Variation in Diffusion of Prescription Drugs: Mechanisms and Cost Implications

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Abstract

In the United States, there is well-documented geographic variation in prescription drug spending and utilization. However, the specific role of physicians, and physician drug adoption behavior on the variation in patient-level prescription drug is still being investigated. This dissertation aims to add to the literature by gaining a better understanding of the role of physician adoption of brand name drugs on geographic variation in patient-level spending, and also utilizing physician peer networks and social network analysis to help elucidate a possible mechanism underlying why some physicians adopt brand name drugs faster than others. The public health relevance of this dissertation rests in improving our understanding of how, and why, new drug adoption drives prescription drug spending in the face of ever rising health care expenditures, and an aging population, that will likely increase demand for chronic disease medications.

Chapter one investigates the association between physician adoption of a moderately novel anti-diabetic drug, sitagliptin, and drug spending in the Medicare and Medicaid populations in Pennsylvania. We found that anti-diabetic drug spending in both populations were remarkably similar, as were the magnitudes of the associations between sitagliptin adoption and higher, local-level, drug spending. These results highlight how in spite of differences in population characteristics, and the administration of drug benefits in these two distinct programs, physician drug adoption, drug spending, and prescriptions follow similar trends.

Chapter two investigates the association between physician adoption of a highly novel anti-coagulant drug, dabigatran, and both drug and medical-related spending in the Medicare population in Pennsylvania. We found that physician adoption of dabigatran was significantly associated with both higher anti-coagulant drug spending, and higher overall medical spending. This finding highlights the importance of physician drug adoption behavior, and suggests that areas with higher rates of dabigatran prescribing are not accompanied by cost-offsets in medical-related spending.

Chapter three utilizes social network analysis and instrumental variable modeling to help estimate the fraction of geographic variation in physician drug adoption that can be attributable to peer/social influence. We found that physician drug adoption decisions were significantly influenced by peer adoption behavior across three distinct chronic disease drug-classes. Additionally, this study highlights that, consistently across the three drug classes studied, peer influence appears to explain roughly half of the geographic variation of physician drug adoption.

Taken together, these findings point to the indication that individual characteristics of patients and physicians should be viewed in conjunction with social networks and peer connections when trying to understand variations in behavior, utilization, and spending across the health care system.

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Preface

As my time in graduate school and writing my dissertation comes to a close, I want to express my utmost gratitude and deep appreciation to all the people who made this journey possible. Foremost, I want to thank my committee chair and advisor Julie Donohue, it was through her remarkable guidance, support, patience, and encouragement that I was able to complete this work and truly begin seeing myself as a health services researcher. She has been an amazing role model and mentor. I also want to thank Joyce Chang, Evan Cole, Julia Driessen, and Mark Roberts for serving on my committee, and for providing incredibly thoughtful feedback, insights, and suggestions on my work. Finally, thank you to the entire faculty and staff in the Department of Health Policy and Management for making it such a welcoming and wonderful place to learn, and for all of your collective contributions to both my professional and personal growth.

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1.0 Association Between Physician Adoption of a New Oral Anti-Diabetic Medication and Medicare and Medicaid Drug Spending

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1.1 Introduction

There is substantial regional variation in prescription drug spending in the United States [1, 2], a finding that is consistent across different classes of drugs, patient populations, and health care payers (e.g. Medicare, VA) [1, 3-5]. Much of this variation is attributed to differences in the extent to which physicians prescribe brand name medications as opposed to generic medications, and not to differences in the volume of prescriptions filled, or to patient characteristics [1]. Regional differences in brand name drug prescribing are likely tied to regional differences in the speed with which physicians adopt new drugs. Studies have evidenced tremendous physician-level variation in adoption speed in several drug categories [6-10]; however, the association between region-level differences of physician adoption of newly introduced brand name drugs and prescription drug spending is still poorly understood.

Improving our understanding of how new drug adoption drives prescription drug spending is paramount for U.S. policy makers in the face of ever rising health care expenditures and an aging population that will likely increase demand for chronic disease medications. We examine the association between physician adoption and drug spending for diabetes for three reasons. First, diabetes is a progressive chronic disease that is increasing in prevalence and accounts for a large

share of prescription drug and medical spending [11-13]. Second, there are multiple FDA approved anti-diabetic drugs available, with varying mechanisms of action, effectiveness, and prices. However, there is little evidence-based guidance for physicians on which medications to prescribe when augmenting therapy [14]. Third, the continual introduction of new brand name anti-diabetic drugs complicates physician decision-making and increases the potential for variation in new drug adoption.

Our study aimed to examine local variation in physician adoption of sitagliptin, a first-in-class oral glycemic lowering agent introduced in October 2006, and to investigate the association between physician adoption of sitagliptin and overall anti-diabetic drug spending in two large, and distinct, payer settings (Medicare and Medicaid). Sitagliptin was the first dipeptidyl peptidase-4 (DPP-4) inhibitor introduced to the market, but was not considered as a first-line treatment option. Therefore, sitagliptin represents the introduction of an expensive brand name drug, considered a moderately novel diabetes treatment, into a market that contained a large number of both generic and brand name treatment options, plus multiple, highly expensive, insulin alternatives [14]. Thus, investigating the role of physician adoption of sitagliptin can highlight how the entry of even one brand name drug in the midst of complex treatment options can influence physician decision making, high variability in new drug adoption, and overall drug spending.

1.2 Methods

1.2.1 Data Sources

We conducted a cross-sectional analysis using data from three sources. First, we obtained Medicare claims and enrollment data from the Centers for Medicare & Medicaid Services (CMS) for all fee-for-service Medicare enrollees who were residents of Pennsylvania (PA) and also enrolled in a Part D plan for 2011 (N=855,361). We obtained all medical claims (MEDPAR, outpatient, carrier, home health, hospice, DME) as well as the Part D Event (PDE) file, which contains prescription details such as drug name, fill date, National Drug Code (NDC), and the total amount paid to the pharmacy from all sources (plan and beneficiary). We obtained beneficiary enrollment dates, demographic information, and ZIP code of residence from the Medicare Beneficiary Summary Files.

Second, we obtained claims, encounter, and enrollment data on all fee-for-service and managed care PA Medicaid enrollees for 2011 (N=1,127,123) from the Pennsylvania Department of Human Services (PADHS) through an intergovernmental agreement. Demographic information and eligibility status were obtained from the Medicaid enrollment file. Prescription drug claims contain information on the drug name, fill date, NDC, and the amount paid to the pharmacy. As we obtained Medicaid data directly from PADHS and not from CMS, we capture drug utilization and medical claims among Medicaid managed care enrollees who make up a majority (~75%) of enrollees in the state. PADHS requires comprehensive reporting of encounter data from the managed care plans with which it contracts so the data provide a reliable and valid measure of utilization among managed care enrollees [15].

Third, we obtained physician-level prescribing data from QuintilesIMS Xponent^{TM} which directly captures >70% of all US prescriptions filled in retail pharmacies, including all payers (Medicare, Medicaid fee-for-service, commercial insurance, cash, and uninsured). Xponent^{TM} utilizes a patented proprietary projection method to represent 100% of prescriptions filled in these outlets and has been widely used by researchers to examine medication use patterns [9, 16-20]. Our Xponent^{TM} data includes all physician prescribers practicing in PA during January 2007-December 2011.

1.2.2 Physician Study Sample

We excluded those physicians who did not prescribe at least one anti-diabetic drug each quarter in 2007 (the first full year following sitagliptin's introduction in October 2006) so that our physician study sample would include only physicians who were regularly seeing diabetes patients, and were thus eligible to adopt sitagliptin (See Appendix Table 1 for list of anti-diabetic study drugs). To ensure that these physicians were then also continuously seeing patients post-sitagliptin's introduction, without also conditioning specifically on sitagliptin prescribing, we further included only those physicians who prescribed $\geq$1 drug each year (2008-2011) from the following widely used medication classes: anti-coagulants, anti-hypertensives, or statins. Physicians were assigned to one of PA's 67 counties using the zip code of their primary practice location. Three small counties (Cameron, Forest, and Sullivan) had ≤ 2 providers prescribing anti-diabetic drugs in 2007 and were excluded from the analysis. The final study sample included 7,614 physicians (See Appendix Figure 1).

1.2.3 Measures of Physician Adoption

Our key independent variables were first measured at the physician-level and then aggregated to the county-level. For each physician in our sample, we measured the first month sitagliptin was dispensed to one of their patients, consistent with previous studies measuring physician adoption of new drugs [21-23]. In order to capture both speed and extent of physician adoption of sitagliptin we then constructed two measures: 1) mean time (in months) to first sitagliptin prescription across all physicians in a county using 2007-2011 data, and 2) percent of physicians within a county prescribing sitagliptin at least once in 2007. For the first measure, we chose to allow a five year period for the study physicians to adopt sitagliptin, this is based on prior literature, which has found that the rate of physicians adopting a newly introduced drug plateaus between three and five years post-market introduction [9, 24]. Additionally, the latter measure was weighted by each physician's total anti-diabetic prescription volume to give higher weight to physicians with high patient volumes:

$$\frac{\Sigma\left(\frac{AD\ prescribing\ volume_{physician}}{AD\ prescribing\ volume_{county}} * \#\text{physicians prescribed sitagliptin in 12 months}\right)}{\#\ of\ physicians\ in\ county}.$$

We conducted a sensitivity analysis including a measure of the percent of physicians in each county adopting sitagliptin not weighted by prescribing volume, and found the results were qualitatively similar.

1.2.4 Medicare and Medicaid Study Samples

We constructed separate study samples and conducted all analyses separately for Medicare and Medicaid (See Appendix Figure 2 and Appendix Figure 3 for study sample construction).

Since Medicare is the primary payer for beneficiaries who have dual eligibility in both Medicare and Medicaid, dual eligible beneficiaries were included in the Medicare study sample and excluded from the Medicaid sample. For both study samples, we included patients if they: had a continuous 12 months of enrollment in 2011, were ≥18 years old on January 1, 2011, were PA residents, filled ≥ 1 prescription for an anti-diabetic medication in 2011, and met the Chronic Condition Data Warehouse (CCW) Algorithm for diabetes [24, 25]. Additionally, because our study drug, sitagliptin, is not indicated for type I diabetes, we limited both study samples to those with type II diabetes. Individuals who met the CCW algorithm were identified as having type II diabetes if they filled at least one oral anti-diabetic medication in 2011, or if they filled only insulin during 2011 but had ≥ 50% of all inpatient and outpatient diabetes related claims coded with type II specific ICD-9 codes (250.x0 or 250.x2).

1.2.5 Dependent Variables: Anti-diabetic Drug Spending

The dependent variables for our analyses were patient-level Medicare and Medicaid anti-diabetic prescription drug spending in 2011. For Medicare, total annual drug spending included both plan payment and beneficiary out-of-pocket spending. For Medicaid, total drug spending included the total plan payment amount, in the case of managed care enrollees, or state payment amount for fee-for-service enrollees. PA Medicaid does require small copayments of its members for some prescription drugs; however, diabetes medications are excluded [26, 27].

1.2.6 Covariates

We included several patient-level variables known to be associated with anti-diabetic drug spending including demographic characteristics, eligibility category and/or type of enrollment status, and clinical factors [28]. Demographic factors include age, sex, and racial or ethnic group (white, black, Hispanic, or other race/ethnicity). For Medicare, enrollment status included indicators for dual eligibility with Medicaid, Part D low-income subsidy (LIS) status, and disability vs. age as reason for eligibility. For Medicaid eligibility, we included categorical variables indicating Temporary Assistance to Needy Families enrollment (TANF), General Assistance enrollment, or Supplemental Security Income enrollment. In Medicaid, we also controlled for whether an enrollee was in fee-for-service or Medicaid managed care. We constructed the Elixhauser co-morbidity index using medical claims as a proxy for overall health status [29]. Finally, we included an indicator of the type of anti-diabetic drug(s) used: oral agents only, injectable agents only (which included all insulins plus exenatide and liraglutide), or a combination of oral and injectable anti-diabetic drugs. As this is a claims based study, no clinical indicators of diabetes disease severity (e.g. hbA1C) were readily available, thus, this measure was included as a potential proxy of diabetes severity, as patients having more intensified treatment with injectable agents or a combination of oral and injectable agents, are likely to have longer disease duration or worse severity, and are more likely to have tried multiple different treatment options than patients on oral agents alone [14].

1.2.7 Statistical Analysis

We first examined descriptive statistics for all study variables in both the Medicare and Medicaid samples. Means (SD) were used to describe all continuous variables and frequencies (percentage) were used to describe all categorical variables. After calculating the two adoption measures, we examined any county-level trends and patterns of these two measures. Second, we examined the distribution of the outcome anti-diabetic drug spending and found it to be highly skewed. After log transforming anti-diabetic drug spending, we found multiple modals of the transformed variable in both the Medicare and Medicaid study populations (Figure 1.2). Therefore, we used finite mixture models to empirically identify the patient subgroups in both the Medicare and Medicaid study samples. Third, we fit the appropriate finite mixture model including the key explanatory adoption variables to investigate the association of regional physician adoption of sitagliptin with anti-diabetic drug spending. All covariates of interest were also included in the final models for adjustment.

1.2.8 Latent Subgroup Identification

We used finite mixture models to empirically identify patient subgroups based on annual anti-diabetic drug spending. Finite mixture models use model-based posterior probabilities to assign individual observations to different subgroups (e.g. an observation will be assigned to the subgroup with the highest posterior subgroup membership probability) and can analytically capture unobservable heterogeneity in the different underlying subgroups. The true number of subgroups in a data set is unknown, and no gold standard exists in determining the "optimal" number of subgroups. The preferred method of model selection is through an iterative estimation

where multiple models with different assumed numbers of subgroups, and no covariates, are fit. We fit models composed of one, two, or three subgroups and examined normal distributions, gamma distributions, or a combination of both normal and gamma distributions. The final number of subgroups, and selection of distributions, were selected based on the Bayesian information criterion (BIC) and the mean posterior probability values [30]. Applying these criteria, the two-component model consisting of two normal distributions had the best model fit for both Medicare and Medicaid (i.e., the lowest BIC and good classification according to high mean posterior probabilities) (Appendix Table 2 and Appendix Table 3). For each individual subgroup, descriptive characteristics were inspected to examine potential patient features associated with group membership (Appendix Table 4).

1.2.9 Association of Sitagliptin Adoption with Anti-diabetic Drug Spending

The two-component finite mixture model, with county-level clustering, was then used to estimate the effect of county-level physician adoption of sitagliptin on patient drug spending in both Medicare and Medicaid. We hypothesized adoption speed (time to first prescription) to be negatively associated with drug spending (i.e. longer time to physician adoption leads to lower spending) and adoption extent (volume-weighted percent of physicians prescribing sitagliptin >1 in the first 12 months) to be positively associated with anti-diabetic drug spending (i.e. a larger share of physician adoption leads to higher spending). In order to account for heterogeneous estimation using different random seed numbers in the finite mixture modeling approach, we ran the modeling 100 times utilizing randomly generated seeds, and then averaged across all the beta coefficients and standard errors to obtain the final result.

Statistical analyses were conducted using SAS software version 9.3 (SAS Institute, Cary, NC) and R software version 3.2.

1.3 Results

1.3.1 Medicare and Medicaid Study Sample Characteristics

Table 1.1 shows the characteristics of the 125,264 PA Medicare, and 54,098 PA Medicaid enrollees with type II diabetes. Average age in the Medicare sample was 72, while, as expected, the Medicaid sample was relatively younger, with an average age of 50. Both samples had very similar gender breakdowns, with close to 60% being female. While the Medicare sample was 85% white, the Medicaid sample was more diverse, with 50% being white, 30% black, and 15% Hispanic. Additionally, regarding eligibility, 38% of the Medicare sample was dually eligible for Medicaid, while nearly three quarters (73%) of the Medicaid sample was enrolled through Supplemental Security Income eligibility. Regarding general health status, the Medicare sample had an average Elixhauser Index of 5.6, indicated high levels of co-morbidity. Similarly, the Medicaid sample had an average Elixhauser Index of 4.7, which, while nominally lower, still indicates the presence of multiple comorbidities. Lastly, the two samples had relatively distinct anti-diabetic drug use. In Medicare nearly two-thirds (64%) of the study sample was filling prescriptions for oral anti-diabetic medications only, 16% were using insulin or a non-insulin injectable drug only (e.g. exenatide and liraglutide), and 19% were filling prescriptions for both oral and injectable drugs. In Medicaid, 54% of the sample used oral anti-diabetic drugs only, 18% filled only prescriptions for insulin or an injectable drug, and 28% filled prescriptions for both oral

and injectable drugs. Overall, while the two samples diverged in many of their demographic and clinical characteristics, all differences were largely expected, and were due to the distinct eligibility requirements of each program.

Table 1.1 Demographic Characteristics of Medicare and Medicaid Study Samples

Characteristic	Medicare (N=125,264)	Characteristic	Medicaid (N=50,836)
Age (Mean, SD)	72.1 (12.0)	Age (Mean, SD)	50.2 (10.1)
Female (N, %)	74,427 (59.4)	Female (N, %)	31,038 (61.1)
Race/Ethnicity (N, %)		Race/Ethnicity (N, %)	
White	105,987 (84.6)	White	25,498 (50.2)
Black	11,481 (9.2)	Black	15,341 (30.2)
Hispanic	4,622 (3.7)	Hispanic	7,476 (14.7)
Other race	3,174 (2.5)	Other race	2,521 (5.0)
Eligibility Type (N,%)		Eligibility Type (N, %)	
Dual Eligible	47,607 (38.1)	General Assistance	6,655 (13.1)
Low Income Subsidy	56,358 (44.9)	Supplemental Security Income	38,076 (74.9)
Disabled	24,910 (19.9)	TANF*	5,720 (11.3)
Type of Drug use (N,%)		Type of Drug use (N, %)	
Oral drug only	80,652 (64.4)	Oral drug only	27,436 (54.0)
Injectable drug only	20,336 (16.2)	Injectable drug only	9,021 (17.8)
Combination Treatment	24,276 (19.4)	Combination Treatment	14,379 (28.3)
Elixhauser (Mean, SD)	5.6 (2.9)	Elixhauser (Mean, SD)	4.7 (2.7)
Drug Spending (Mean, SD)	$1,340 ($1,764)	Drug Spending (Mean, SD)	$1,291 ($1,881)

*TANF=Temporary Assistance for Needy Families

Data sources: Medicare data from CMS, Medicaid data from PADHS

1.3.2 Anti-diabetic Drug Spending

Unadjusted average per capita spending on anti-diabetic drugs was $1,340 (SD $1,764) in Medicare and $1,242 (SD $1,844) in Medicaid (Table 1.1). Figure 1.1 shows the non-transformed and log-transformed distributions and density plots for anti-diabetic drug spending for both the Medicare and Medicaid study samples.

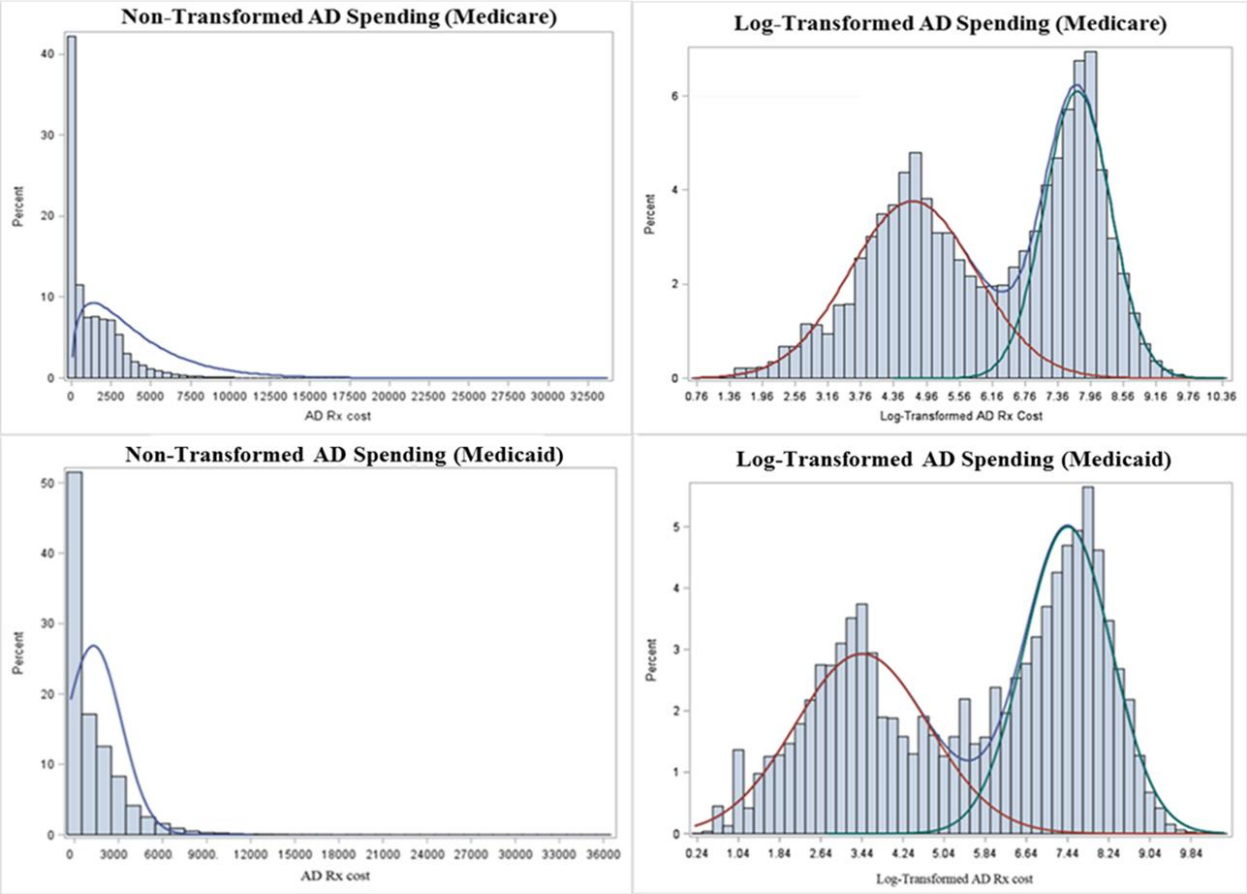


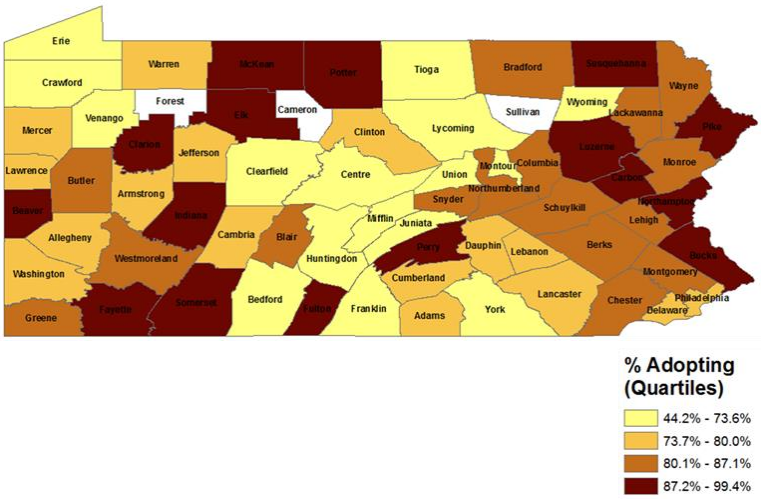
Figure 1.1 Drug Spending Distributions for the Medicare and Medicaid Study Samples

1.3.3 Physician Adoption of Sitagliptin

A total of 7,614 PA physicians prescribed anti-diabetic drugs in our study sample. The number of physicians who prescribed anti-diabetic drugs in each county varied from seven to 1,136. (Appendix Table 5).

Both the adoption time (mean time to first sitagliptin prescription), and adoption extent (percent of physicians prescribing sitagliptin at least once in its first 12 months) measures showed high variability across the counties (Figure 1.2). Overall, average time to first prescription of sitagliptin was slightly less than a year (11.2 ± 3.5 months), though the time did vary markedly by county from 2.3 months (Potter County) to 19.1 months (Mifflin County). Average weighted fraction of physicians in each county prescribing sitagliptin at least once in the first 12 months of market availability was 78% ± 12%. Again, there was substantial variation between the counties from 44% of physicians adopting (Venango County) to 99% of physicians adopting (Elk County).

Weighted Percent of AD Prescribers Adopting Sitagliptin



Mean Time (Months) to First Sitagliptin Prescription

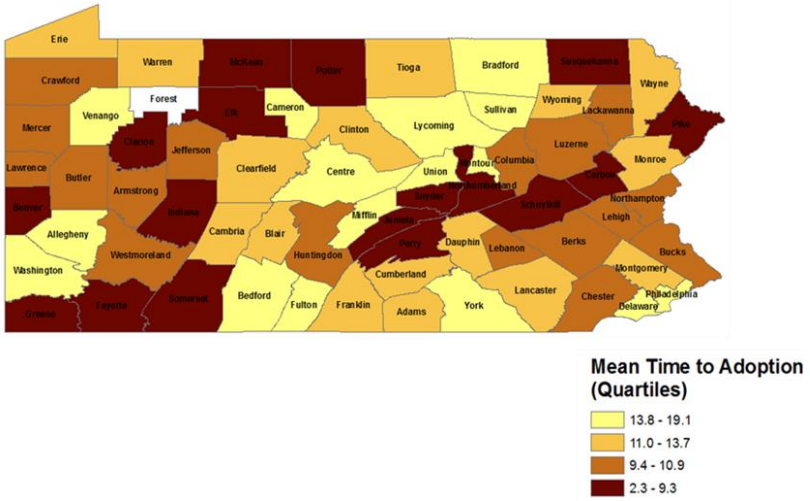


Figure 1.2 Measures of Sitagliptin Adoption by Pennsylvania County

1.3.4 Characteristics of Subgroups

In Medicare, 55% of beneficiaries were categorized into the component with lower mean anti-diabetic drug spending, and 45% was categorized into the component with higher mean anti-diabetic drug spending (See Appendix Table 4). The largest difference in observable characteristics between the two spending components was in the type of anti-diabetic drugs used,

with 85% of beneficiaries in the lower spending component utilizing oral drugs only vs. 38% of beneficiaries in the higher spending component.

Similarly, 57% of Medicaid beneficiaries were categorized in the component with lower mean anti-diabetic drug spending, while 43% were in the component with higher mean anti-diabetic drug spending (See Appendix Table 4). Again, the largest difference in observable characteristics between the two spending components was in the type of anti-diabetic drugs used, with 66% of enrollees in the lower spending component utilizing oral drugs only, while only 38% of enrollees in the higher spending component utilizing oral drugs only.

1.3.5 Association of Sitagliptin Adoption with Overall Drug Spending

For the Medicare study sample, the finite mixture model results indicated that having a higher percent of physicians within a county adopting sitagliptin was associated with higher annual anti-diabetic drug spending on average (Table 1.2). The magnitude, and variation, of this result differed between the two spending components. For example, a 10% increase in the number of physicians within a county adopting sitagliptin was associated with an average increase of 3.5% (95% CI: 2.0 – 4.9) in annual per capita anti-diabetic drug spending for the lower spending component. That same 10% increase was associated with a smaller, and non-statistically significant, average increase of 1.5% (95% CI: -3.6 – 6.5) in anti-diabetic drug spending in the higher spending component. In comparison, mean time to first prescription of sitagliptin was found to have no statistically significant association with drug spending in either spending component.

Table 1.2 Results from the Finite Mixture Model in the Medicare Study Sample

Medicare Characteristic	Spending Component					
	Low			High		
	Average Beta Coefficient	Average Standard Error	95% CI Standard Error	Average Beta Coefficient	Average Standard Error	95% CI Standard Error
Intercept	7.480	0.069	[7.345 , 7.615]	7.396	0.310	[6.789 , 8.004]
Time to Sitagliptin Adoption*	0.001	0.003	[-0.005 , 0.006]	-0.003	0.006	[-0.016, 0.010]
% Adopting Sitagliptin*	0.345	0.072	[0.203 , 0.487]	0.148	0.258	[-0.359 , 0.654]
Age	-0.002	0.000	[-0.003 , -0.001]	0.001	0.001	[-0.001 , 0.003]
Female	-0.033	0.011	[-0.054 , -0.012]	-0.015	0.015	[-0.044 , 0.013]
Race (Ref=White)						
Black	-0.272	0.027	[-0.325 , -0.218]	-0.443	0.017	[-0.475 , -0.410]
Hispanic	-0.218	0.030	[-0.277 , -0.160]	-0.257	0.033	[-0.321 , -0.192]
Race other	-0.072	0.039	[-0.149 , 0.004]	0.018	0.036	[-0.052 , 0.088]
Eligibility						
Dual Eligible	-0.006	0.022	[-0.048 , 0.037]	-0.029	0.028	[-0.084 , 0.027]
Low Income Subsidy	0.202	0.021	[0.161 , 0.243]	0.305	0.025	[0.255 , 0.354]
Disabled	-0.146	0.018	[-0.182 , -0.110]	-0.113	0.018	[-0.148 , -0.077]
Drug Type (Ref= Combo)						
Oral only	-2.252	0.013	[-2.278 , -2.226]	-2.108	0.017	[-2.142 , -2.074]
Injection only	-0.178	0.017	[-0.211 , -0.145]	-0.260	0.023	[-0.305 , -0.216]
Elixhauser	-0.012	0.002	[-0.016 , -0.008]	-0.007	0.003	[-0.012 , -0.002]

Data sources: Medicare data from CMS, Medicaid data from PADHS, XPonent™ from QuintilesIMS

*Adoption variables measured in XPonent™ from QuintilesIMS

The results for the Medicaid study sample were similar in average magnitude to the Medicare results. For example, a 10% increase in the number of physicians within a county adopting sitagliptin was associated with a smaller, and non-statistically significant average increase of 2.9% (95% CI: -0.4 – 6.3) in annual per capita anti-diabetic drug spending for the lower spending component. That same 10% increase was associated with a significant average increase of 5.3% (95% CI: 0.3 – 10.3) in anti-diabetic drug spending for the higher spending component. Again, and similarly to Medicare, mean time to first prescription of sitagliptin was not statistically significantly associated with drug spending in either component (Table 1.3).

Table 1.3 Results from the Finite Mixture Model for Medicaid Study Sample

Medicaid Characteristic	Spending Component					
	Low			High		
	Average Beta Coefficient	Average Standard Error	95% CI Standard Error	Average Beta Coefficient	Average Standard Error	95% CI Standard Error
Intercept	6.355	0.195	[5.973, 6.736]	6.283	0.265	[5.765, 6.802]
Time to Sitagliptin Adoption†	0.294	0.170	[-0.039, 0.627]	0.529	0.255	[0.029, 1.028]
% Adopting Sitagliptin†	0.005	0.006	[-0.006, 0.017]	-0.004	0.006	[-0.016, 0.007]
Age	0.018	0.001	[0.016, 0.020]	0.019	0.001	[0.017, 0.022]
Female	-0.004	0.020	[-0.044, 0.036]	0.019	0.022	[-0.024, 0.062]
Race (Ref=White)						
Black	-0.252	0.026	[-0.303, -0.200]	-0.414	0.032	[-0.476, -0.352]
Hispanic	-0.073	0.029	[-0.129, -0.017]	0.224	0.039	[0.147, 0.302]
Race other	0.124	0.049	[0.027, 0.220]	-0.093	0.052	[-0.194, 0.008]
Eligibility						
General Assistance	-0.287	0.031	[-0.348, -0.227]	-0.320	0.031	[-0.381, -0.258]
TANF*	-0.256	0.033	[-0.320, -0.191]	-0.273	0.038	[-0.348, -0.197]
Waiver	-0.662	0.100	[-0.859, -0.466]	-0.702	0.155	[-1.006, -0.399]
Drug Type (Ref=Combo)						
Oral Drug Only	-3.360	0.023	[-3.405, -3.314]	-3.113	0.025	[-3.162, -3.063]
Injectable Drug Only	-0.089	0.030	[-0.148, -0.031]	-0.125	0.032	[-0.188, -0.062]
Elixhauser	-0.019	0.004	[-0.026, -0.011]	-0.009	0.004	[-0.017, -0.002]

*TANF=Temporary Assistance for Needy Families

Data sources: Medicare data from CMS, Medicaid data from PADHS, XPonent™ from QuintilesIMS

† Adoption variables measured in XPonent™ from QuintilesIMS

1.4 Discussion

Our study reports three key findings. First, we found substantial county-level variation in both the time to adoption and in the proportion of physicians adopting sitagliptin in PA. Second, we found that the extent of physicians adopting sitagliptin was associated with higher anti-diabetic drug spending in both Medicare and Medicaid although effect sizes were relatively small. Third,

we found that the distributions of anti-diabetic drug spending in the Medicaid and Medicare populations were remarkably similar, as were the magnitudes of the associations between sitagliptin adoption and drug spending in spite of differences in population characteristics and the administration of drug benefits in the two programs.

The high variability in physician adoption rates of sitagliptin by county in both average time to first prescription (2.3 – 19.1 months) and share of physicians prescribing sitagliptin (44% to 99% of physician) is consistent with previous findings. Studies have shown that physicians' take up new brand name drugs at different rates, and that the proportion of brand name versus generic drug use can vary across geographic regions [3-5, 31-34]. Physician adoption of new drugs is likely influenced by many factors including practice setting (e.g. group vs. solo practice) [19, 35, 36], specialty [17, 22, 23], exposure to pharmaceutical promotion [6, 18, 21, 35], and even physician social networks [20].

Furthermore, while prior studies have highlighted the variation in physician drug adoption, our study is one of the first to show an association between the speed and extent of physician adoption of a new drug and prescription drug spending. This finding is consistent with the literature showing the diffusion of health care technologies is one of the main drivers of health care cost growth [37]. The impact of technological advancement on increased health care spending is perhaps nowhere more evident than with prescription drugs. For example, the recent double-digit annual growth rate in prescription drug spending from 2013 to 2014 has largely been attributed to the introduction of new prescription drugs [38]. Growth in prescription drug spending has also coincided with an increasing number of new drugs gaining FDA approval annually, which reached a recent peak in 2015 with 45 new drugs entering the market [39], and underscores the on-going role that new drug adoption will likely play in health care spending. Although the magnitude of

the effect of sitagliptin adoption on spending was relatively small in the anti-diabetic drug class, our findings point to a potential mechanism underlying the geographic variation in prescription drug spending, namely, differences in diffusion of new drugs at the local-level. This finding could lead to interventions by payers looking to improve the efficiency of prescription drug use, by combining information on the new drug adoption behavior of physicians with information on the clinical value of new drugs, and ultimately targeting physicians for interventions such as academic detailing [40].

A strength of our study was the ability to investigate the association between physician drug adoption on prescription drug spending in both Medicare and Medicaid. This shows a more complete picture of the role of physician drug adoption since these two payers serve distinct patient populations, and have structural differences in benefit design and formulary policy. Interestingly, even though the Medicare and Medicaid study populations differed in fundamental ways such as average age (72 vs. 50 years old), racial composition (85% vs. 50% white), and average Elixhauser comorbidity index (5.6 vs. 4.7), the overall distribution of anti-diabetic drug spending in each program was remarkably similar (Figure 1.1). This similarity is surprising not only due to differences in patient populations served, but also due to differences in benefit design and cost-containment tools used in the two programs. For example, Medicare plans use tiered formularies, prior authorization, and patient cost sharing to steer patients to drugs for which Prescription Drug Plans (PDPs) have negotiated larger rebates [41]. In contrast, Medicaid programs participate in the Medicaid Drug Rebate Program, which requires broad coverage of medications, and use prior authorization tools, but impose no patient cost sharing [42]. Though we did not limit our physician study sample by type of payment received, one possibility for the similar spending patterns between the two programs is that the same physicians are serving both patient populations, and

their prescribing patterns remain generally stable across payers. Interestingly, the key driver of whether enrollees were in the high or low spending component was type of anti-diabetic drug use. Subjects treated with an oral anti-diabetic drug were much more likely to be assigned to the lower spending component, while subjects treated with an injectable anti-diabetic drug such as insulin were much more likely to be assigned to the higher spending component. Additionally, it is likely that the patients in the higher spending component have more severe or uncontrolled diabetes and have already failed first line oral treatment options, thus giving their treating physician multiple options in how to escalate their care, either by adding multiple oral drugs to their treatment plan, or moving on to injectable insulin. That insulin is a key driver of anti-diabetic drug spending could partially explain the relatively small effect size of sitagliptin adoption on spending, and is consistent with a recent study that found that, in Medicaid, reimbursement prices for intermediate acting insulins have grown 284% from 2001 to 2014, and by 455% for premixed insulins in the same time period [43].

Our study has several limitations. First, this study was conducted in one state, and even though PA has been shown to track closely with national averages in measures of age, gender, educational attainment, income, and measures of health care utilization, our findings might not be nationally representative [44-46]. Second, we investigated the impact of one new drug within one chronic disease drug class; in light of the fact that multiple therapeutic options exist within the diabetes drug class, and the choice set changes over time as new drugs enter the market, our results regarding sitagliptin might not generalize to the drug class as a whole. Additionally, these results might not be generalizable to other unique disease conditions. Third, like other studies using claims data, our drug spending measures do not include rebates negotiated by Part D plans in Medicare, rebates provided under the Medicaid drug rebate program, or any differences in charges by

pharmacies that might be owned by managed care companies. Thus our spending measures reflect an over-estimation of the true spending amount [47]. Lastly, since there is no gold standard on how physician adoption of new prescription drugs should be measured, we defined adoption through time to first prescription, and the proportion of physicians adopting sitagliptin weighted by prescribing volume, both of which have been utilized in past studies that have investigated physician up-take of new drugs [9, 21-23, 48, 49]. Other measures of physician adoption exist, such as measures that take the share of prescriptions written for a new drug into account [50], and could strengthen the findings.

1.5 Conclusion

This study represents the first analysis that aims to better understand regional variation in physician adoption of a newer anti-diabetic brand name prescription drug, and to determine that higher physician drug adoption is associated with higher prescription drug spending. Future research should focus on examining this association in other drug classes, and on further elucidating the underlying mechanisms surrounding why some physicians adopt brand name drugs faster than others.

2.0 The Association Between Physician Adoption of Dabigatran and Patient-Level Drug and Medical Spending in a Medicare Population

2.1 Introduction

Non-valvular atrial fibrillation (Afib) is a common cardiac arrhythmia associated with increased risk of stroke, transient ischemic attack, and other debilitating clinical complications. Consistent treatment with oral anti-coagulant therapy reduces stroke risk by close to 60% [51]. However, until the introduction of dabigatran (Pradaxa) in 2010, only one oral anti-coagulant treatment option was available in the US: the vitamin K antagonist warfarin. Dabigatran has been shown to have comparable clinical effectiveness to warfarin while also offering advantages, such as fewer dietary restrictions and on-going lab monitoring [52]. However, when first introduced, it came at a price approximately four times higher than warfarin [53]. Dabigatran's introduction arguably had important financial implications for Medicare given that the program covers over 80% of patients with non-valvular Afib [54] and accounts for $15 billion (60%) in afib-related expenditures [54,55]. Dabigatran's introduction offers an opportunity to study how physician prescribing patterns and expenditures respond when an innovative, though substantially more expensive, brand name drug enters market dominated by a single treatment option.

Variation in new drug uptake, and physician prescribing in general, has been well documented with research showing clear differences in prescribing patterns by geographic region across multiple chronic diseases [1, 3, 5]. In terms of anti-coagulant prescribing patterns, a recent study found the probability of an Afib patient being treated with a new oral anti-coagulant (such as dabigatran) versus warfarin varied greatly across the United States, with the lowest likelihood

of treatment with a new oral-anticoagulant in the Midwest (36%), and the highest likelihood in the Southeast (51%) [56]. However, the association between local differences in physician adoption of dabigatran with both prescription drug and non-drug medical spending has not yet been fully elucidated.

In this paper we examine local variation in physician adoption of dabigatran in Pennsylvania, the 5th most populous state in the US, and one that tracks closely in national averages in measures of age, sex, educational attainment, income, and health care utilization. Using comprehensive information on physician prescribing, we estimate the association between physician adoption of dabigatran and both anti-coagulant drug spending and non-drug medical spending in a Medicare population. We hypothesize that more rapid and expansive physician adoption of dabigatran will be positively associated with anti-coagulant drug spending due to its higher price. However, the association between dabigatran adoption and non-drug medical spending is less clear. Some studies of novel drug adoption in other therapeutic areas have shown cost-offsets with reduced medical spending owing to better disease management and resultant declines in outpatient and inpatient care [57-60]. Therefore, we may find a negative association between dabigatran adoption and non-drug medical spending. Alternatively, if areas with greater physician adoption of dabigatran are also more likely to adopt other innovative, and more costly, medical technologies we may find a positive association between dabigatran adoption and non-drug medical spending [61].

2.2 Methods

2.2.1 Data Sources

We conducted a longitudinal analysis using data from two sources that together provide for adequate measurement of physician adoption of dabigatran and its consequences for healthcare expenditures. First, to construct measures of patient-level spending, we obtained Medicare claims and enrollment data from the Centers for Medicare & Medicaid Services (CMS) for all fee-for-service Medicare enrollees in PA who were enrolled in a Part D plan in 2009-2012. We obtained all medical claims (MEDPAR, outpatient, carrier, home health, hospice, DME) as well as the Part D Event (PDE) file, which contains prescription details such as drug name, fill date, National Drug Code (NDC), and the total amount paid to the pharmacy from all sources (plan and beneficiary). We obtained beneficiary enrollment dates, demographic information, and ZIP code of residence from the Medicare Beneficiary Summary Files.

Second, to construct measures of physician adoption of dabigatran, we obtained physician-level prescribing data from QuintilesIMS Xponent^{TM} database which directly captures >70% of all US prescriptions filled in retail pharmacies, including all payers. Xponent^{TM} utilizes a patented proprietary projection method to represent 100% of prescriptions filled in these outlets and has been widely used by researchers to examine medication use patterns [9, 16, 17, 21]. Because it includes all payers, the Xponent^{TM} database provides a more complete measurement of physician adoption than would Medicare claims data alone. Our Xponent^{TM} data includes all physician prescribers practicing in PA during 2009-2012.

2.2.2 Physician Study Sample

All physician-level data on number of anti-coagulant prescriptions dispensed was extracted from QuintilesIMS Xponent^{TM} database (January 2009 - December 2012). To identify physicians eligible to adopt dabigatran, we included physicians who prescribed at least one anti-coagulant during the 2009-2010 time period who also prescribed ≥1 anti-coagulant in the 15 months post-dabigatran's introduction. Three small counties (Cameron, Forest, and Sullivan) had ≤ 3 providers prescribing anti-coagulant drugs and were thus excluded from analyses. In total, 19,861 PA physicians ever prescribed an anti-coagulant drug during our study period, with our final study sample including 7,785 physicians.

2.2.3 Measures of Physician Adoption

Our key independent variables were first measured at the physician-level and then aggregated to the county-level. Physicians were assigned to one of PA's 67 counties using the zip code of their primary practice location. We chose to use county as our geographic unit of analysis instead of using HRR because past studies showing substantial variation in health care utilization within HRRs [62]. In order to capture both speed and extent of physician adoption of dabigatran at the county-level we then constructed two measures: 1) mean time (in months) to first dabigatran prescription across all physicians in a county, and 2) percent of physicians within a county prescribing dabigatran at least once in the first year of market availability. The latter measure was weighted by each physician's total anti-coagulant prescription volume to account for the fact that physicians with high patient volumes are more likely to drive changes in drug or medical spending.

2.2.4 Patient Study Sample

To be included in the study sample patients had to meet the following criteria: age ≥18 years old, residents of PA, and continuous enrollment for at least one calendar year during the study period in fee-for-service Medicare. It is important to note that we did not require continuous enrollment for all 4 years of our study period (2009-2012). Instead, we created yearly cohorts with patients being required to meet the same inclusion/exclusion criteria for each separate study year of interest (a patient could thus contribute to one year, all four years, or in between). We took this approach to limit selection bias of only including the healthiest patients with long survival time, given that past studies have shown that Medicare beneficiaries with Afib have an annual mortality rate as high as 25% [63]. Clinical criteria for inclusion in the study sample were 1) meeting the Chronic Condition Data Warehouse (CCW) Algorithm for Afib, 2) having no diagnosis for valvular heart disease or a blood clot in the 12 month pre- and post-Afib diagnosis (treatment guidelines differed in their recommendations regarding use of warfarin vs. a newer drug such as dabigatran for these patients during the time period of study), and 3) filling ≥ 1 prescription for an anti-coagulant (e.g., warfarin, jantoven, coumadin, dabigatran, rivaroxaban) in at least one of the study years. We included rivaroxaban, (another novel anti-coagulant drug that was FDA approved to help reduce the risk of stroke and systemic embolism in patients with non-valvular Afib in late 2011) to have as complete patient cohort as possible, though we did not measure physician adoption of this product due to the short follow-up period available post-FDA approval.

2.2.5 Dependent Variables

Anti-coagulant drug spending was calculated quarterly at the patient-level, and included both Medicare and out-of-pocket spending. Overall, spending for warfarin including generic and branded products (e.g., jantoven, coumadin), dabigatran, and rivaroxaban was included in the anti-coagulant drug spending measure. The Consumer Price Index (CPI) was used to adjust all spending to 2012 dollars.

Non-drug medical spending was calculated quarterly at the patient-level, and included both Medicare and out-of-pocket spending for all inpatient, outpatient, professional, laboratory, home health, durable medical equipment, and hospice claims. We created three categories of non-drug medical spending: 1) overall non-drug medical spending, 2) Afib-related medical spending, calculated using all medical claims with an Afib related ICD-9 code in the primary or secondary position , and 3) Non-Afib related medical spending, calculated using all medical claims without an Afib related ICD-9 code in the primary or secondary position. The CPI was used to adjust all spending to 2012 dollars.

2.2.6 Patient Covariates

We adjusted spending for several patient-level variables such as age, sex, and race/ethnicity. For the race variable, we collapsed African-American, Hispanic, and all other race/ethnicity categories since they cumulatively made up less than 5% of our patient cohort, creating a simple dichotomous variable. To adjust for health status we included risk scores that CMS uses to adjust payments to Part D and Medicare Advantage Plans: Prescription Drug Hierarchical Condition Category (CMS-RxHCC), which was only included in the prescription

drug spending model, and the Hierarchical Condition Category (HCC), which was included in the medical spending model. CMS-RxHCC and CMS-HCC are prospective risk scores calculated by using a patient's prior-year diagnoses, their eligibility status, community versus institutional residence, and whether they are a new versus continuing enrollee; higher values indicate worse health status and thus higher expected health care costs [64, 65]. We included an indicator for beneficiaries filling their prescriptions in Long Term Care (LTC) pharmacy, since these beneficiaries are likely to have different health statuses and spending patterns than beneficiaries who are community dwelling.

2.2.7 Statistical Analysis

Considering the time-dependent, hierarchical nature of our data structure we ran a three-level, mixed effects model with unstructured covariance and a maximum likelihood estimation. A three-level model was required to account for both the longitudinal design (each beneficiary had repeated spending measures), as well as the geographic clustering of beneficiaries within counties. We ran separate models investigating the association of physician adoption of dabigatran with anti-coagulant drug spending, and with non-drug medical spending. As both spending measures were highly skewed, we used log-transformed spending as the outcome variable in both multi-level modeling strategies. To confirm our modeling decision, we checked the distribution of our log-transformed spending variables and found no major deviation from normality. Lastly, due to the clear, time-dependent, trend in anti-coagulant drug spending that aligns with the introduction of dabigatran in late 2010 (Figure 2.1a), we further explored a variety of linear spline functions for representing this differential time trend between periods.

Drug Spending Model: For the drug spending model, we ultimately included all patient-level covariates, six time-varying linear splines to align with the clear time dependent changes in spending, and physician adoption measures as fixed effects, as well as county and time-level random effects. This modeling structure was necessary in order to account for both the time-varying nature of drug spending, as well as the fact that each patient contributed different amounts of time to the cohort (e.g. some patients only contributed four quarters of data, while others contributed 16). Additionally, we initially included adoption over time interaction variables to further investigate how adoption interacts with spending over time, though they were dropped from the final model due to model fit considerations.

Medical Spending Model: For the medical spending models, there was no clear time-dependent trend in spending (Figure 2.1b); consequently, we did not include time as multiple spline functions, but instead as a single variable. Thus, for all three medical-spending models, we ultimately included all patient-level covariates, a time variable (specified based on whether pre (0) or post (1) dabigatran introduction to the market), and physician-level adoption measures as fixed effects, and county and time-level random effects.

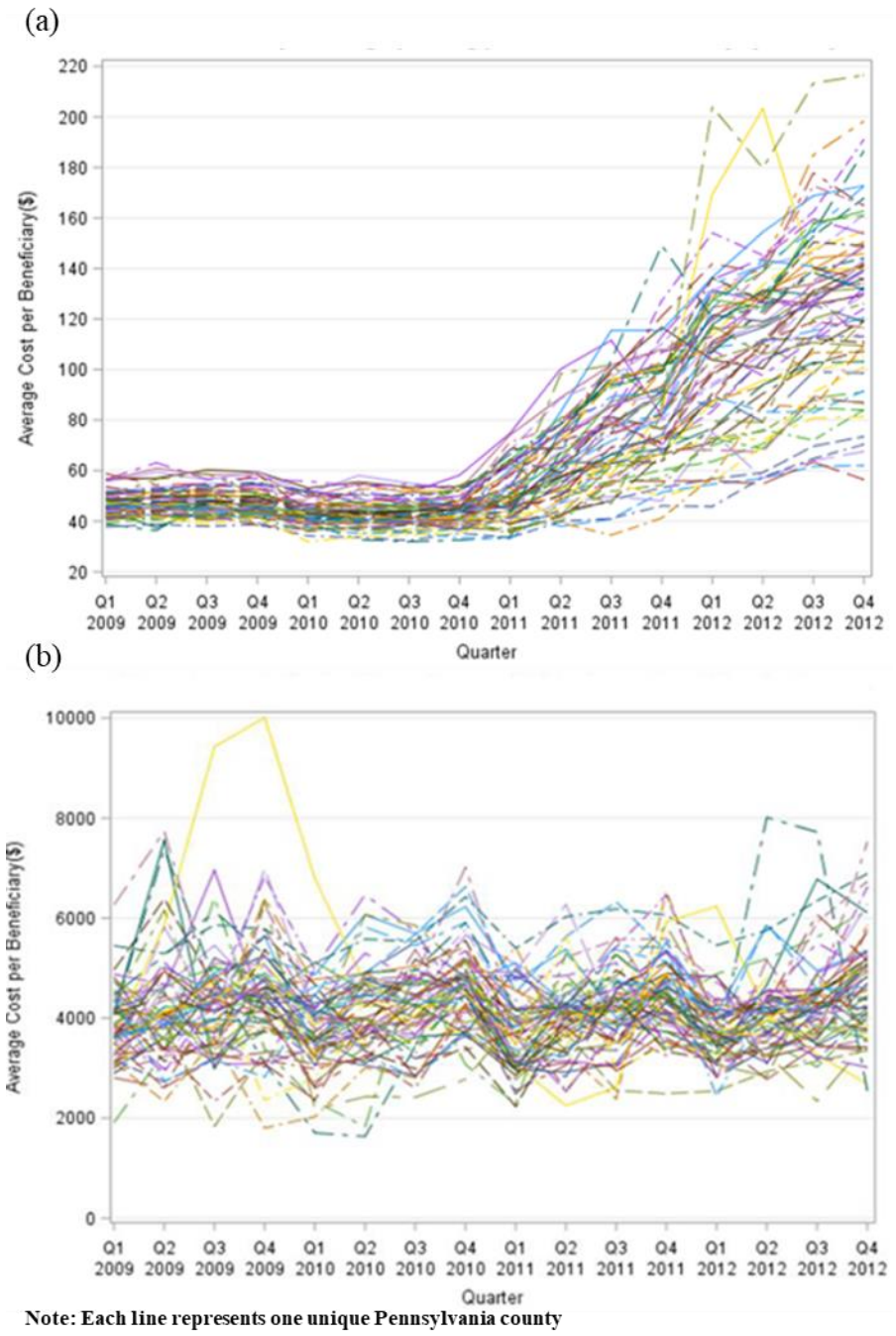


Figure 2.1 Mean Quarterly Anti-Coagulant Drug (a) and Non-Drug (b) Spending per Medicare Beneficiary by PA County

As model diagnostics, we first checked for collinearity between any of our explanatory variables. As no issues arose, we ran the separate models and checked model fit through both residual plots, as well as a plot of predicted versus observed values.

Statistical analyses were conducted using SAS software version 9.3 (SAS Institute, Cary, NC) and Stata software version 15 (College Station, TX).

2.3 Results

2.3.1 Patient Descriptives

Demographics of the patient cohort are described in Table 2.1. Overall, the patient demographics were stable regardless of study year of interest, with the average age being approximately 79 years, 55% of the cohort being female, and 95% being white. As expected, average annual spending on anti-coagulants clearly shows an increasing trend starting in 2011, while average annual medical spending remains stable across the years.

Table 2.1 Characteristics of Medicare Study Sample by Study Year

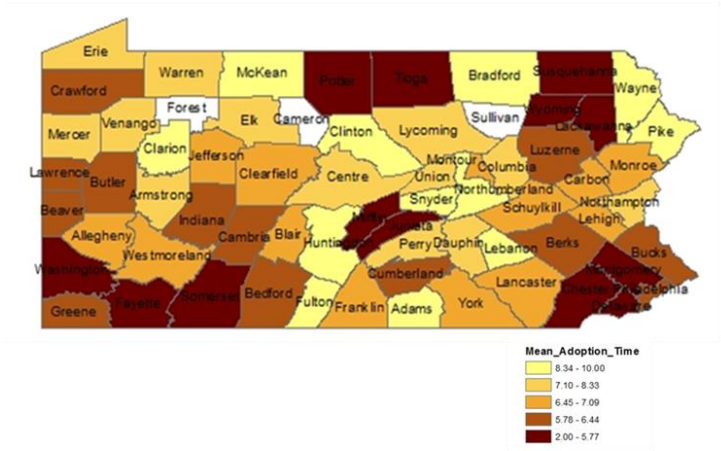
Characteristic	2009	2010	2011	2012
N	22,640	23,249	24,275	26,871
Age (Mean, SD)	79.0 (8.9)	78.8 (9.1)	78.8 (9.1)	78.5 (9.1)
Female (N, %)	13,117 (57.9)	13,120 (56.4)	13,271 (54.7)	14,341 (53.4)
Race/Ethnicity (N%)				
White	21,705 (95.9)	22,105 (95.1)	23,082 (95.1)	25,492 (94.9)
All other	935 (4.1)	1,114 (4.9)	1,193 (4.9)	1,379 (5.1)
Long Term Care (N, %)	2,799 (12.4)	2,466 (10.6)	2,267 (9.4)	2,195 (9.2)
RxHCC (N, %)	2.0 (1.3)	1.9 (1.2)	1.9 (1.2)	1.9 (1.2)
HCC (N, %)	1.2 (0.4)	1.1 (0.4)	1.1 (0.4)	1.1 (0.4)
Annual AC Drug Spending (Mean, SD)	$159.11 ($126.52)	$145.62 ($127.78)	$229.80 ($409.90)	$383.68 ($711.71)
Annual Total Medical Spending (Mean, SD)	$16,876 ($25,740)	$17,270 ($26,285)	$16,777 ($26,014)	$17,018 ($26,006)

2.3.2 Physician Adoption of Dabigatran

A total of 7,614 PA physicians prescribed anti-diabetic drugs in our study sample. Both the adoption time (mean time to first dabigatran prescription), and adoption extent (percent of

physicians prescribing dabigatran at least once in its first 12 months) measures showed high variability across the counties (Figure 2.2). Overall, average time to first prescription was slightly more than six months (6.9 ± SD 1.4 months), though the time did vary markedly by county, from 2.0 months (Juanita county) to 10.0 months (Snyder county). Average weighted fraction of physicians in each county prescribing dabigatran at least once in the first 12 months of market availability was 61% ± 15%. Again, there was substantial variation between the counties from 13% of physicians adopting (Montour county) to 91% of physicians adopting (Somerset county).

(a) Mean Time (Months) to First Dabigatran Prescription



(b) Weighted Percent of AC Prescribers Adopting Dabigatran

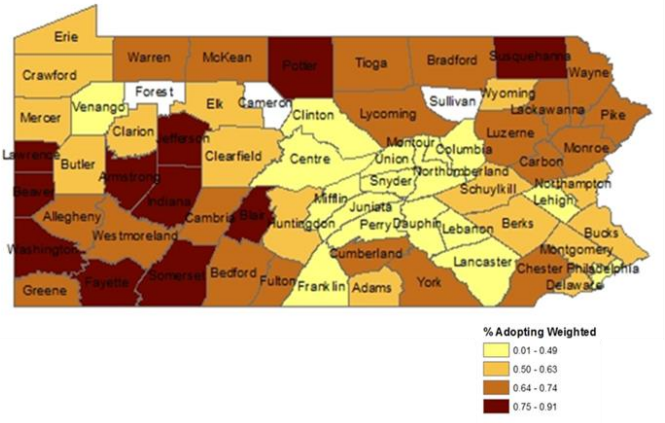


Figure 2.2 Variation in Dabigatran Adoption Time and Extent by Pennsylvania County

2.3.3 Association of Dabigatran Adoption with Anti-Coagulant Drug Spending

The three-level, mixed effects model results indicate that both speed (mean time to adoption), and extent (weighted percent of physician adopting) of dabigatran adoption were associated with higher annual anti-coagulant drug spending. For example, a 10% increase in the number of physicians within a county adopting dabigatran was associated with an average increase of 2.0% (95% CI: 2.0 – 3.0) in annual per capita anti-coagulant drug spending. Additionally, having physicians within a county adopting dabigatran one month sooner was associated with an average increase of 3.4% (95% CI: 2.5 – 4.0) in annual per capita anti-coagulant drug spending. The time variables show that before dabigatran's introduction in the fourth quarter of 2010, anti-coagulant prescription drug spending was slightly decreasing from 2009 to 2010. As expected, starting from the beginning of 2011 there is instead a significantly increasing trend in drug spending from half year to the next. See Table 2.2 for all modeling coefficients and significance levels.

Table 2.2 Results from the Anti-Coagulant Drug Spending Model

Variable	Beta Coefficient	Robust Standard Error	95% CI Standard Error
Intercept	3.819	0.049	[3.722 , 3.915]
2009 (Quarter 1 -Quarter 4)	-0.002	0.001	[-0.024 , 0.002]
2010 (Quarter 1 -Quarter 4)	-0.022	0.001	[-0.024 , -0.019]
2011 (Quarter 1 -Quarter 2)	0.011	0.003	[0.004 , 0.017]
2011 (Quarter 3 -Quarter 4)	0.045	0.003	[0.040 , 0.051]
2012 (Quarter 1 -Quarter 2)	0.007	0.003	[0.001 , 0.013]
2012 (Quarter 3 -Quarter 4)	0.019	0.002	[0.014 , 0.024]
Age	-0.002	0.001	[-0.003 , -0.001]
Race (Ref=White)	0.040	0.017	[0.007 , 0.072]
Sex (Ref=Male)	0.024	0.007	[0.010 , 0.039]
RxHCC	-0.066	0.009	[-0.084, -0.048]
Long Term Care	0.500	0.010	[0.481 , 0.520]
Time to Dabigatran Adoption	-0.032	0.004	[-0.040 , -0.025]
% Adopting Dabigatran	0.002	0.030	[0.002, 0.003]

2.3.4 Association of Dabigatran Adoption with Non-Drug Medical Spending

The three-level, mixed effects overall medical spending model results indicate that both speed and extent of physician adoption of dabigatran were associated with higher annual non-drug medical spending (Table 2.3). For example, a 10% increase in the number of physicians within a county adopting dabigatran was associated with an average increase of 7.0% (95% CI: 1.0 – 9.0) in annual per capita medical spending. Additionally, having physicians within a county adopting dabigatran one month sooner was associated with an average increase of 4.6% (95% CI: 3.8 – 5.4) in annual per capita medical spending. The quarterly time variables show a slight increase in medical spending over time. See Table 2.3 for all modeling coefficients and significance levels.

Table 2.3 Results from the Anti-Coagulant Non-Drug Medical Spending Model

Variable	Beta Coefficient	Robust Standard Error	95% CI Standard Error
Intercept	5.404	0.044	[5.319 , 5.490]
Quarter	0.013	0.001	[0.012 , 0.015]
Age	0.003	0.003	[-0.002 , 0.008]
Race (Ref=White)	0.088	0.021	[0.047 , 0.130]
Sex (Ref=Male)	-0.055	0.008	[-0.072 , -0.039]
HCC	1.696	0.015	[1.666, 1.725]
Long Term Care	0.096	0.004	[0.070 , 0.123]
Time to Dabigatran Adoption	-0.046	0.004	[-0.054 , -0.038]
% Adopting Dabigatran	0.007	0.001	[0.001, 0.009]

Interestingly, neither adoption measure was associated with Afib related non-drug medical spending model. Whereas, estimates of the association between adoption measures and non-Afib related spending were comparable to the overall spending results. A 10% increase in the number of physicians within a county adopting dabigatran was associated with an average increase of 3.6% (95% CI: 2.0 – 4.1) in annual per capita, non-Afib medical spending in our Afib cohort. Additionally, having physicians within a county adopting dabigatran one month sooner was associated with an average increase of 2.3% (95% CI: 1.6 – 3.1) in annual per capita, non-Afib related, medical spending.

2.4 Discussion

Our study reports three key findings. First, we found substantial county-level variation in both the time to adoption and in the proportion of physicians adopting dabigatran across

Pennsylvania. Second, we found that physician adoption of dabigatran was significantly associated with both higher anti-coagulant drug spending, and higher overall non-drug medical spending in this Medicare cohort. Third, we did not find an association (either positive or negative) between physician adoption and Afib-related medical spending, suggesting that areas with higher rates of dabigatran prescribing are not followed by cost-offsets in Afib related medical spending. Rather, we there was an increase non-Afib, related medical spending following dabigatran's introduction.

The high variability in physician adoption rates of dabigatran by county in both average time to first prescription (2.0 – 10.0 months) and share of physicians prescribing dabigatran (13% to 91% of physician) is consistent with previous findings. Studies have reported both physician-level and region-level variation in adoption of new drugs [1, 3, 5, 66]. Physician adoption of new drugs is likely influenced by many factors including physician social networks [20], practice setting (e.g. group vs. solo practice) [18], specialty [19], and exposure to pharmaceutical promotion [21].

Our finding that faster and more extensive adoption of dabigatran was associated with higher anti-coagulant drug spending in Medicare is perhaps not surprising given that dabigatran's price was approximately four higher than warfarin during our study period. However, we also found that Medicare beneficiaries in counties with faster and more extensive adoption of dabigatran had significantly higher non-drug medical spending than those in counties that were slower, less extensive adopters. Interestingly, the effect was driven largely by non-Afib related, as opposed to Afib-related spending. To the extent that we have adequately captured Afib-related spending using diagnosis codes in our data, our findings point to a lack of a medical cost offset for dabigatran. There have been multiple cost-effectiveness studies utilizing clinical trial data and list prices to model the possible drug and medical cost differential between patients being prescribed

dabigatran vs warfarin, with a majority indicating the potential cost effectiveness of dabigatran [67]. Studies utilizing real world data show mixed results [68-72]. For example, one recent study found that patients with non-valvular Afib initiating treatment with dabigatran (vs. warfarin) had significantly higher annual pharmaceutical spending, but significantly lower annual medical spending - leading to a cost offset in total health care spending of $1,940 per year [68]. However, another similar study reported that while non-valvular Afib patients initiating treatment with dabigatran had significantly higher annual pharmaceutical spending, there was no statistically significant decrease in medical spending, and thus no cost-offset [71]. Our study adds to the literature by constructing two measures of physician adoption behavior and examining the relationship between physician adoption and three categories of Medicare spending.

A possible explanation for our finding that dabigatran adoption was associated with higher total non-drug spending, particularly non-Afib related, is that physicians who adopt a highly novel drug such as dabigatran may be more likely to adopt other novel (and inherently more expensive) medical technologies. Additionally, it is possible that physicians within small geographic areas exhibit similar behavior with regards to diffusion of medical technologies – possibly due to sociological factors such as professional norms, or exchange of ideas through interpersonal relationships and physician social networks [61]. Lastly, multiple studies have investigated physician adoption of novel drugs across their entire scope of practice. But, results have been mixed, and have identified very few observable characteristics of "early adopting" physicians [73-75]. For example, one past study showed only weak correlations (all $r<0.49$) for physicians concomitantly prescribing novel brand-named drugs across multiple drug classes used for the treatment of relatively common conditions such as hypertension, migraines, osteoarthritis, and peptic ulcer or gastro-esophageal reflux diseases [73]. Another study found some consistent

prescribing behavior among physicians classified as “late adopters” of novel drugs, though they did not find similar consistent behavior among any group of “early adopters” [75]. While beyond the scope of our study, our results point to the possibility that some physicians might behave consistently over time in regards to adoption of new medical technologies. Furthermore, our findings suggest that a potential mechanism underlying the geographic variation in medical spending could be the similarities in diffusion of new technologies at the local-level. This is an important discovery as it is consistent with the well-known finding in health economics that the diffusion of health care technologies is one of the main drivers of health care cost growth [37]. This finding could also have major policy implications, as physicians who are found to be early adopters of certain medical technologies could then be targeted for interventions to promote the use of evidence-based technologies with high clinical value.

Our study should be viewed in light of some limitations. First, this study was conducted in one state, and even though Pennsylvania has been shown to track closely with national averages on most demographic and socioeconomic measures as well as health care utilization, our findings might not be nationally representative [44]. Second, anti-coagulants have other uses (e.g. prevention deep vein thrombosis); however, our results are specific to non-valvular Afib patients and thus might not be generalizable to other patient cohorts. Third, our patient cohort was quite elderly and had poor health status (average age was approximately 80, and more than 10% of the cohort was consistently in long-term care), and while this is consistent with the non-valvular Afib patient population as a whole, our findings, particularly in regards to non-drug medical spending, might not be generalizable to other patient populations or chronic disease categories. Lastly, no gold standard for defining physician adoption currently exists, therefore other definitions of adoption could yield other results.

2.5 Conclusion

This study represents the first analysis that aims to better understand regional variation in physician adoption of dabigatran in order to determine whether higher physician adoption of dabigatran is associated with both higher prescription drug spending, and with higher non-drug medical spending. Future research should focus on further elucidating the underlying mechanisms surrounding why some physicians adopt medical technologies faster than others, assessing whether there are certain physicians consistently adopting varied novel medical technologies, and determining the best policy interventions to ensure high physician-level adoption of evidence-based, high quality treatments.

3.0 Role of Peer Social Networks on Geographic Variation in Prescription Drug Diffusion

3.1 Introduction

There is well-documented geographic variation in prescription drug spending across the United States [1, 2] that is not fully explained by patient characteristics, health status, or prescription volume [3-5]. Instead, variation in prescription drug spending is associated with differences in physician prescribing of more costly brand name drugs, many of which are new to the market [6-9]. Additionally, a physician's propensity to quickly adopt new, high cost, drugs into their prescribing repertoire can serve as another possible determinate of geographic variation in drug spending. Individual characteristics, such as age, sex, specialty, practice setting are important in understanding physician prescribing behavior, in general, and physician decisions to adopt new drugs and other health technologies, in particular [33, 76-77]. Additionally, external influences on prescribing, such as the institutions where a physician trained, the culture of the health care organizations within which they practice, the payers that finance their patient's care and their exposure to pharmaceutical promotion can also have important effects on prescribing behavior and new medical technology adoption [78-81].

Research using a variety of study designs also indicates that a physician's decision to adopt a new drug is likely to be influenced by their peers. A survey conducted on both primary care physicians and hospitalists found that 69% and 74%, respectively, listed their own colleagues as an important source of information for learning about new drugs [82]. Both formal (based on training institutions, or practice-based settings), and informal (based on shared patients), peer networks have been shown to provide an important source of information about novel

pharmaceuticals [82-86]. Thus, in addition to official institutional sources of clinical knowledge such as professional associations (e.g. the American Medical Association) and academic literature, peer networks can also play an important informational role between physicians, as they often communicate with each other and can gain direct knowledge regarding the existence of new drugs on the market, plus the benefits and/or disadvantages that those drugs can pose. Lastly, peer networks may influence physician behavior by transmitting norms, or cues, that can influence a physician's decision-making on whether or not to adopt a new drug or medical technology. These norms could encourage conservative prescribing, and slow adoption of new treatments that have not yet established a robust safety profile [87, 88], while others could instead emphasize the importance of treatment innovation and rapid adoption [89].

One useful framework for examining the effect of peers on diffusion of information, and the possible role of peer influence in regards to geographic differences in new drug adoption is social network analysis. Social network analysis is a well-known methodology that has been used to help illustrate complex inter-personal relationships in diverse disciplines, and that in the health sciences has been used to try to better understand both patient, and physician-level behavior [90-95]. Interestingly, multiple studies have found that peer interactions are associated with both a physician's likelihood to adopt a new medical innovation or drug [96, 97] and the timing of that adoption [98, 99]. Additionally, other studies have found that peer interactions are associated with physician adoption of new drugs [100-103]. While most prior studies relied on small samples of physicians self-reporting information on social ties, one recent paper used claims data from Medicare and Medicaid to estimate the magnitude of peer influence using patient-sharing information on a larger scale. The paper estimated that for every 10 percentage-point increase in

the fraction of peers in the patient sharing network adopting one of three new drugs physicians were 6-8% more likely to adopt the new drug of interest [103].

While social network analysis has been used to estimate the magnitude of peer influence on physician adoption of new drugs, it has not been used as a possible mechanism underlying geographic variation in drug use and spending. We aim to examine geographic variation in physician adoption of three first-in-class chronic disease medications (the anti-coagulant dabigatran (Pradaxa), the anti-diabetic sitagliptin (Januvia), and the anti-hypertensive aliskiren (Tekturna). We then estimate the fraction of variation that is attributable to peer influence using social network and instrumental variables, while additionally adjusting for other individual factors known to influence physician prescribing. We hypothesize that peer influence will explain a substantial share of the variation in new drug adoption after controlling for physician characteristics.

3.2 Methods

3.2.1 Data Sources

We obtained data and constructed physician-level measures from three separate data sources. First, physician-level prescribing data were obtained from QuintilesIMS's Xponent^{TM} database which directly captures >70% of all US prescriptions filled in retail pharmacies and utilizes a patented proprietary projection method to represent 100% of prescriptions filled in these outlets. We obtained data on all prescriptions dispensed in Pennsylvania between 2007-2011 for the oral anti-coagulant and anti-diabetic classes (127 products in total). Xponent^{TM} data were used

to identify physicians eligible to adopt each of the three new drugs, and to construct the new drug adoption measures.

Second, we obtained information on physician characteristics from the American Medical Association (AMA) Masterfile. The Masterfile contains information on physician demographic characteristics (age, sex), specialty, practice setting, and training (e.g., medical school and year of graduation; residency program and year completed). The Masterfile data was used to create the physician-level characteristics included in our analyses.

Lastly, we obtained Medicare and Medicaid administrative claims for Pennsylvania enrollees. Specifically, we obtained claims for all fee-for-service Medicare enrollees who were residents of PA, and also enrolled in a Part D plan in 2007-2012 from Centers for Medicare & Medicaid Services (CMS). We also obtained 2007-2012 claims for all fee-for-service and all managed care enrollees in PA's Medicaid program through a Business Associate Agreement with the Pennsylvania Department of Human Service. Medicaid and Medicare claims data were used to construct the physician peer social network.

3.2.2 Physician Study Samples

Our physician sample initially included all providers who practiced in PA. We then created three separate physician cohorts, one for each of the study drugs of interest. To ensure that each cohort only included physicians who were actively prescribing the specific drug class of interest, we excluded physicians who did not reach a minimal threshold of prescriptions in the drug class as a whole in the first 15 months after the new drug of interest was introduced (defined as ≥1 prescription per quarter). We also excluded physicians who did not have an AMA record, or a Pennsylvania practice address. The final cohorts include 7,785 anti-coagulant prescribers eligible

to adopt dabigatran, 8,257 anti-diabetic prescribers eligible to adopt sitagliptin, and 9,974 anti-hypertensive prescribers eligible to adopt aliskiren.

We believe that investigating physician prescribing behavior surrounding three different drugs gives strength to our study and the generalizability of our findings. This is because while all three are used to treat prevalent chronic conditions and are first-in-class drugs, each enters a vastly different, disease-specific, drug market containing differing levels of available prescription substitutes.

3.2.3 Measure of Physician Adoption

For all three drugs of interest, we defined a prescriber as an "adopter" of the drug if they wrote at least the median number of prescriptions among physicians prescribing the new drug at least once in its first 15 months on the market. While other definitions of adoption do exist, there is a lack of consensus regarding a "gold standard" of adoption in the literature. Prior studies have mostly used a threshold of one prescription to define drug adoption by a physician, however this practice is imperfect because it risks classifying prescription refills (e.g. when a physician is simply refilling a prescription that another physician initially wrote) as a drug adoption event. Therefore, we decided on conditioning adoption on reaching the median prescription threshold of each physician cohort since we believe this measure to be clinically meaningful, while also helping mitigate the risk of misclassifying refills as true drug adoption events. Additionally, this definition has been used in past studies investigating peer influence on drug adoption behavior, and it has been shown to be robust to different definitions of adoption [102].

The measure of physician adoption is the dependent variable in our regression model and is also used to construct the measure of peer adoption (e.g., fraction of peers in the social network adopting new drug).

3.2.4 Peer Network Construction

The patient-sharing social network was constructed using a previously validated approach that uses administrative claims data to identify shared patients [104]. This approach deems that two physicians are connected if they both submit claims for services delivered to the same patient in a given time period. Barnett et al. validated this approach by comparing the patient-sharing networks constructed with Medicare data on a sample of 616 physicians in the Boston, MA HRR against self-reported physician relationships for patient referral, sharing of information, or medical advice. They found that 85% of patient-sharing relationships could be positively verified from the claims when physicians shared at least nine patients, and that 70% of relationships could be verified when physicians share at least one patient [104].

While Barnett et al's approach included only Medicare patients, we will expand on the methodology by additionally including Medicaid patients, leading to a more complete peer network that can account for more links between physicians. Specifically, we identified two physicians as connected if both had claims in the Medicare carrier files for at least one unique enrollee, or if they both had claims in the Medicaid professional files for at least one unique enrollee, or had shared patients in Medicare and in Medicaid. All patients who were dually eligible for both Medicare and Medicaid were only included in the Medicare claims; this was done to create non-overlapping patient populations. We identified all claims submitted by sample physicians during the same period over which adoption of the new drug was measured for each cohort

(depending on the date of introduction of the study drug of interest). We did not limit claims studied to those for patients with either diabetes or non-valvular Afib in particular, but instead included all patients cared for by our sample physicians. Over 90% of study physicians billed for at least one Medicare enrollee with an average number of Medicare patients equal to 215-290, depending on the physician cohort. Approximately 80% of study physicians submitted claims for one or more Medicaid enrollees with an average number of Medicaid patients equal to 136-169, depending on the physician cohort [106]. We used the network analysis library "Igraph" in python for the patient-sharing network analysis.

3.2.5 Peer Adoption Measure

For each physician in the network, we created a measure of peer adoption (e.g. the fraction of a physician's peers who adopted the new drug of interest). We applied weights to the peer adoption measure equal to the number of patients shared. Thus, the peer adoption measure was equal to the fraction of peers adopting the new drug of interest with each peer weighted by the total number of Medicare and/or Medicaid patients shared. This was done to account for the differential type of relationship that two physicians might have depending on how many patients they share (e.g. two physicians who share 100 patients are likely to interact more often than two physicians who share ten patients).

3.2.6 Statistical Analysis

We used a linear probability model to estimate both the roles of peer adoption rates (calculated from the constructed patient-sharing network), and geographic variation across Pennsylvania HRRs on physician adoption. The model is specified as:

$$y_i = \beta_0 + x_i'\beta_1 + x''\beta_2 + \gamma_P \bar{y}_{Pi} + \lambda_P \bar{c}_{Pi} + \varepsilon_i$$

The vector term $x_i'\beta_1$ represents the influence of physician *i*'s own characteristics (the vector x_i) have on his/her propensity to adopt. These are all characteristics that have been shown to be associated with new drug adoption, and include: an indicator for whether the physician was male (reference) or female, year of medical school graduation, an indicator variable for location of medical school (US or non-US), an indicator variable denoting medical school ranking (top 20 according to the 2011 *US News and World Report*), a variable for the share of a physicians' prescriptions filled by patients aged <65 years, 65-84, or 85+, and a variable for the share of prescriptions paid for by Medicaid, Medicare, vs. commercial insurance plans.

The vector term $x''\beta_2$ represents the influence of geographic variation in physician prescribing practices on a physician's propensity to adopt. We used Hospital Referral Region (HRR) as our geographic unit of interest. HRRs represent regional health care markets and are commonly used in the geographic variation literature [45]. Thus, the vector term $x''\beta_2$ includes variables accounting for the differing adoption rates by HRR in Pennsylvania (with Philadelphia, the largest, as reference). A small number of physicians with practices physically located in Pennsylvania were assigned to a non-Pennsylvania HRR based on their zip code, so we included an additional 15th category for any non-PA HRR.

The term $\gamma_P \bar{y}_{Pi}$ measures the weighted peer influence from the patient sharing network, and the term $\lambda_P \bar{c}_{Pi}$ measures the proportion of physician *i*'s peers in the patient sharing network who are in a specialty that is relevant to the drug of interest (e.g., cardiology for dabigatran, endocrinology for sitagliptin). The proportion of peers who are specialists is included directly as a covariate in the model since we believe that this measure may have a direct influence on a physician's prescribing behavior (e.g. a primary care physician might not prescribe a novel drug for a complex patient if he can instead refer the patient to a specialist he is connected to). Lastly, the error term ε_i represents unobserved factors affecting physician adoption.

Our analysis had to account for the challenges to causal inference with social network data. In particular, the directionality of influence among peers is hard to discern (e.g. is *physician A* influencing *physician B*, or the other way around). Additionally, physicians may already choose to interact with peers who are similar to them (known as homophily in social network analysis) further complicating the estimation of causal effects. To address these possible sources of bias, we apply an instrumental variables approach commonly used in econometrics. This approach has been previously used to establish whether an individual's propensity to engage in behavior is affected by the prevalence of that behavior among the individual's peers [105]. For our study, we will use the personal characteristics of peers (e.g. sex, year or medical school graduation) as exogenous "instruments" that predict peer adoption rates.

We estimate this instrumental variables model using two-stage least squares (2SLS). In this method, a linear model is estimated to generate predicted peer adoption rates in the patient sharing network (the first-stage model has the observed adoption rates ($\overline{y}_{Pi}$) as the dependent variables, and has the individual characteristics (x_i), and the means of peer characteristics ($\overline{x}_{Pi}$) as the independent variables. This first-stage model predicts the peer adoption rates. These predicted

values are then used in place of the observed adoption rates to estimate the main model in the second stage.

3.2.7 Measuring Variance

We use three commonly used statistics (standard deviation (σ), population variance (σ^2), and coefficient of variance (CV)) to quantify how much variability in physician adoption rates across HRRs can be explained by our peer-effects model compared to simple OLS regression. The population variance for each modeling strategy will be calculated as:

$$population\ variance = \frac{\sum_{HRR=1}^{15} number\ of\ providers \times (HRR\ \text{coefficient})^2}{\sum_{HRR=1}^{15} number\ of\ providers}$$

The standard deviation is calculated simply as the square root of the population variance.
In turn, the coefficient of variance for each modeling strategy will be calculated as:

$$coefficient\ of\ variance = \frac{\sqrt{population\ variance}}{mean\ adoption\ rate}$$

(Since the coefficient of variance is unit-less, it provides a useful way to compare relative variation between different models and cohorts).

We will additionally calculate adjusted adoption rates by HRR to directly compare values between the unadjusted, OLS adjusted, and the instrumental variable with peer-network model.

This study was approved by the University of Pittsburgh IRB.

3.3 Results

3.3.1 Physician Characteristics

Our three Pennsylvania physician cohorts consisted of 7,785 physicians prescribing anti-coagulants, 8,257 physicians prescribing anti-diabetics, and 9,975 physicians prescribing anti-hypertensives. Full descriptive characteristics can be found in Table 3.1. Overall the three cohorts were relatively similar in age (being on average approximately 50 years old), and gender (being on average 75% male). Regardless of cohort, the vast majority of physicians practiced in metropolitan settings (roughly 90% of each cohort), and as expected the largest concentration of physicians were located in the Philadelphia (roughly 30%-35%) and Pittsburgh (roughly 22%) HRRs, which are the two largest metropolitan areas in Pennsylvania.

Table 3.1 Demographics of Physician Cohorts

	AC Physicians	AD Physicians	AH Physicians
N	7,785	8,257	9,974
Female (%)	1,931 (24.8)	2,229 (27.0)	2,474 (24.8)
Years Since Med School Graduation			
<10	827 (10.6)	1,044 (12.6)	1,244 (12.5)
10-19	2,043 (26.2)	2,362 (28.6)	2,732 (27.4)
20-29	2576 (33.1)	2,943 (35.6)	3,581 (35.9)
30+	2339 (30.0)	1,908 (23.1)	2,417 (24.2)
Primary Care vs. Specialty			
Specialty	1,042 (13.4)	274 (3.3)	1,417 (14.2)
PCP	5,579 (71.7)	5,748 (69.6)	5,959 (60.8)
Other Physicians	1,164 (15.0)	2,235 (27.1)	2,598 (26.0)
Payer Mix (%)			
Cash	3.6 ± 5.6	4.0 ± 7.4	4.9 ± 8.1
Commercial	50.0 ± 21.2	57.9 ± 23.8	60.4 ± 21.4
Medicaid fee-for-service	5.5 ± 12.1	8.5 ± 15.1	6.7 ± 12.4
Medicare	41.0 ± 19.7	29.6 ± 19.9	28.0 ± 17.3
Practice Location			
Rural	910 (11.7)	914 (11.1)	1,020 (10.2)
Metropolitan	6,875 (88.3)	7,343 (88.9)	8,954 (89.8)
Medical School Location			
US	6,090 (78.2)	6,489 (78.6)	7,827 (78.5)
Foreign	1,695 (21.8)	1,768 (21.4)	2,147 (21.5)
Medical School Ranking			
Top 20	769 (9.9)	880 (10.7)	1,127 (11.3)
Non-Top 20	7,016 (90.1)	7,377 (89.3)	8,847 (88.7)
HRR region			
Allentown	690 (8.9)	692 (8.4)	837 (8.4)
Altoona	153 (2.0)	151 (1.8)	170 (1.7)
Danville	309 (4.0)	285 (3.5)	340 (3.4)
Erie	339 (4.4)	339 (4.1)	384 (3.9)
Harrisburg	612 (7.9)	596 (7.2)	723 (7.3)
Johnstown	131 (1.7)	124 (1.5)	140 (1.4)
Lancaster	375 (4.8)	373 (4.5)	404 (4.1)
Philadelphia	2,409 (30.9)	2,808 (34.0)	3,549 (35.6)
Pittsburgh	1,657 (21.3)	1,785 (21.6)	2,179 (21.9)
Reading	337 (4.3)	337 (4.1)	383 (3.8)
Sayre	72 (0.9)	78 (0.9)	87 (0.9)
Scranton	193 (2.5)	192 (2.3)	228 (2.3)
Wilkes-Barre	166 (2.1)	158 (1.9)	190 (1.9)
York	233 (3.0)	235 (2.9)	253 (2.5)
Non-PA HRR	109 (1.4)	104 (1.3)	107 (1.1)

3.3.2 Unadjusted Rates of Physician Adoption by HRR

There were high levels of variation in physician adoption of all three drugs across Pennsylvania HRRs. For dabigatran, the prescribing physicians in the Johnstown HRR had the highest proportion of adopters (67.2%), with the Danville HRR having the lowest proportion of adopters (33.7%). For sitagliptin, the prescribing physicians in the Reading HRR had the highest proportion of adopters (62.5%), with the York HRR having the lowest proportion of adopters (38.3%). For aliskiren, the prescribing physicians in the Non-PA HRR had the highest proportion of adopters (34.6%), with the York HRR having the lowest proportion of adopters (9.9%)

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Table 3.2 Unadjusted Physician Adoption Rate vs. Philadelphia HRR

HRR region	AC Adoption Rate Diff	AD Adoption Rate Diff	AH Adoption Rate Diff
Allentown	1.0%	16.2%	9.4%
Altoona	22.0%	10.4%	2.7%
Danville	-8.4%	2.3%	-1.1%
Erie	14.9%	7.5%	1.6%
Harrisburg	-3.3%	8.9%	-2.3%
Johnstown	25.2%	14.6%	6.9%
Lancaster	-3.6%	9.9%	0.8%
Philadelphia	0.0%	0.0%	0.0%
Pittsburgh	17.5%	5.7%	3.1%
Reading	4.0%	17.0%	14.7%
Sayre	9.4%	4.8%	5.8%
Scranton	16.0%	15.2%	13.4%
Wilkes-Barre	8.6%	15.6%	8.3%
York	21.9%	-4.3%	-3.9%
Non-PA HRR	18.5%	19.9%	20.8%

As our full analysis uses the largest HRR (Philadelphia) as the reference HRR to which all others are then compared, Table 3.2 displays the relative unadjusted differences in physician rates of adoption versus Philadelphia. These results again help highlight the high variation in adoption between HRRs in Pennsylvania all shown relative to Philadelphia. For example, prescribing physicians in the Johnstown HRR adopted dabigatran at a 26% higher rate than physicians practicing in Philadelphia.

3.3.3 Adjusted Estimates of Peer Effects on Adoption

In the fully-adjusted instrumental variable model, we found that peer effects on adoption were strong and significant across all three of our drugs of interest. For dabigatran, our model shows that a 10% increase in the fraction of a physician's peers adopting the drug leads to a 5.6% increase in the probability that they themselves will adopt the drug into their practice (SE = 0.15, $p<0.001$). Similarly for sitagliptin, the same 10% increase in physician peers adopting the drug leads to an 8.5% (SE = 0.15, $p<0.001$) increase in probable drug adoption. Lastly for aliskiren, a 10% increase in physician peer adoption leads to the probability of a physician's own drug adoption increasing by 7.8% (SE = 0.29, $p<0.001$). Taken together, these results suggest that physician peer effects may play an integral role in physician decision making, and in new drug uptake across diverse drug classes. Full modeling results can be found in Table 3.3.

Table 3.3 Adjusted HRR Effects on New Drug Adoption

	AC			AD			AH		
	OLS[#1]	OLS[#2]	IV with network	OLS[#1]	OLS[#2]	IV with network[#1]	OLS[#1]	OLS[#2]	IV with network
Network measure			0.560*			0.852*			0.784*
Allentown	0.010	0.002	-0.012	0.162*	0.108*	0.035	0.094*	0.069*	0.017
Altoona	0.220*	0.238*	0.019	0.104*	0.038	0.057	0.027	-0.003	0.042
Danville	-0.084*	-0.074*	0.012	0.023	-0.065*	0.034	-0.011	-0.043*	0.032
Erie	0.149*	0.165*	0.054	0.075*	0.005	0.025	0.016	-0.015	0.042
Harrisburg	-0.033	-0.037*	-0.008	0.089*	0.010	0.020	-0.023	-0.056*	0.040*
Johnstown	0.252*	0.231*	0.039	0.146*	0.028	0.043	0.069*	0.013	0.036
Lancaster	-0.036	-0.034	-0.012	0.099*	0.024	0.014	0.008	-0.030	0.034*
Pittsburgh	0.175*	0.170*	0.040*	0.057*	0.027*	0.019	0.031*	0.019*	0.023*
Reading	0.040	0.048*	-0.025	0.170*	0.114*	0.008	0.147*	0.122*	-0.024
Sayre	0.094	0.064	0.019	0.048	-0.057	0.012	0.058	0.018	0.010
Scranton	0.160*	0.126*	0.029	0.152*	0.073*	0.002	0.134*	0.100*	0.027
Wilkes-Barre	0.086*	0.093*	0.031	0.156*	0.100*	0.010	0.083*	0.054*	0.026
York	0.219*	0.261*	0.042	-0.043	-0.137*	0.060	-0.039	-0.078*	0.039*
Non-PA	0.185*	0.194*	0.034	0.199*	0.144*	0.010	0.208*	0.171*	0.034

3.3.4 Variation Explained by Peer Effects

For all three drug categories of interest, the fully-adjusted instrumental variable peer-effect modeling had the lowest measure of variation in rates of adoption across HRRs versus both the unadjusted, and the traditionally adjusted OLS regression results (Table 3.4). For example, when looking at the anti-coagulant modeling, both the unadjusted results and the OLS regression results have relatively similar measures of standard deviation (0.113 vs. 0.114), variance (0.013 vs. 0.013), and coefficient of variance (0.229 vs. 0.223). These measures showcase how the level of variation in adoption rates across HRRs is not decreased, or explained, by the individual physician characteristics included in the traditional OLS modeling strategy. However, with regards to the coefficient of variance, the variation in adoption rates across HRR is decreased by close to factor

of 2.5 with the instrumental variable peer effect modeling as compared to the OLS modeling (0.223 vs. 0.091, a 50.2% reduction in variation).

Table 3.4 Change in Variance Across Differnent Models

	AC			AD			AH		
	OLS#1	OLS#2	IV with network	OLS#1	OLS#2	IV with network	OLS#1	OLS#2	IV with network
Variance across HRRs	0.012	0.012	0.002	0.005	0.006	0.002	0.005	0.005	0.002
Coefficient of variance	0.223	0.229	0.091	0.143	0.155	0.083	0.423	0.420	0.249
Population variance across HRRs	0.013	0.013	0.003	0.007	0.003	0.001	0.003	0.002	0.001

OLS#1 models include hospital referral region only
OLS#2 models include physician sex, graduation year, specialty, metropolitan, US v. foreign med school grad, top 20 med school grad, payer mix, patient age categories and hospital referral region
IV with network models the same covariates as OLS#2, hospital referral region. With IV model estimated using 2SLS, and including fraction of peers who are specialists as an additional covariate, with the network measure with characteristics of peers used as instrumental variables.

The magnitude of this result can be further highlighted when directly comparing the instrumental variable adjusted rates of adoption by HRR to both unadjusted, and OLS adjusted rates (Figure 3.1), as this Figure shows how both the spread, and difference in magnitude of adoption rates are considerably decreased with the peer effect model. Similar decreases in variation were also found for the anti-diabetic cohort (variation across HRR decreased by a factor of 1.9, or a 46.4% reduction), and the anti-hypertensive cohort (variation across HRR decreased by a factor of 1.7, or a 40.7% reduction) (Table 3.4).

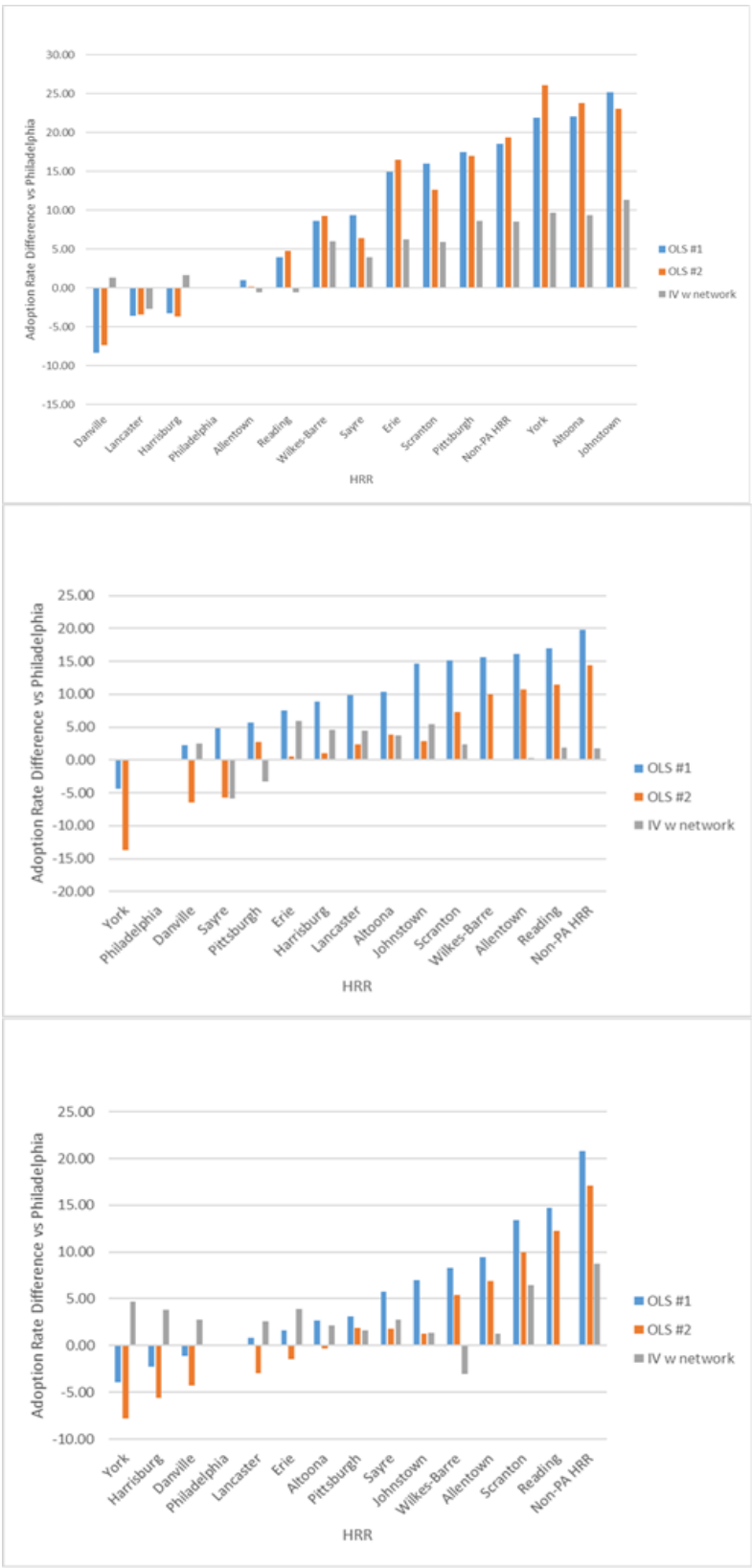


Figure 3.1 Adjusted AC, AD, AH Adoption Rate Differences

3.4 Discussion

Our study reports three key findings. Firstly, and similar to numerous other studies investigating geographic variation in the adoption of new drugs and other health care technologies, we found a significant variation in physician adoption of three diverse first-in-class drugs. Secondly, and consistent with an earlier study [104], we found that physician drug adoption decisions were influenced by peer adoption behavior. We found that, depending on the drug class, a 10% increase in the fraction of peers adopting led to a 5.6% - 8.5% increase in the likelihood of adoption for the three novel drugs of interest. Lastly, this study highlights that peer influence appears to be explain roughly half of the geographic variation of drug adoption. Importantly, this finding which was consistent across the three distinct, commonly prescribed, chronic disease drug classes, points to a possibly mechanism underlying geographic variation in health care utilization.

While geographic variation in prescription drug spending and utilization across the United States is a well-documented phenomenon, there continues to be a lack of consensus on what factors, or combination of factors, influence this variation. Past studies have mainly focused on the role of individual and/or institutional characteristics on physician drug adoption, and have found that adoption can be influenced, to some degree, by factors including practice setting (e.g. group vs. solo practice) [35, 36], specialty [22, 23], and exposure to pharmaceutical promotion [6, 18]. Our study builds on this literature and shows that, after accounting for individual and institutional variables, peer influence, and the type of social "eco-system" surrounding a physician, then accounts for close to half of the remaining variability in adoption rates. Interestingly, this finding was remarkably consistent across three distinct chronic disease drug classes, each varying in novelty and place in existing treatment guidelines (e.g. first-line vs. second-line treatment, etc.). This strength in generalizability across drug classes provides further evidence that peer

connections, and specifically peer behavior, can be a key underlying mechanism driving a substantial portion of the variation in drug adoption and utilization.

Importantly, since our physician patient-sharing network was constructed using readily available administrative data, this finding can be harnessed by various stakeholders in the health care industry to help increase the uptake of evidence-based, efficient, and cost-effective prescribing behavior. Or alternatively, to help decrease wasteful, or potentially dangerous, behavior. This methodology additionally offers a possible opportunity to build on existing health system structures for information dissemination and quality improvement such as continuing education and academic detailing (peer-to-peer educational outreach used to improve clinical practice in a specific area) [40], by helping target highly connected physicians whose behavior might, in turn, influence other physicians in their constructed patient-sharing network.

Additionally, in view of the consistency of these results across multiple drug classes and physician specialties, this finding also offers a novel occasion to help better quantify how 'key opinion leaders' for distinct clinical domains are classified. While used frequently in the health care sector by pharmaceutical companies in the marketing and promotion of pharmaceuticals and medical devices (and across disciplines for increasing utilization of certain practices or technologies), no real academic consensus currently exists on how to most accurately identify 'key opinion leaders'. Moving forward, in conjunction with the existing literature investigating the potential of influential individuals to help aid the spread and diffusion of new technologies [18, 40, 107, 108], our study has the potential to provide a systemic way in which 'key opinion leaders' could easily and uniformly be identified, and subsequently targeted for interventions.

Our study does have some limitations. First, this study was conducted in one state, and even though Pennsylvania has been shown to track closely with national averages in measures of

health care utilization [109], our findings might not be nationally representative to other specific geographic regions. Second, while we are investigating three distinct drug classes, our findings might not be generalizable to other clinical practices or all medical technologies. Third, there were certain sources of influence on prescribing behavior that we were not able to quantify with our current data sources, and thus were not controlled for in the modeling strategy. Namely, due to data constraints we had no information on 1) patient health status, 2) formulary placement of the study drug of interest, or 3) amount of pharmaceutical promotion for the study drug of interest. These three factors are likely influencing at least a portion of the remaining geographic variation in prescribing behavior, and future studies could benefit from fully quantifying them.

3.5 Conclusion

These findings point to the fact that individual characteristics of physicians should be viewed in conjunction with social networks and peer connections when trying to understand variations in behavior and spending across the health care system, and also when trying to define opinion leaders to best target interventions aimed at promoting evidence-based prescribing.

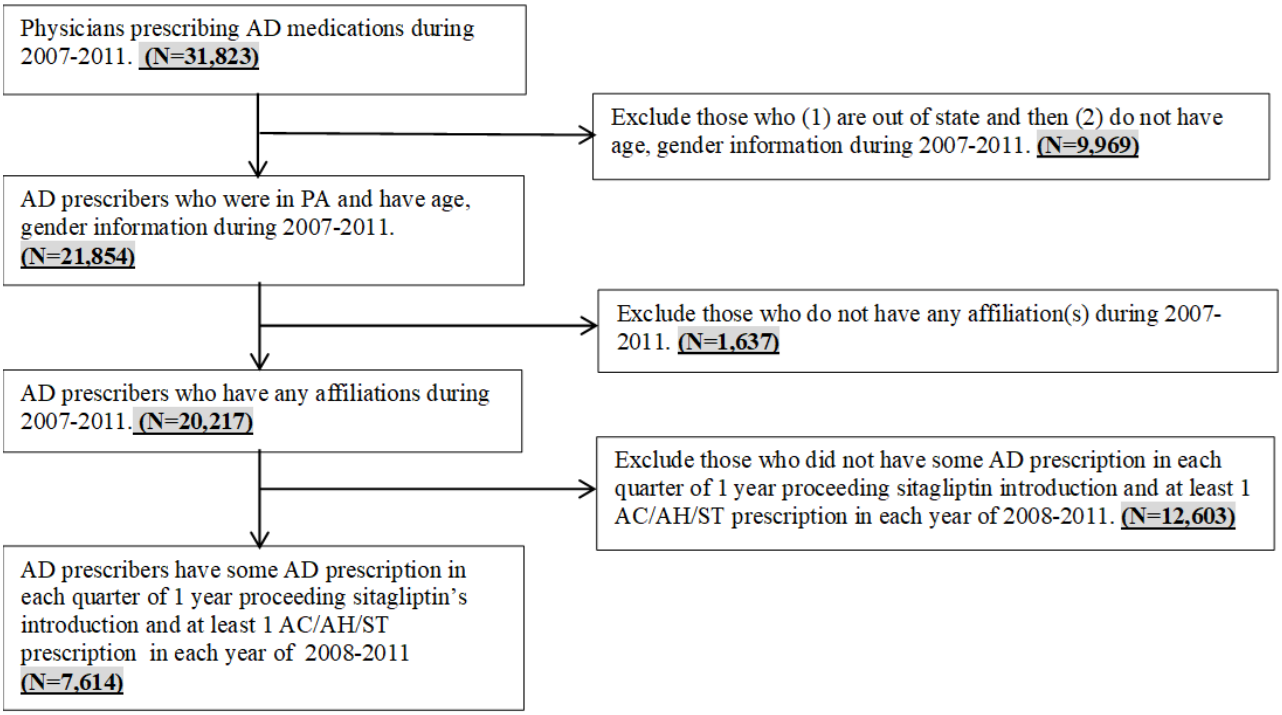
Appendix Additional Tables and Figures

Table Appendix 1 List of all Anti-Diabetic Drugs included in Study

Drug Name	Active Ingredient	Drug Sub-Class
Acarbose	Acarbose	Alpha-glucosidase inhibitors
Precose	Acarbose	Alpha-glucosidase inhibitors
Cycloset	Bromocriptine Mesylate	Dopamine-2 Agonists
Chlorpropamide	Chlorpropamide	Sulfonylureas
Byetta	Exenatide	Incretin mimetics
Amaryl	Glimepiride	Sulfonylureas
Glimepiride	Glimepiride	Sulfonylureas
Glipizide	Glipizide	Sulfonylureas
Glipizide Er	Glipizide	Sulfonylureas
Glipizide Xl	Glipizide	Sulfonylureas
Glucotrol	Glipizide	Sulfonylureas
Glucotrol Xl	Glipizide	Sulfonylureas
Glipizide-Metformin	Glipizide/Metformin Hcl	Oral combination therapy
Diabeta	Glyburide	Sulfonylureas
Glyburide	Glyburide	Sulfonylureas
Glyburide Micronized	Glyburide,Micronized	Sulfonylureas
Glynase	Glyburide,Micronized	Sulfonylureas
Glucovance	Glyburide/Metformin Hcl	Oral combination therapy
Glyburide-Metformin Hcl	Glyburide/Metformin Hcl	Oral combination therapy
Humulin 70-30	Hum Insulin Nph/Reg Insulin Hm	Insulin
Novolin 70-30	Hum Insulin Nph/Reg Insulin Hm	Insulin
Novolin 70-30 Innolet	Hum Insulin Nph/Reg Insulin Hm	Insulin
Novolog	Insulin Aspart	Insulin
Levemir	Insulin Detemir	Insulin
Lantus	Insulin Glargine,Hum.Rec.Anlog	Insulin
Lantus Solostar	Insulin Glargine,Hum.Rec.Anlog	Insulin
Apidra	Insulin Glulisine	Insulin
Apidra Solostar	Insulin Glulisine	Insulin
Humalog	Insulin Lispro	Insulin
Humalog Mix 50-50	Insulin Npl/Insulin Lispro	Insulin
Humalog Mix 75-25	Insulin Npl/Insulin Lispro	Insulin
Humulin R	Insulin Regular, Human	Insulin
Novolin R	Insulin Regular, Human	Insulin
Novolog Mix 70-30	Insuln Asp Prt/Insulin Aspart	Insulin
Tradjenta	Linagliptin	Dipeptidyl peptidase 4 (DPP-4)

Table Appendix 1 continued

Victoza 2-Pak	Liraglutide	Incretin mimetics
Victoza 3-Pak	Liraglutide	Incretin mimetics
Fortamet	Metformin Hcl	Biguanides
Glucophage	Metformin Hcl	Biguanides
Glucophage Xr	Metformin Hcl	Biguanides
Glumetza	Metformin Hcl	Biguanides
Metformin Hcl	Metformin Hcl	Biguanides
Metformin Hcl Er	Metformin Hcl	Biguanides
Riomet	Metformin Hcl	Biguanides
Glyset	Miglitol	Alpha-glucosidase inhibitors
Nateglinide	Nateglinide	Meglitinides
Starlix	Nateglinide	Meglitinides
Humulin N	Nph, Human Insulin Isophane	Insulin
Novolin N	Nph, Human Insulin Isophane	Insulin
Novolin N Innolet	Nph, Human Insulin Isophane	Insulin
Actos	Pioglitazone Hcl	Thiazolidinediones (TZD)
Actoplus Met	Pioglitazone Hcl/Metformin Hcl	Oral combination therapy
Actoplus Met Xr	Pioglitazone Hcl/Metformin Hcl	Oral combination therapy
Duetact	Pioglitazone/Glimepiride	Oral combination therapy
Symlin	Pramlintide Acetate	Amylin Analogue
Symlinpen 120	Pramlintide Acetate	Amylin Analogue
Symlinpen 60	Pramlintide Acetate	Amylin Analogue
Prandin	Repaglinide	Meglitinides
Prandimet	Repaglinide/Metformin Hcl	Oral combination therapy
Avandia	Rosiglitazone Maleate	Thiazolidinediones (TZD)
Avandaryl	Rosiglitazone/Glimepiride	Oral combination therapy
Avandamet	Rosiglitazone/Metformin Hcl	Oral combination therapy
Onglyza	Saxagliptin Hcl	Dipeptidyl peptidase 4 (DPP-4)
Kombiglyze Xr	Saxagliptin Hcl/Metformin Hcl	Oral combination therapy
Janumet	Sitagliptin Phos/Metformin Hcl	Oral combination therapy
Januvia	Sitagliptin Phosphate	Dipeptidyl peptidase 4 (DPP-4)
Tolazamide	Tolazamide	Sulfonylureas
Tolbutamide	Tolbutamide	Sulfonylureas



*Note: AD = Anti-diabetic
AH = Anti-hypertensive
AC = Anti-coagulant
ST = Statin

Figure Appendix 1 Study Flow Chart of Anti-Diabetic Prescribers in Pennsylvania

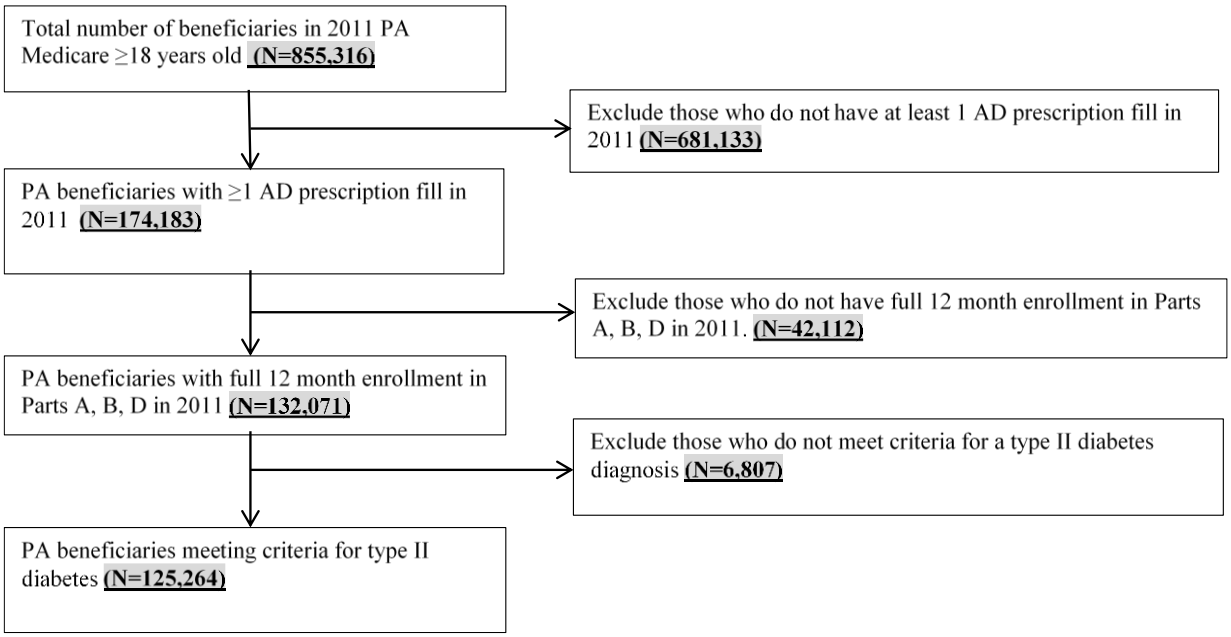


Figure Appendix 2 Study Flow Chart of Medicare Study Sample

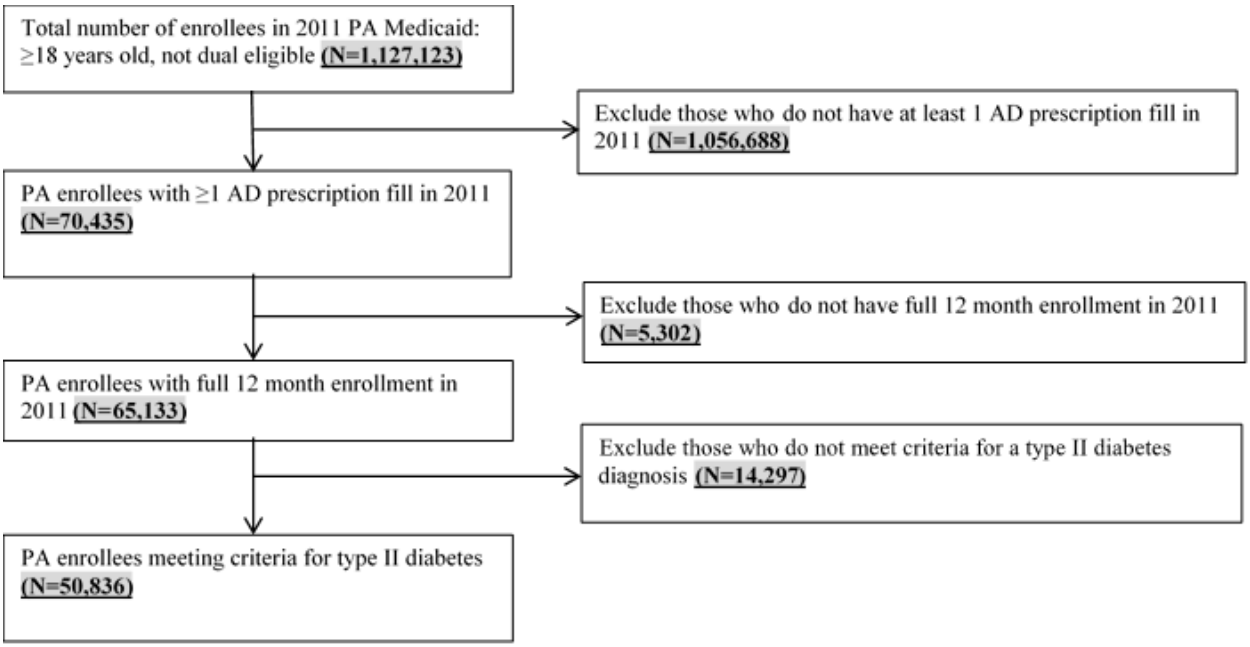


Figure Appendix 3 Study Flow Chart of Medicaid Study Sample

Table Appendix 2 Comparison of Model Fit Statistic (BIC) of Finite Mixture Models for Medicare

Number of Components	Distributions	BIC
1	Normal	495,119
1	Gamma	507,373
2	2 Normal	457,754
2	2 Gamma	460,713
2	1 Normal, 1 Gamma	457,823

Table Appendix 3 Comparison of Model Fit Statistic (BIC) of Finite Mixture Models for Medicaid

Number of Components	Distributions	BIC
1	Normal	227,798
1	Gamma	234,073
2	2 Normal	209,052
2	2 Gamma	208,988
2	1 Normal, 1 Gamma	209,674

Table Appendix 4 Comparison characteristics between components for Medicare and Medicaid Study Samples

	Medicare			Medicaid	
Variable	Lower Component	Higher Component	Variable	Lower Component	Higher Component
Age (Mean, SD)	72.4 (12.0)	72.1 (12.0)	Age (Mean, SD)	50.1 (9.9)	50.3 (10.3)
Female (%)	59.1	59.8	Female (%)	63.3	58.3
Race/Ethnicity (%)			Race/Ethnicity (%)		
White	84.4	84.7	White	50.7	49.4
Black	9.5	8.9	Black	29.2	31.5
Hispanic	3.6	3.9	Hispanic	15.1	14.2
Other race	2.5	2.6	Other race	5..0	4.9
Eligibility Type (%)			Eligibility Type (%)		
Disabled	18.8	21.3	General Assistance	13.4	12.7
Dual Eligible	35.1	41.9	Supplemental Security Income	74.1	75.9
Low Income Subsidy	42.0	49.2	TANF	11.7	10.6
Type of Drug use (%)			Type of Drug use (%)		
Oral drug only	85.8	37.6	Oral drug only	66.2	37.6
Injectable drug only	7.4	27.4	Injectable drug only	0	41.5
Combination	6.8	35.1	Combination	33.8	20.9
Elixhauser (Mean, SD)	5.3(2.9)	5.6(3.0)	Elixhauser (Mean, SD)	4.5(2.5)	4.9(2.9)

* TANF=Temporary Assistance for Needy Families

Table Appendix 5 Number of AD Prescribers and Patients

County Name	Number of AD Prescribers	Number of AD Medicare Patients	Number of AD Medicaid Patients
Adams	35	1,149	134
Allegheny	1,001	4,913	4,134
Armstrong	25	428	327
Beaver	70	784	586
Bedford	14	624	246
Berks	210	4,599	1,833
Blair	83	1,558	635
Bradford	42	1,039	253
Bucks	373	4,570	843
Butler	74	855	405
Cambria	87	1,227	680
Cameron	2	122	29
Carbon	25	1,392	175
Centre	68	1,098	278
Chester	236	3,908	494
Clarion	17	703	196
Clearfield	36	1,376	458
Clinton	18	448	185
Columbia	34	893	247
Crawford	41	1,521	423
Cumberland	161	2,231	358
Dauphin	174	1,992	986
Delaware	369	5,134	1,638
Elk	13	805	150
Erie	190	2,936	1,316
Fayette	59	1,131	1,202
Forest	0	122	24
Franklin	76	2,013	299
Fulton	7	321	52
Greene	16	401	314
Huntingdon	16	853	225
Indiana	41	579	349
Jefferson	18	875	281
Juniata	4	361	70
Lackawanna	142	3,368	724
Lancaster	309	5,618	1,476

Table Appendix 5 continued

Lawrence	39	765	443
Lebanon	62	1,471	384
Lehigh	253	4,366	1,266
Luzerne	168	5,884	1,122
Lycoming	55	1,680	461
McKean	14	879	194
Mercer	65	1,488	576
Mifflin	19	840	225
Monroe	65	2,054	541
Montgomery	608	6,547	1,097
Montour	29	193	55
Northampton	193	4,736	891
Northumberland	31	1,878	377
Perry	18	472	105
Philadelphia	1,136	12,688	15,972
Pike	13	845	116
Potter	4	284	72
Schuylkill	70	2,754	559
Snyder	13	471	91
Somerset	33	719	304
Sullivan	1	139	28
Susquehanna	14	692	121
Tioga	18	681	147
Union	23	493	86
Venango	21	878	251
Warren	13	816	128
Washington	114	1,181	701
Wayne	17	958	143
Westmoreland	186	1,708	1,253
Wyoming	16	393	97
York	217	4,364	1,005
Total	7,614	125,264	50,836

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