, or lack thereof, of prescribing data relied upon an operational and compatible electronic health record system, and was unlikely to be due to prescribing patterns themselves, we assumed the

data were missing at random when sites were missing data for one or two consecutive years. To avoid excessive extrapolation of observed time trends, for sites with missing prescribing data in more than two consecutive years, we removed the time trend for the site and estimated a single, across-year prevalence. Finally, site-specific estimates were unstable when prevalences were extremely low (e.g., for medications with very low prescribing prevalences). If there were less than 20 prescriptions for a medication in any year, we also removed the time trend and estimated a single, across-year prevalence.

Prescribing patterns by demographic characteristics

To examine the prescribing patterns by gender, race, and age, we fit and summarized logistic regression models similar to those described above. To estimate prescribing patterns across the age distribution, we substituted age in for the year variable using restricted cubic spline functions to permit non-linear age trends. To capture prescribing patterns for each of gender and race we combined site-specific estimates from the model

$$\log\left(\frac{p_s(d)}{1-p_s(d)}\right) \equiv lo_d(t) = \alpha_0 + I(D=d)\alpha_d + I(Site=s)\alpha_s + I(D=d)I(Site=s)\alpha_{sd}$$

where $I(D=d)$ is an indicator variable for a demographic subgroup d (e.g., male, female, white, black, etc.).

eTable 1. CPIC Level A Drugs and Associated Genes Included in Study

Medication Name	Drug Class**	Gene(s)	GenBank ID(s)	Alternative Drugs
Abacavir	HIV antivirals	*HLA-B*57:01*	3106	
Allopurinol	other	*HLA-B*58:01*	3106	
Amitriptyline	TCA	*CYP2C19, CYP2D6*	1557, 1565	
Atazanavir	HIV antivirals	*UGT1A1*	54685	
Azathioprine	immunosuppressant	*TPMT, NUDT15*	7172, 55270	
Capecitabine	chemotherapeutic	*DPYD*	1806	
Carbamazepine	anti-seizure	*HLA-B*15:02, HLA-A*31:01*	3106, 3105	
Citalopram	SSRI	*CYP2C19*	1557	
Clopidogrel	--	*CYP2C19*	1557	prasugrel, ticagrelor
Codeine	analgesic	*CYP2D6*	1565	
Desflurane	anesthetic	*RYR1, CACNA1S*	6261, 779	
Escitalopram	SSRI	*CYP2C19*	1557	
Fluorouracil	chemotherapeutic	*DPYD*	1806	
Fluvoxamine	SSRI	*CYP2D6*	1565	
Irinotecan	chemotherapeutic	*UGT1A1*	54685	
Isoflurane	anesthetic	*RYR1, CACNA1S*	6261, 779	
Ivacaftor	other	*CFTR*	1080	
Mercaptopurine	immunosuppressant	*TPMT, NUDT15*	7172, 55270	
Nortriptyline	TCA	*CYP2D6*	1565	
Ondansetron*	--	*CYP2D6*	1565	
Oxcarbazepine	anti-seizure	*HLA-B*15:02*	3106	
Oxycodone	analgesic	*CYP2D6*	1565	
Paroxetine	SSRI	*CYP2D6*	1565	
Peginterferon	hepatitis C antivirals	*IFNL3*	282617	
Peginterferon Alfa-2a	hepatitis C antivirals	*IFNL3*	282617	
Peginterferon Alfa-2b	hepatitis C antivirals	*IFNL3*	282617	
Phenytoin	anti-seizure	*HLA-B*15:02, CYP2C9*	3106, 1559	
Rasburicase	other	*G6PD*	2539	
Ribavirin	hepatitis C antivirals	*IFNL3*	282617	
Sevoflurane	anesthetic	*RYR1, CACNA1S*	6261, 779	
Simvastatin	--	*SLCO1B1*	10599	atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin
Succinylcholine	anesthetic	*RYR1, CACNA1S*	6261, 779	
Tacrolimus	immunosuppressant	*CYP3A5*	1577	
Tamoxifen	--	*CYP2D6*	1565	
Thioguanine	immunosuppressant	*TPMT, NUDT15*	7172, 55270	
Tramadol	analgesic	*CYP2D6*	1565	
Voriconazole	--	*CYP2C19*	1557	
Warfarin	--	*CYP2C9, VKORC1*	1559, 79001	dabigatran, apixaban, rivaroxaban

*The antiemetic tropisetron is also a CPIC level A drug, but not available in the US. **No drug class is listed when there is only one CPIC level A drug in the class.

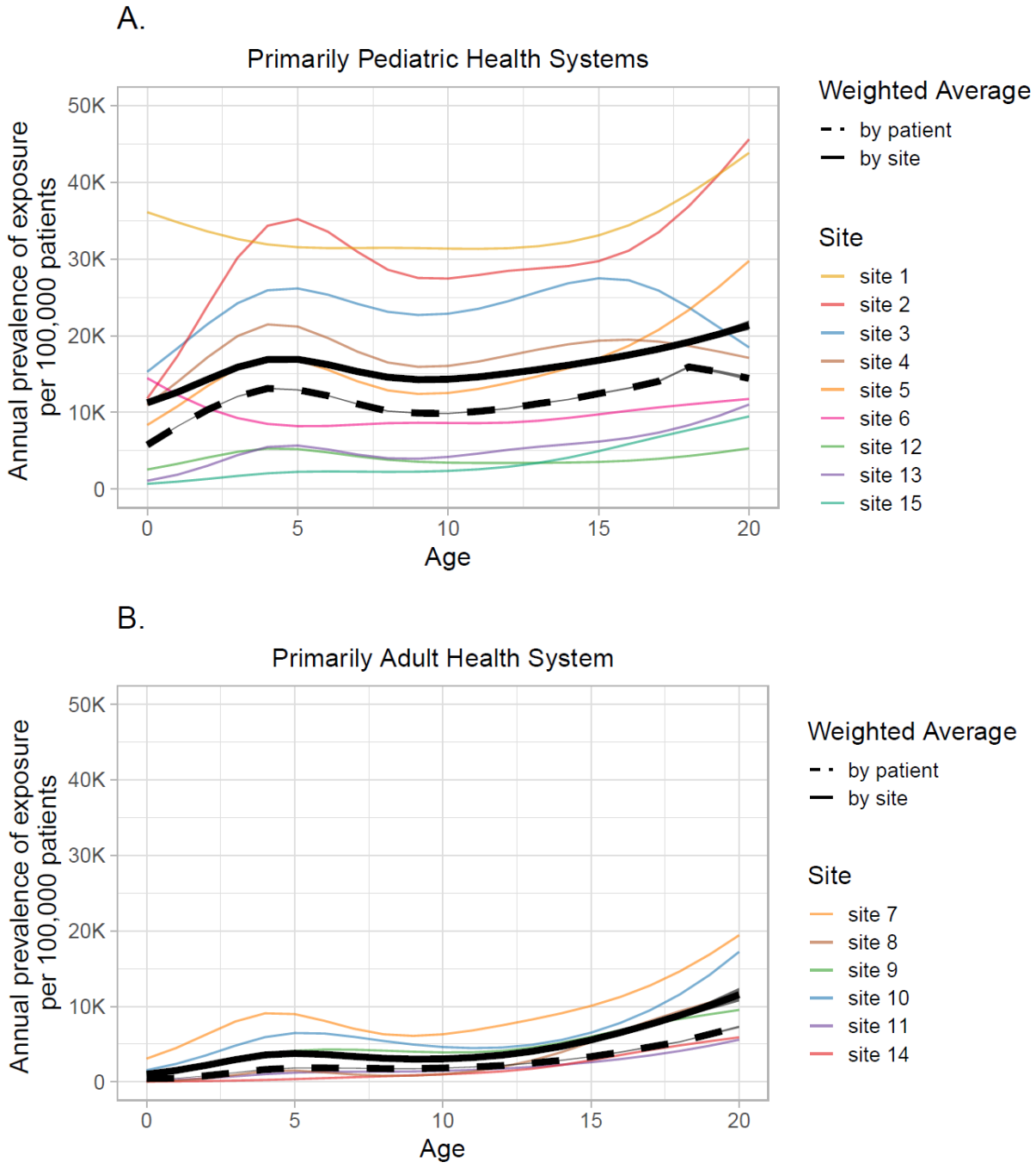
eTable 2. Characteristics of the Patient Populations and Sites' Description

Demographics																
Site	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Age in years (median, IQR)	9.0 4.0-15.5	7.0 3.0-12.0	8.0 4.0-14.0	7.0 3.0-13.0	8.0 3.0-14.0	10.0 4.0-16.0	9.0 4.0-14.0	19.0 17.0-20.0	18.0 16.0-19.0	16.0 8.0-19.0	15.5 10.0-18.0	6.0 3.0-12.0	10.0 5.0-14.5	18.8 17.0-20.0	15.0 9.0-18.0	13.0 4.5-18.0
Female (%)	48.5	49.9	48.3	49.7	50.7	50.7	52.3	67.7	62.4	60.7	58.3	47.4	48.2	66.7	58.1	49.8
White (%)	41.5	82.9	74.0	74.7	64.7	72.8	22.0	53.9	12.2	23.2	86.9	62.8	61.9	50.0	74.1	51.7
African American (%)	7.4	8.2	15.0	18.7	7.4	18.5	17.9	33.9	70.2	34.9	9.4	6.8	18.1	42.3	11.9	33.7
Asian (%)	11.3	0.4	1.4	1.6	1.6	2.3	1.2	1.1	0.8	0.2	0.5	2.5	1.4	0.9	4.1	2.4
American Indian or Native Alaskan (%)	0.7	0.1	0.1	0.2	0.6	0.4	0.3	0.2	0.0	0.2	0.2	0.6	0.2	0.1	1.0	0.7
Pacific Islander	1.1	0.0	0.1	0.1	0.4	0.0	0.0	0.1	0.0	0.2	0.1	0.2	0.1	0.0	0.2	0.0
Unknown/ Other (%)	38.2	8.4	8.9	4.6	25.8	5.8	58.2	10.1	17.3	40.8	2.6	27.3	17.1	7.3	9.4	12.1
Site characteristics																
Site	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Annual No. patients with encounters (median)[a]	18,726	85,222	165,658	221,172	102,945	51,914	77,893	69,682	4,790	44,032	799,964	234,305	376,515	90,249	172,802	351,018
Annual No. patients with target Rx (median)[b]	6,216	24,187	37,053	38,230	13,364	5,160	2,984	2,870	238	2,382	10,803	29,380	11,985	2,843	5,897	3,817
Years included in data	2012-2017	2013-2017	2012-2017	2011-2015	2011-2017	2011-2016	2011-2017	2012-2016	2016-2017	2011, 2014-2016	2011-2015	2011-2017	2011-2017	2011-2017	2011-2017	2011-2015
Clinical setting	AMC	CH	AMC	AMC	AMC	AMC	AMC	AMC	CH	CH	AMC	AMC	CH	AMC/ CH	AMC/ CH	AMC
Organization	Health System	Health System	Health System	Individual Hospital	Health System	Health System	Health System	Health System	Individual Hospital	Health System	Health System	Individual Hospital	Health System	Health System	Health System	Health System
Facility Structure	FSPH	FSPH	PS	FSPH	PS	PS, FSPH	PS	PS	PS	PS	PS	FSPH	FSPH	PS	PS	PS
No. licensed beds	373	309	687	315	1,620	267	3,815	2,940	114	Up to 350	8,400	479	390	1,157	2,071	2,578

No. ambulatory visits	1,149,883	269,468	1,050,970	> 1,000,000	2,574,489	334,956	> 3,499,000	5,747,434	40,621	952,851	4,700,000	574,929	823,660	1,300,000	> 2,100,000	1,530,470
No. Emergency room visits	98,526	89,935	179,857	176,926	356,946	49,141	536,443	359,568	26,410	102,950	957,000	173,085	79,508	103,743	326,198	453,362
Surgical procedures	38,306	3,042	35,292	24,135	66,111	17,678	N/A	77,869	N/A	10,764	220,000	19,362	18,158	20,000	90,411	75,274
EHR vendor	Epic	Cerner	Epic	Cerner	Epic	Other	Epic	Epic/ Other	Other	Epic/ Other	Epic	Epic	Epic	Cerner	Epic	Epic
Changes in EHR	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	Yes
Encounter and medication data pull																
Site	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Encounter type	Inpt, Outpt, ED	Inpt, Outpt, ED	Inpt, Outpt, ED	Outpt, ED	Inpt, Outpt, ED	Inpt, Outpt	Inpt, Outpt, ED	Inpt, Outpt, ED	Inpt, Outpt, ED	Inpt, Outpt, ED	Outpt, ED	Inpt, Outpt, ED	Inpt, Outpt, ED	Inpt, Outpt, ED	Inpt, Outpt, ED	Inpt, Outpt, ED
Encounter data pull	Manual review	Manual review	Manual review	Encoun-ter filtering	Manual review	Encoun-ter filtering	Manual review	Manual review	Manual review	Manual review	Encoun-ter filtering	Manual review	Manual review	Manual review	Manual review	Manual review
Medication query	Epic clarity ID	Med expan-sion	Trade, generic names/ RxNorm ID	Med expan-sion	Med expan-sion	Med expan-sion	Trade, generic names	Med expan-sion	Med expan-sion	RxNorm ID	Med expan-sion	Med expan-sion	Epic med Clarity ID, trade, generic names	Med expan-sion	Med expan-sion	RxNorm ID
No. of Target Medications	40	34	44	40	39	39	44	42	11	34	36	43	42	42	41	31

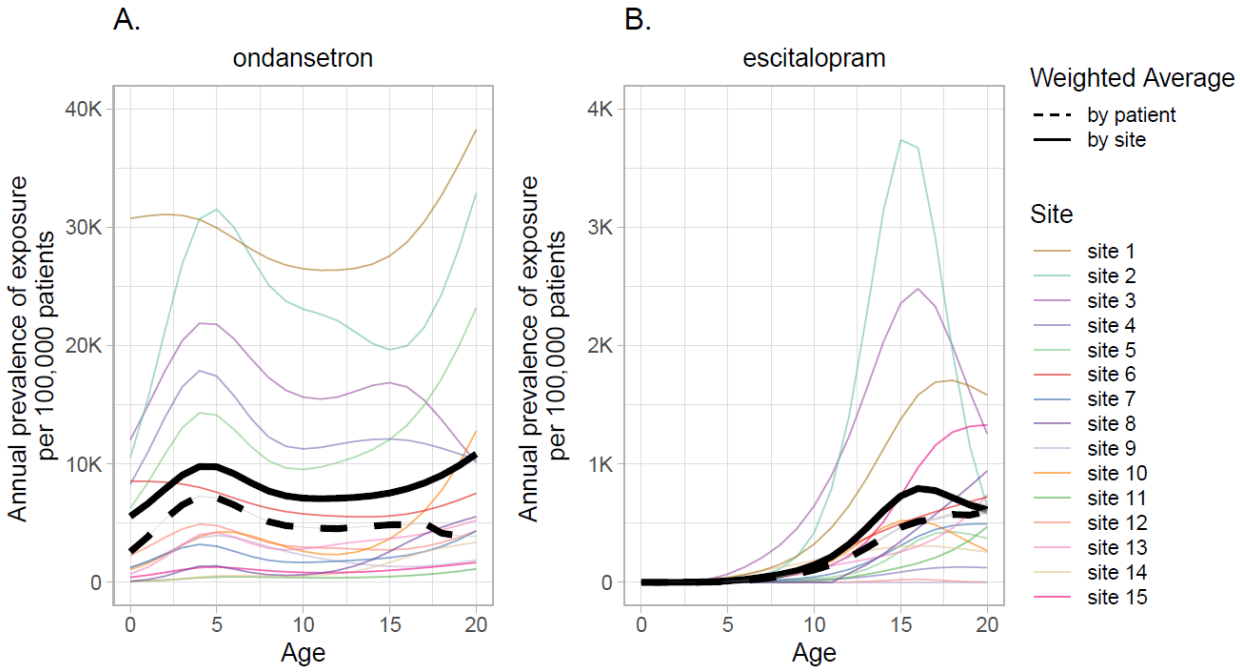
Abbreviations: No. : Number; a and b: denotes unique patients; Rx: Prescriptions; IQR: Interquartile range; AMC: Academic Medical Center, CH: Community Hospital; PS: Pediatric service within adult care Health System, FSPH: Free Standing Pediatric Hospital; EHR: Electronic Health Records; Changes in EHR denotes any changes in EHR during study years for that site; Inpt: Inpatient; Outpt: Outpatient; ED: Emergency Department; Encounter filtering: Encounter filter based on prescription rate (sites 4 and 11) or inpatient, outpatient class type (site 6); Med: Medication; Med expansion: Querying and extracting medication data using an extended generic name list; Target Medication: CPIC Level A or alternative medications; N/A: not available.

eFigure 1. Annual Prevalence of Exposure to at Least 1 CPIC Level A Drug by Age Differs by Hospital Type



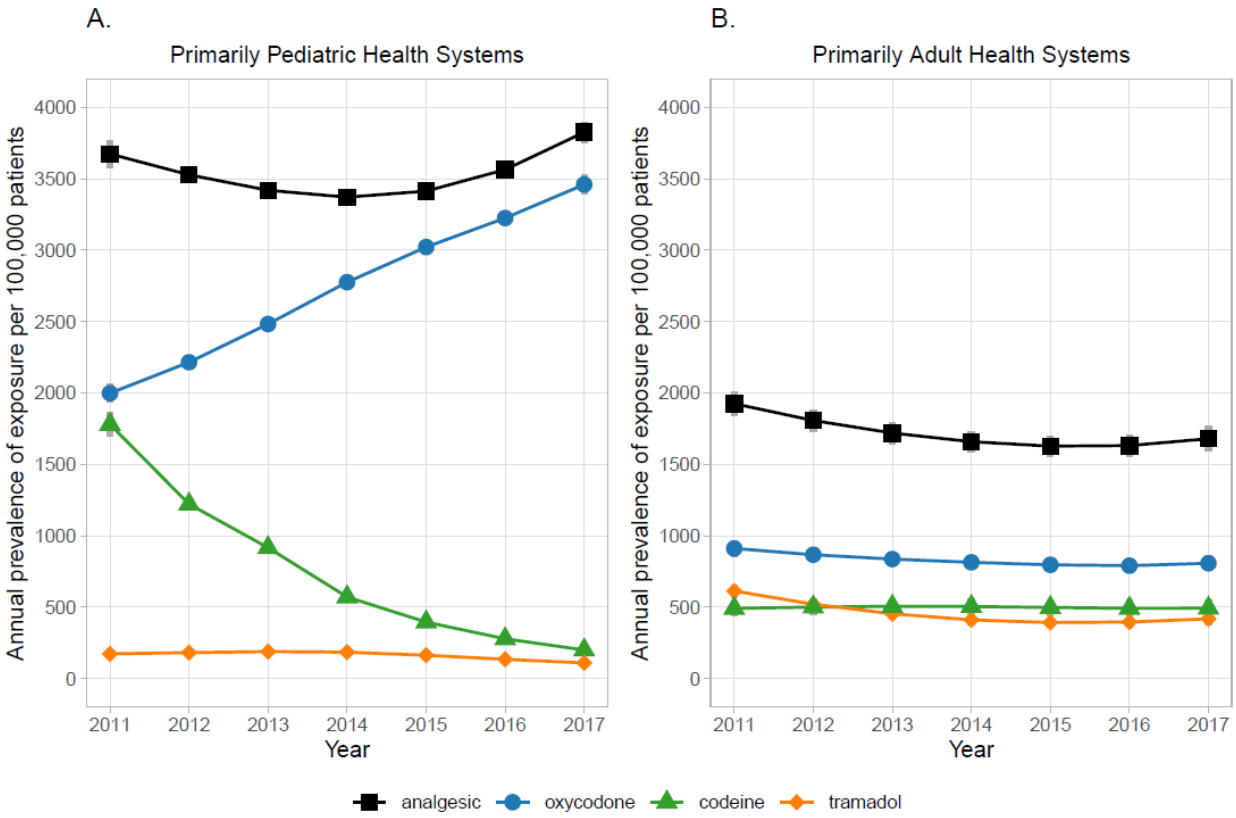
Sites identified themselves as primarily pediatric (A) or adult health systems (B). One site did not have demographic data available for encounters and is excluded from these analyses. The annual prevalence of exposure is shown for 2015. The mean prevalence of exposure across all sites was calculated in two ways: equal site weighting (solid black line) and proportional to site size weighting (dashed black line). The 95% confidence bands for the two means are filled in gray but may be too narrow to be observed.

eFigure 2. Prevalence of Exposure for Ondansetron and Escitalopram by Age



The mean prevalence of exposure across all sites was calculated in two ways: equal site weighting (solid black line) and proportional to site size weighting (dashed black line). One site did not have demographic data available for encounters and is excluded from these analyses. The 95% confidence bands for the two means are filled in gray but may be too narrow to be observed.

eFigure 3. Prevalence of Exposure to Analgesics by Age Stratified by Hospital Type



Annual prevalence of exposure for analgesics was averaged using equal site weighting. A, only primarily pediatric health systems. B, only primarily adult health systems. The estimated prevalence of exposure for the analgesic (black line) is taken from the drug class model, whereas those for oxycodone, codeine, and tramadol are taken from the individual drug model. The 95% confidence bands for the means are filled in gray but may be too narrow to be observed.