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Analyzing the Impact of the FDA Oncologic Drug Advisory Committee Decision on Continued Utilization of Avastin for the Treatment of Metastatic Breast Cancer

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Analyzing the impact of the Oncologic Drug Advisory Committee recommendation on Avastin prescribing for women with metastatic breast cancer

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2010

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Abstract

Analyzing the impact of the Oncologic Drug Advisory Committee recommendation on Avastin prescribing for women with metastatic breast cancer

By Caitlin M. Koris

Objectives

Breast cancer is the second most common cause of cancer-related death. Women with metastatic disease have low survival rate due in part to the lack of effective treatments. In 2008, the U.S. Food and Drug Administration (FDA) granted an accelerated approval of Avastin to treat metastatic breast cancer (MBC) in combination with paclitaxel. In July 2010, the Oncologic Drug Advisory Committee (ODAC) voted unanimously to withdraw the approval. This decision was contested by many including the European Medicine Agency (EMA) and the National Comprehensive Cancer Network (NCCN). Despite this disagreement, the FDA revoked the approval by the end of 2011. This study examined the impact of ODAC's decision on prescribing practices.

Methods

Truven MarketScan™ claims data from 2006 – 2011 was used as the data source. The sample included women ≥18 years who received specific chemotherapy agent listed in the NCCN treatment guidelines for MBC. A difference-in-difference model compared Avastin use before/after the 2010 ODAC decision using colorectal cancer to form the control group.

Results

Providers were about 41% ($p<0.0001$) less likely to prescribe Avastin after 2010. Region impacted this associated. Prescribers in North central, South and West were approximately 3.3 – 10.0% ($p<0.0001$) more likely to prescribe Avastin than prescribers in the Northeast.

Conclusion

The magnitude of the utilization decrease in 2011 is higher than expected. However, we speculate that conflicting information on Avastin's effectiveness led to greater reliance on the ODAC decision by providers. Only one other study has examined the impact of ODAC and our results are consistent with their findings. The impact of region on prescribing practices may be due to the high concentration of academic medical centers in the North east. The FDA needs to fully understand the impact of their advisory bodies on influencing providers when considering the public's health needs.

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INTRODUCTION

The U.S. Food and Drug Administration (FDA) must simultaneously protect consumers from harmful products and make effective treatments available quickly. These treatments must go through several stages of clinical trials before the evidence is sufficient to demonstrate its safety and effectiveness and it is made available to consumers. When patients are in desperate need for medications to treat a life threatening illness the time it takes for a drug to get approved may be too long.

In 1992, the FDA adopted regulations that allowed pharmaceutical products to enter the market before all safety and efficacy studies were concluded to allow promising products to get to patients faster when an unmet medical need existed. This 'accelerated approval' utilizes surrogate endpoints as a proxy for clinical benefit, which takes longer to measure.[1] Products that receive an accelerated approval must continue undergoing further clinical testing using primary endpoints that more stringently evaluate safety and effectiveness.[1] Many oncologic products are eligible for accelerated approval mechanisms because of the desperate need for effective treatments; this is especially true for metastatic breast cancer.

Breast cancer is the most prevalent cancer in women in the developed world and is the second most common cause of cancer-related death. Women with metastatic disease typically have a 5-year survival of only 24% due in part to the lack of effective treatments.[2] Treatment for breast cancer is extremely dependent on histology of the tumor and status of three main biomarkers: estrogen receptor, progesterone receptor and Human Epidermal Growth Factor Receptor 2 (HER2).[2] Those with the HER2 negative mutation have limited treatment options.

History of Avastin

Early clinical testing by Roche-Genentech on its new monoclonal antibody bevacizumab (trade name Avastin) demonstrated effectiveness to treat metastatic breast cancer for the HER2 negative population. Avastin was already FDA approved as a first-line treatment for metastatic colon and rectum cancer, as a second-line treatment for colorectal cancer, and for the treatment of metastatic non-small cell lung cancer. In February of 2008, the label was updated to include Avastin in combination with paclitaxel as a first-line treatment for women with metastatic HER2 negative breast cancer. The FDA granted the drug an accelerated approval contingent on the completion of the studies AVADO and RIBBON-1.

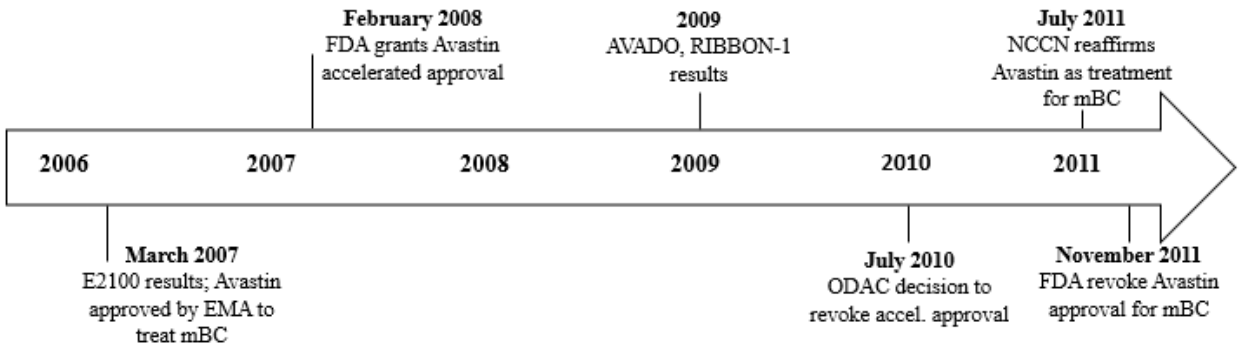
Three years later in July 2010, a group of independent medical reviewers called the Oncology Drug Advisory Committee (ODAC) were brought before the FDA to review evidence from the AVADO and RIBBON-1 trials. The FDA relies on advisory committees like ODAC to provide independent expertise and guidance on the safety and efficacy of medical products. There are over 50 committees utilized by FDA made up of experts from academia, physicians, consumers, and patients.[3] Members of advisory committees are thoroughly investigated for potential conflicts of interest.[3] The July 2010 ODAC meeting was held over two days in a public forum. During that time oncologists, Roche-Genentech, patients, and other experts presented to the committee. At the end, ODAC voted unanimously to withdraw Avastin's accelerated approval and gave this recommendation to the FDA.

In anticipation of the FDA's ultimate decision about the approval of Avastin, the National Comprehensive Cancer Network (NCCN) met in July 2011 to review AVADO and RIBBON-1 and provide their own recommendation. NCCN is a consortium of the top 25 leading cancer centers that develop recommendations for prevention, diagnosis, and management of most cancers.

Hospitals and providers look to the NCCN's treatment guidelines when making medical decisions.[4] In addition, most major payers, including US Healthcare, Aetna, and CMS use NCCN guidelines to determine coverage policies.[4] The NCCN committee voted unanimously in favor of Avastin; they reaffirmed the positive benefits of Avastin and left it as a treatment option for women with metastatic breast cancer in the 2011 treatment guidelines.[5] This created discordance between the two expert groups NCCN and ODAC.

Later in 2011, FDA Commissioner Dr. Margaret Hamburg announced that the agency revoked Avastin's approval due to severe side effects and limited proof of benefit. "After reviewing the available studies it is clear that women who take Avastin for metastatic breast cancer risk potentially life-threatening side effects without proof that the use of Avastin will provide a benefit, in terms of delay in tumor growth that would justify those risks. Nor is there evidence that use of Avastin will either help them live longer or improve their quality of life."[6] The removal of metastatic breast cancer indication on the drug's label occurred on December 20, 2011. The interpretation of clinical trial results was an integral piece of the ODAC recommendation and FDA decision.

Figure 1. Timeline of Avastin History



Clinical Trials

Avastin is a monoclonal antibody that works against vascular endothelial growth factor. Its activity hampers a tumor's ability to grow a new network of blood vessels which allow it to spread. By interfering with angiogenesis, Avastin is thought to help halt the growth of metastatic breast cancer.[7] Evidence gathered in a phase III trial, called E2100, led to the FDA's accelerate approval for the treatment of metastatic breast cancer.[8-10]

Study E2100 randomized patients to receive either paclitaxel or paclitaxel plus Avastin. The results published in early 2008 concluded that adding Avastin to paclitaxel significantly prolonged the time a patient can live with a disease without it getting worse (progression-free survival) compared to paclitaxel alone by about 5.5 months (median, 11.8 vs 5.9 months; $p<0.001$) [10]. However, there was no significant difference in overall survival in the two study arms. Toxicity profiles were similar, but 15% of those receiving Avastin had severe hypertension and severe headaches while those receiving only paclitaxel did not.[10, 11]

In 2009, results from two additional phase III trials called AVADO and RIBBON-1 became available. In the AVADO study, women receiving Avastin in combination with a taxane saw an improved progression-free survival of 1.9 months ($p<0.001$).[12] In the RIBBON-1, the trial results found improved progression-free survival of 1.2- 2.9 months dependent on the chemotherapy regime. In both studies there was no improvement to overall survival [13]. The results of these studies and the decision by ODAC once more ignited concerns about the benefits of using a surrogate endpoint like progression-free survival as a substitute for overall survival. In metastatic breast cancer, patients frequently receive 3-6 lines of treatment, making it exceedingly difficult to measure the overall effect of just one regime. Therefore, surrogate endpoints like progression-free survival are commonly employed. In a survey to 564 physicians, 57.3% felt

progression-free survival was a good substitute. [14]. ODAC expressed concerns stating that the "FDA believes that in accepting progression free survival as a regulatory endpoint, a close examination of the magnitude of improvement in progression free survival must be closely evaluated in a risk-benefit analysis. Because the treatment with [Avastin] is associated with considerable toxicity, the magnitude of progression free survival improvement, especially if not supported by an improvement in overall survival, should be substantial, clinically meaningful, and be able to be replicated in additional trials."[3]

Impact of Cost

There has been significant speculation about the role of cost in the Avastin case. Avastin can cost around $8,000 per month or $85,000 for 11 courses[15]. It is not considered cost-effective in breast cancer patients based on commonly-accepted thresholds [16-18]. A survey of physician participants found overwhelming agreement (78%) that cost played a role in the FDA's decision to withdraw approval for Avastin [14]. However, the FDA reviews drug/device applications without giving any weight to economic cost. The United Kingdom National Institute for Health and Clinical Excellence (NICE) has publicly stated that the benefits do not outweigh the cost; "uncertain clinical benefit, combined with the amount of money the National Health Service is being asked to pay for the drug."[15]

Despite the ODAC and NCCN disagreement, debate over the benefits of progression-free survival surrogate endpoint, and the high drug costs there is continued use of Avastin to treat women with metastatic breast cancer. This study will examine the impact of ODAC's recommendation to the FDA on the continued use of Avastin. It will quantify the impact to help us understand of the influence that an expert panel and/or government 'approval' can have on provider behavior.

LITERATURE REVIEW

Technology Diffusion

Once a medication is released into the market it can be challenging to remove it. Diffusion theory studies how new technologies are disseminated through different channels over time within markets and society.[19, 20] Diffusion theory can help us understand the factors exerting influence on removing a technology from the market. It has been especially difficult to remove Avastin from the market because of its continued availability for the treatment of other cancers such as colorectal and glioblastoma. Because of its continue availability, Avastin can still be prescribed "off label" by physicians for the breast cancer patients. It is not uncommon for cancers to be treated with an off-label medication after discussions between a physician and patient.[4, 15]

Studies conducted by Johnson et al. and Dagher et al. reviewed 35 products (drugs and biologics) that received an accelerated approval for 47 indications from December 1992- July 2010. They found that 26 indications were converted to regular approval following the required confirmatory post-approval trials. Three indications did not show clinical benefit in the post-approval trials and were eventually removed from the market.[21] This includes: amifostine (Ethyol), gemtuzumab ozogamicin (Mylotarg), and Gefitinib (Iressa). Interestingly, all three were intended for an oncologic indication. It took 10 years for amifostine to be removed from the market and gemtuzumab ozogamicin 10.1 years, leading Johnson et al and Dagher et al to conclude that there are inefficiencies in removing ineffective drugs from the market.[1, 21] However, gefitinib was removed in 2.4 years following its accelerated approval but this drug remained available to patients receiving benefit from it before 9/15/2005.

Withdrawal of drugs from the market has remained relatively constant over the past decade. An average of 1.5 drugs per year (range from 0-4) have been withdrawn since 1993.[22] However,

with prescription drug use increasing by 42% from 1997- 2002, it is possible that the impact of these withdrawals is of greater public health concern.[22]

Impact of FDA Regulations/Policies

The impact of FDA Advisory Committee/Panel recommendations have been widely studied in the literature. The bulk of the literature quantitatively describes the impact of these recommendations on antidepressant prescribing. Around the mid-2000s there was significant concern about the association between antidepressants and suicidality in children and teenagers. After two meetings on September 13-14, 2004 the FDA Psychopharmacologic Drugs Advisory Committee and Pediatric Advisory Committee advised these drugs increased suicide risk among children. Later that year, the FDA issued a "black box warning." Black box warning is a regulatory tool that requires manufacturers to explain severe product risks to consumers in clear language on the product's label. This all led to significant decreases in antidepressant prescribing between 18-31%.[23-26] The impact on prescribing practices had differential impacts based on physician type (i.e. primary care, psychiatrist, other) and age group.[26] One study conducted a survey asking Canadian physicians if the Advisory Committees influence their prescribing behavior. Eighty percent of those who knew about the warning changed their behavior.[27]

These studies all found advisory committees to have a significant impact. However, advisory committee recommendations are not happening in a vacuum. Physician prescribing can be influenced by many things such as scientific evidence from clinical trials, peers, direct-to-consumer advertising (DTCA), physician- directed marketing, and the media. One study by Bradford et al. (2014) measured the impact of black box warnings on prescribing of pain medications accounting for these outside factors.[28] After controlling for pre-released information (i.e. media, DTCA, etc.) and found the black box warning led to a 2.8% ($p<0.01$)

decrease in the probability of patients having an NSAID (nonsteroidal anti-inflammatory drugs) prescription for a COX-2 medication.[28]

Few studies have quantified the impact of an ODAC recommendation. One study, by Presusser et al. looked at the impact of ODAC's recommendation to withdraw Avastin for the treatment of metastatic breast cancer on prescribing practices in Austria- where the drug remains approved by the European Medicine Agency (EMA).[29] The study looked at the absolute number of Avastin prescriptions administered in all Austrian acute care hospitals using a national health care database from January 2006 - June 2011. Avastin prescriptions for other indications were also studied during this time frame which served as the comparison group. Results showed there was a steady decline in Avastin prescriptions for metastatic breast cancer falling 51% by June 2011. Minor changes in the control group indicated that Austrian physicians were significantly influenced by the FDA's statement.

The literature on the impact of advisory meetings and black box warnings is extensive. However, there has been minimal quantitative work looking at the impact of ODAC meetings on prescribing of chemotherapies. To fill this gap, we studied the impact of a 2010 ODAC decision on Avastin prescribing in the U.S.

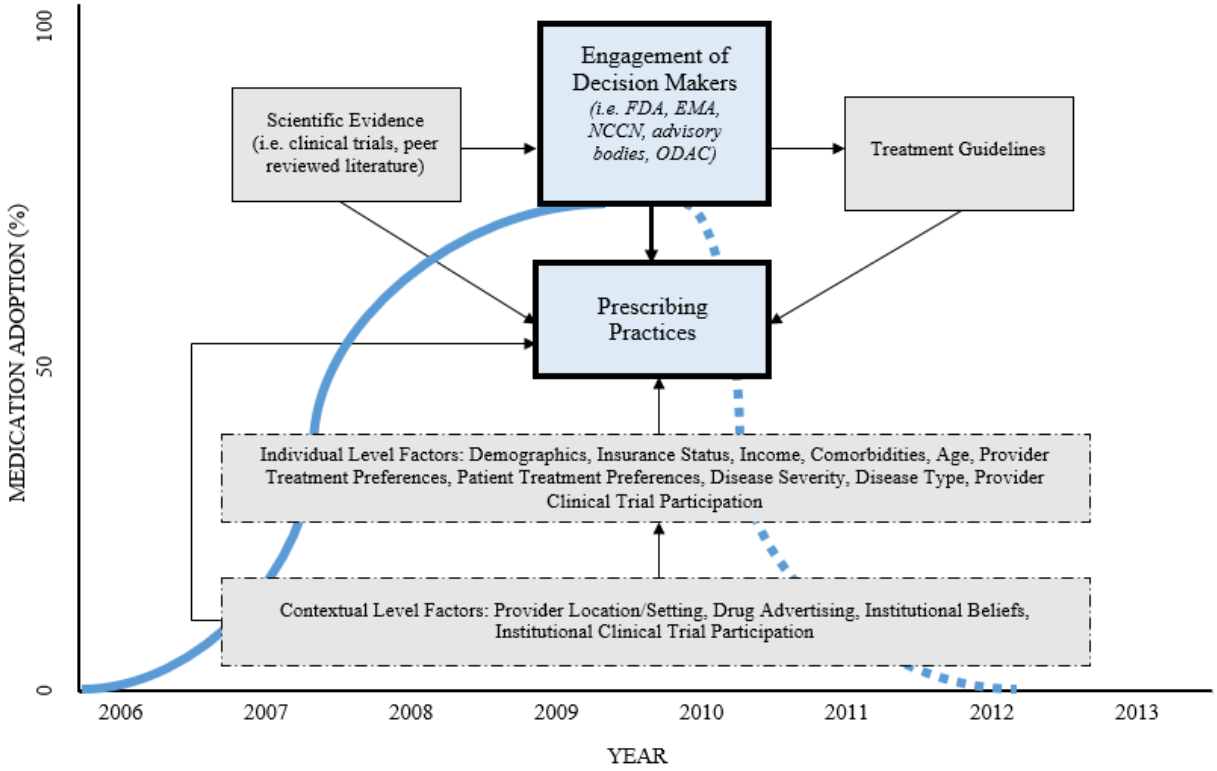
METHODS

Conceptual Model

The conceptual model for this study is drawn from diffusion theory. This theory looks at the process through which "an innovation is communicated through certain channels over time among members of a social system."[19] Diffusion studies have found a "S-shaped curve" will commonly predict technology adoption. The diffusion of a technology is dependent on societal pressure and individual perception of the product.[19, 20, 30] Individuals adopt a technology after others have used it successfully. It is unclear whether these influences also impact the withdrawal of a new technology from the market. In situations of technology 'abandonment,' society has already accepted the technology and everyone has used it. Despite the uncertainty of the role diffusion theory has in technology abandonment, it was still used to help inform the research.

The research question focuses in on the tail of the "S-shaped curve" in the conceptual model (Figure 2.) to show that technology use falls rapidly when initially withdrawn from market. It then continues to fall but at a decreasing rate before leveling off to zero. Factors that cause technology use (in this case the chemotherapy drug Avastin) to fall at a decreasing rate include conflicting advice from key opinion leaders, contradictory statements between NCCN and FDA advisory body, and differing interpretations of clinical trial results. These factors create confusion and lead to continued use of the technology in the market. Patient characteristics such as mutation status, disease severity, and treatment history also continue to influence the use of the technology because there are minimal treatment options for women with HER2 negative metastatic breast cancer. The influence of additional characteristics like individual and physician preference also cannot be measured.

Figure 2. Conceptual Model of Diffusion Theory



Study Sample Identification

Institutional Review Board: Emory University

An exemption was received on 11/11/2014 since this study uses secondary data that are de-identified.

Data Source

This study will use Truven Analytics MarketScan™ claims data from 2006 – 2011.

Background

It is challenging to identify enrollees in claims data with metastatic disease. Although primary cancer diagnoses are included in claims data, information on secondary neoplasms (indicating metastatic disease) is underreported.[31] Algorithms that only rely on International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) codes for a primary cancer and secondary neoplasm will artificially inflate the number of metastatic cases.[31] Some

have estimated this method will only capture around 50% with truly metastatic disease and potentially include those who are not truly metastatic.[31] Algorithms using ICD-9-CM codes and additional indicators such as chemotherapy procedures and specific chemotherapy agents have better specificity and accuracy in identifying metastatic disease.[31, 32] Therefore, a combination of diagnosis and chemotherapy regimens used to treat MBC will be used as inclusion/exclusion criteria for this study (Figure 3.).

The chemotherapy agents selected for the inclusion criteria were pulled from The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. This list (Table 1. and Table 2b.) mainly includes chemotherapies administered as single agents. According to NCCN guidelines, single agents are the preferred treatment for metastatic disease as they help preserve quality of life for these women.[33] Combination therapy is typically used to treat stage I, II, or III disease, therefore, women receiving combination therapy will be excluded.[34] This is true for all combinations except for those including Avastin (Table 2b.).Women with early stage disease may receive chemotherapy, however, surgery and radiation is the most common treatment[35].

Study Sample Identification

Using the outpatient file of MarketScan^{TM} data, women 18 years and older with a breast cancer diagnosis were identified in the claims data. This was done by reviewing the diagnosis code variables for any ICD-9-CM code containing 174.xx. This coding remained consistent throughout the study period. Women with colorectal cancer were also identified using diagnosis codes 153.xx, 154.0, 154.1, 154.8. These women served as the control group in the analysis. All other women not meeting these requirements were excluded.

After claims related to breast cancer were identified and all others excluded, they were screened for the type of claim by looking at the procedure variable. Only women with a breast cancer diagnosis receiving either a single chemotherapy agent or chemotherapy agent in combination with Avastin were included. The complete list of single and combination therapy agents can be found in Table 1. All other women not meeting these requirements were excluded.

Figure 3. Algorithm for Identification of Study Sample: Metastatic Breast Cancer

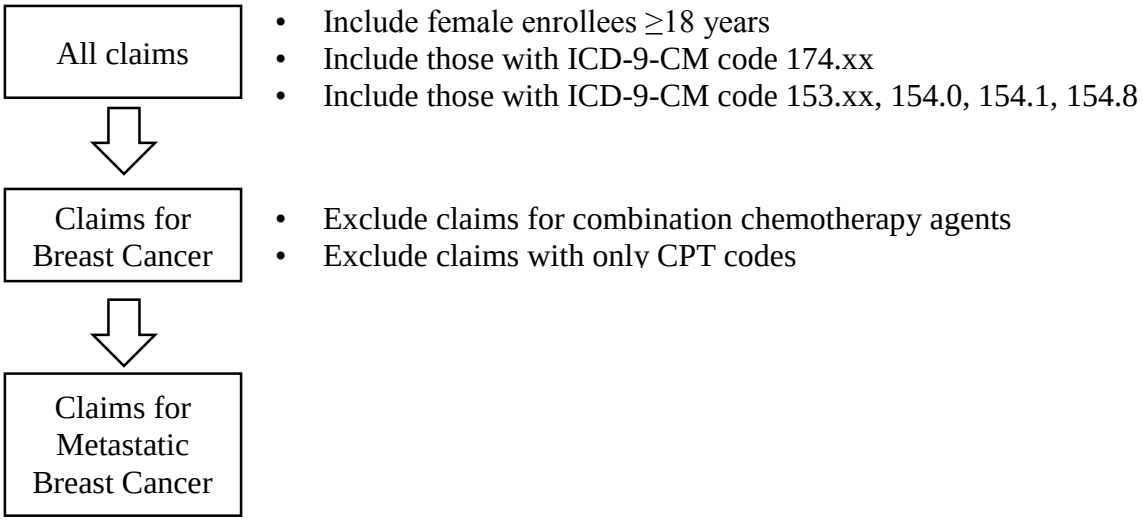


Table 1. Single and Combination Agents Used to Treat Metastatic Breast Cancer According to NCCN Guidelines and Medical Coding in Truven MarketScan™ data

Chemotherapy Agent	HCPCS
Bevacizumab (Avastin)	J9035 (injection, 10mg)
Combination Agents:	
Avastin, Paclitaxel	J9035, J9264
Avastin, Docetaxel	J9035, J9171
Avastin, Vinorelbine	J9035, J9390
Single Agents:	
Gemcitabine (Gemzar)	J9201 (injection, 200mg)
Capecitabine (Xeloda)	J8520 (oral, 150mg)
Paclitaxel (Abraxane)	J9264 (injection, 1mg)
Doxorubicin	J9000 (injection 10mg)
Taxotere (Docetaxel)	J9171 (injection, 1 mg)
Carboplatin	J9045 (injection, 50mg)
Cyclophosphamide	J9096 (lyophilized, 1g)
Cisplatin	J9062 (injection, 50mg)

Epirubicin	J9178 (injection, 2mg)
Ixabepilone	J9207 (injection, 1mg)
Vinorelbine	J9390 (injection 10mg)
Eribulin (Halaven)	J9179 (injection, 0.1mg)

Coding in Claims Data

Truven MarketScanTM is a commercial claims database. The procedure variable is coded in either Current Procedure Terminology (CPT) or Healthcare Common Procedure Coding System (HCPCS). CPT codes indicate a chemotherapy agent was administered and specifies the route of administration and dosage, however, it does not report which drug was administered. HCPCS refer to the specific agent being administered along with the dosage which can allow for more appropriate billing. Chemotherapy agents used to treat metastatic disease are expensive and HCPCS code are used on the claims for providers to receive full reimbursement from payers.[36, 37] Dichotomous variables will be created for the 13 specific chemotherapy agents and 3 chemotherapy combinations recommended by the NCCN and international guidelines. These variables (*drug1-13, combo1-3*) were generated from the procedure variable using the HCPCS coding. Creation of these variables will show what treatment regiments each woman received each year.

Variables

Independent Variable

The independent variable is the year of treatment from 2006 to 2011. A dichotomous variable called *post* was created that organized the years 2006- 2010 as the 'pre' policy shock period and 2011 as the 'post' policy shock period. A robustness test was conducted to determine how the year 2010 should be categorized.

Dependent Variable

The dependent variable will be measured by the construct *Avastin use*. This will be generated as a proportion; the denominator includes all women receiving single-agent chemotherapy and the numerator includes the subset of those women using Avastin. The algorithm for creating this proportion is described above. It is built off of previously published literature on how to identify metastatic disease in claims data. [31, 38]

Covariates

Covariates include enrollee age, insurance type, and enrollee location by U.S. region at time of first chemotherapy agent claim. *Enrollee age* is a continuous variable from 18 years upward. *Insurance type* is a categorical variable and includes Health Maintenance Organization (HMO), Point of Service (POS), POS with capitation, Exclusive Provider Organization (EPO), Preferred Provider Organization (PPO), Consumer Directed Health Plan/High Deductible Health Plan (CDHP/HDHP), and Basic/Major Medical. Only CDHP and HDHP were grouped together. *Region* refers to location of enrollee claim and is categorical including Northeast, North central, South, West, and Unknown. The outpatient file of Truven MarketScan^{TM} contains 13 variables. The data is organized by claim; therefore, each patient may appear multiple times in the data set with a different service date and specific claim. Demographic and insurance details are available in the enrollment file of the claims data. The enrollment and outpatient files can be linked by the unique patient identifier. All covariates were merged into the dataset from the Enrollment file in the Truven MarketScan^{TM} data.

Research Question

This research is studying the impact of the FDA's Oncologic Drug Advisory Committee decision in 2010 on the continued use of the chemotherapy Avastin to treat women with metastatic breast cancer.

Hypothesis

The hypothesized relationship is that there will be a significant decrease in Avastin use immediately following the ODAC decision, however, this use will not fall to zero.

Research Design

Using Truven MarketScan^{TM} claims data, this study measured the relationship between the year of the Avastin claim and the proportion of women treated with Avastin using a quasi-experimental research design.

Data Analysis

A difference-in-difference model was used to analyze Avastin use. This analysis was performed using statistical software SAS version 9.4 and STATA SE. In the analysis, an interaction term was generated by the variables *treatment* and *post.* This allowed us to quantify the change in Avastin use before and after the FDA decision. Covariates *age, region,* and *insurance* were included in the model. The proportion of women that received Avastin to treat colorectal cancer (an FDA approved indication since 2004) served as the control in order to rule out the possibility of any general changes in Avastin use unrelated to the FDA such as supply problems. Similar methodology was utilized by Preusser et al. to study the impact of the 2010 ODAC statement on absolute counts of Avastin administration in Austria, outside of FDA jurisdiction.[29]

The use of control groups strengthens the internal validity of the study. In addition, comparing utilization over time within the same population controls for intrinsic factors specific

to patients that may change over time. This helps strengthen confidence in the association seen between the independent/dependent variables.

Sensitivity Analysis

A sensitivity test was conducted in order to determine if the year of the ODAC decision (2010) should be categorized as 'pre' or 'post.' The difference-in-difference model was run three times. In the first iterations, 2010 was included in 'pre.' In the second iteration it was included in 'post' and in the third it was excluded. When 2010 was excluded, the coefficient on the interaction term most closely resembled the first iteration where 2010 was categorized in 'pre.' Additionally, the trend line through 2010 more closely resembles the trend line in 2006-2009 (Figure 1.). For these two reasons, 2010 was categorized as 'pre.'

RESULTS

During the study period from 2006-2011 there were 82,195 women with metastatic breast cancer and 91,391 women with colorectal cancer. The average age of women with metastatic breast cancer is around 52 years for breast cancer and around 54 years for colorectal cancer (Table 2a.). The difference in age between the two groups is statistically significant. The two groups also have similar regional distributions around the U.S, however, these differences are also statistically significant. The majority of the study sample resides in the south; 46% of those with breast cancer and 45% of those with colorectal cancer. The next major residence is north central U.S.; 26% and 25% respectively. Around 13-15% of the study population lives in the Northeast and 14-15% in the West.

The most common insurance type for women with breast cancer and colorectal cancer is Preferred Provider Organization (PPO) at 67-68%. The second most common plan type is Health Maintenance Organization at 12%. Point of Service (POS) plans are the third most common type held by around 9% of both groups. POS plans with capitation are held by less than 1% of women in both groups. The remaining insurance plan types (Exclusive Provider Organization, Consumer Driven Health Plan/High Deductible Health Plan) are used by less than 5% of the sample. Despite similarities, all differences in plan type between women with breast cancer and colorectal cancer are statistically significant ($p<0.0001$).

Avastin use also differed between women with metastatic breast cancer and colorectal cancer. Avastin was prescribed 8.66% to women with breast cancer compared to 6.89% for women with colorectal cancer over a 5 year period. All sample characteristics are summarized below in Table 2a.

TABLE 2a. Characteristics of women with metastatic breast cancer and colorectal cancer between 2006 -2011

	Metastatic Breast Cancer n= 82,195	**Colorectal Cancer** n= 91,391	p-value*
Mean age (std dev)	51.87 (7.51)	54.31 (6.90)	<0.0001*
Region (%)			
Northeast	12.56	14.51	<0.0001*
North central	25.84	25.23	
South	45.69	45.01	
West	15.03	14.28	
Unknown	0.88	0.98	
Health Insurance Plan month 1 (%)			
Basic/ Major Medical	3.82	4.83	<0.0001*
EPO	1.45	1.59	
PPO	68.71	67.33	
CDHP/ HDHP	4.08	4.11	
HMO	12.40	12.17	
POS	8.87	9.32	
POS with capitation	0.67	0.65	
Avastin Use 2006-2011 (%)			
Prescribed	8.66	6.89	<0.0001*
Not Prescribed	91.34	93.11	

* Significance level α= 0.01

Table 2b. describes the use of chemotherapy agents used by women with metastatic breast cancer by year, from 2006-2011. The proportion of women using Avastin as a single agent increases from 6.12% in 2006 to 11.24% in 2009 then decreases to 4.46% by 2011. Similar trends are seen when Avastin is used in combination with chemotherapies Paclitaxel, Docetaxel, and Vinorelbine. Avastin and Paclitaxel in combination increases from 1.67% in 2006 to 3.66% in 2009 then decreases down to 1.26% in 2011. Avastin and Docetaxel increases from 0.84% in 2006 to 1.16% in 2009 then decreases down to 0 by 2011. Avastin and Vinorelbine in combination remains around 0.65-0.68% between 2006 -2009 then decreases to 0.17% by 2011. The most frequently used chemotherapy agents between 2006 -2011 are Doxorubicin and Herceptin; around 35.1% and 37% respectively. Anti-metabolite drug Gemcitabine is used consistently between 2006

-2011 at an average of 6.4%. Taxane drug Paclitaxel is also used consistently over the years at an average of 7.3%.

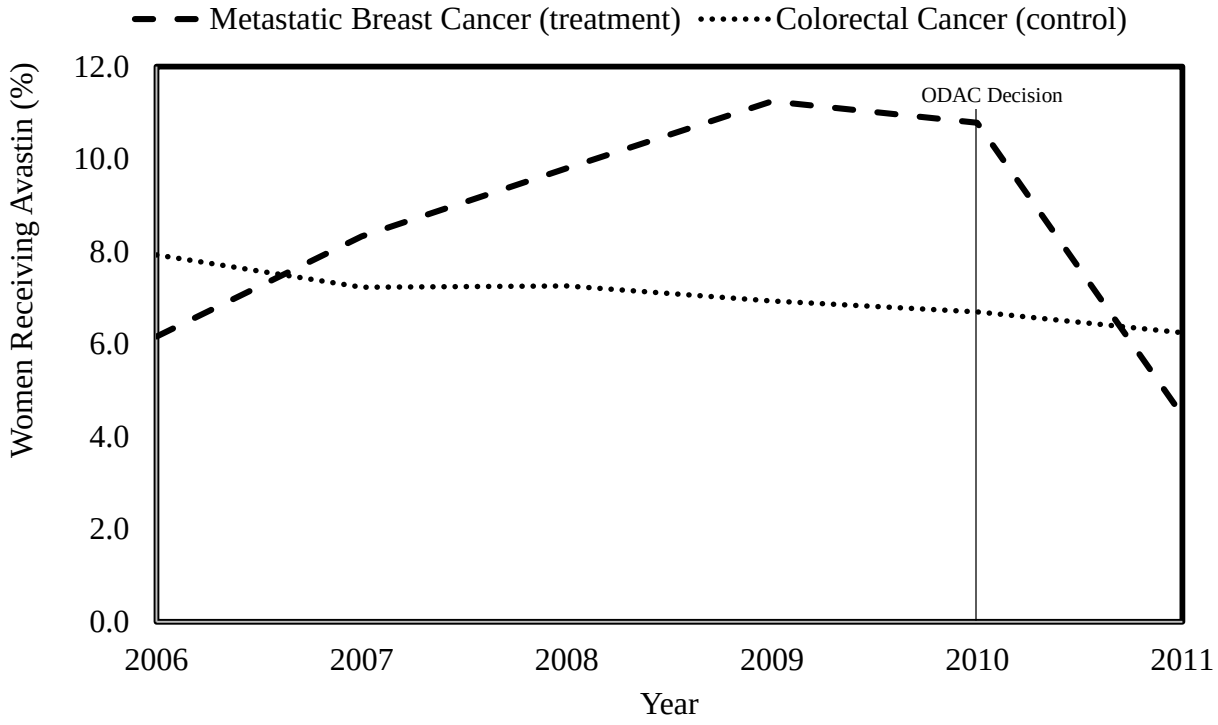
TABLE 2b. Chemotherapy Use by Women with Metastatic Breast Cancer, 2006-2011

Annual utilization frequencies of chemotherapy agents (%)	**Year**					
	2006 (n= 6,452)	**2007** (n= 12,090)	**2008** (n= 14,259)	**2009** (n=16,816)	**2010** (n= 15,667)	**2011** (n= 17,446)
Targeted Therapy						
Avastin	6.12	8.33	9.80	11.24	10.74	4.46
Chemotherapy Combinations with Avastin						
Avastin, Paclitaxel	1.67	2.80	3.38	3.66	3.61	1.26
Avastin, Docetaxel	0.84	0.84	0.92	1.16	0.00	0.00
Avastin, Vinorelbine	0.68	0.85	0.65	0.68	0.43	0.17
Anti-metabolites						
Gemcitabine	7.36	6.15	5.88	5.97	6.45	6.59
Capecitabine	0.26	0.37	0.25	0.26	0.20	0.31
Taxane						
Paclitaxel	5.42	7.39	7.53	7.71	7.99	7.80
Anthracyclines						
Doxorubicin	43.21	37.12	28.38	27.82	36.08	38.08
Other Single Agents						
Docetaxel	19.96	22.27	27.66	26.94	0.13	0.02
Carboplatin	3.75	3.27	2.99	2.89	6.03	5.62
Cyclophosphamide	0.67	0.56	0.37	0.34	1.88	0.01
Cisplatin	0.20	0.17	0.18	0.14	0.29	0.01
Epirubicin	4.85	4.20	2.92	2.24	3.76	3.93
Ixabepilone	0.00	0.00	0.01	3.06	3.64	2.92
Other microtubule agents						
Vinorelbine	5.24	4.90	4.24	4.00	4.45	4.27
Eribulin	0.00	0.00	0.00	0.00	0.00	0.02
Treatment for HER2+						
Herceptin	34.44	34.85	34.92	33.55	40.38	42.52
Lapatinib	0.00	0.06	0.16	0.09	0.10	0.12

Figure 3. depicts the rise in Avastin adoption and then the decrease in use following the ODAC ‘policy shock’ in 2010 for the treatment of metastatic breast cancer. The figure also includes the utilization of Avastin to treat colorectal cancer as the control group against which the

Avastin 'intervention' group is measured. A small decline in Avastin use from 8-6% for colorectal cancer is observed during the study period.

Figure 3. Proportion of Women Receiving Avastin Annually between 2006 -2011



In Table 3. we present the marginal effects of the 2010 ODAC decision. The model shows that there is a statistically significant 4.6 percentage point reduction, or a 40.9% decrease, in women receiving Avastin for treatment of their metastatic disease after 2010 from a base of 11%. A statistically significant 1.5 percentage point increase of drug use following 2010 was seen in women living in North central, South, and Western regions of the U.S. Using the baseline proportions displayed in Table 2., we find a 5.80% increase for women living in North central, 3.28% increase for women living in the South, and 9.98% increase for women living in the West. Age and most insurance categories do not have a statistically significant impact on Avastin use following the 2010 policy shock. However, women on Point of Service (POS) plans with capitation

did see a statistically significant 2.5 percentage point increase in Avastin use after the policy (0.005). This can be translated into a 3.7% increase.

Table 3. Difference in Difference Model of Avastin Use Comparing Time Period 2006-2010 to Time Period 2011

Avastin	**Marginal Effects**	**Std. Error**	**p-value***	**Baseline Proportion**
Policy Effect (post x treatment)	-4.588	0.330	<0.001*	11.24
Post	-0.683	0.224	0.002*	--
Treatment	2.726	0.154	<0.001*	--
Age	0.015	0.009	0.120	51.87
Region (*reference North east)*				
North central	1.473	0.235	<0.001*	25.84
South	1.535	0.217	<0.001*	45.69
West	1.533	0.261	<0.001*	15.03
Unknown	0.533	0.734	0.468	0.88
Health Insurance Plan *(reference basic/major medical)*				
EPO	-0.245	0.640	0.702	1.45
PPO	0.496	0.336	0.141	68.71
CDHP/HDHP	0.992	0.467	0.034	4.08
HMO	-0.303	0.382	0.426	12.40
POS	0.031	0.397	0.939	8.87
POS with capitation	2.528	0.893	0.005*	0.67
_cons	0.046	0.007	<0.001*	--

* Significance level α= 0.01

DISCUSSION

Summary

The FDA ODAC decision resulted in an approximately 41% decrease in the utilization of Avastin to women with metastatic breast cancer between 2006- 2011. The decrease in utilization is expected given ODAC's association with the FDA which has prominence and legal reach.

Conclusion

Although a decrease was hypothesized, the magnitude is surprisingly high. However, we speculate that conflicting information on Avastin's effectiveness caused primarily by E2100, AVADO, and RIBBON-1 clinical trials and continued promotion of Avastin benefits by NCCN and EMA led to greater reliance on the ODAC decision by providers. . As described earlier, NCCN is an alliance of 25 of the world's leading cancer centers who develop recommendations for prevention, diagnosis, and management of most cancers. Most major public and private payers such as Aetna, Center for Medicaid & Medicare Services, United Healthcare, etc. base their coverage determinations on NCCN guidelines, which are published annually.[4] EMA is Europe's equivalent to the FDA; they are a regulatory body for the entire European Union.[39] Following ODAC's decision, they released a statement saying "For Avastin in combination with paclitaxel, the Committee concluded that the benefits continue to outweigh the risks, because the available data have convincingly shown to prolong progression-free survival of breast cancer patients without having a negative effect on the overall survival."[39] Despite these supporting statements the ODAC recommendation had the greatest influence on prescribers.

Interestingly, the likelihood of women continuing to receive Avastin after the ODAC decision was impacted by region. As discussed in the results, women living in the South, West, or North central U.S. were more likely to receive Avastin then women living in the Northeast.

Although there are many distinguishing regional factors, one salient variable is the high concentration of academic medical centers (AMC) in the Northeast. AMCs are typically first to adopt and disseminate new knowledge and technology[20] and are the institutions most likely to conduct clinical trials. This may have caused the ODAC findings to the population in this region faster than in other regions of the United States.

Limitations

This study does face limitations. The main threat to internal validity is with the identification of women with metastatic disease given the limitations of working with claims data. Specifically, women that received combination therapy but had their drugs administered on separate days were captured as receiving a single agent and were included in the study sample although it is unlikely they had metastatic disease. This may have artificially inflated the study sample size. Concomitantly, women eligible for the sample may have been inadvertently excluded due to poor utilization of ICD-9-CM codes for secondary neoplasm by medical coders or by use CPT code was used instead of a specific agent HCPC code.[31, 32] Despite these limitations, a rigorous algorithm utilizing both procedure and diagnosis codes were used to build the sample.[31] This is currently the best way to identify the sample when there is no option to link to electronic health records.[31, 32]

There are many advantages to working with MarketScan^{TM} data including large sample size, detailed information on procedure and product utilization, and strong external validity. Despite these advantages to working with MarketScan^{TM} data, it can be criticized as having limited external validity as women who carry public insurance or no insurance are not included. However, both public and private insurance cover medications (even those off-label) that are listed in NCCN guidelines. In addition, it is unlikely that physicians treating those with public insurance are

significantly different from those treating patients with private insurance. We caution against applying these results to women without insurance, however, this is likely to be a small number.

Recommendations for Future Studies

Additional studies examining the impact of ODAC recommendations on specific demographic and clinical populations is important. This would help reveal the magnitude of the ODAC recommendation on Avastin by providing additional context. Other studies examining the impact of expert bodies like NCCN on drug utilization is also recommended. In particular, it would be interesting to examine the difference in impact between the ODAC decision in July 2010 and the NCCN decision in 2011. We also recommend conducting a study that uses claims data linked to electronic health records. This would improve the internal validity of study sample creation by improving the accuracy of identifying metastatic breast cancer within claims data. Finally, a study that explores the relationship between supply factors such as concentration of academic medical centers and clinical trial participation on prescribing of controversial medication would be of interest. This would help us understand whether the regional variation observed in our study was caused by these factors.

Policy Implications

This study is the first to examine an ODAC decision by quantifying its impact on drug utilization in the U.S. One other study quantified this but within Austria. Understanding the impact of expert bodies like ODAC is vitally important. It demonstrates the influence they carry on prescribers choices even before a decision is reached by the FDA. In addition, findings from this study indicate that women were less likely to be prescribed Avastin if they were located in the Northeast region. Although the data cannot definitely prove this is due to the concentration of

academic medical centers, it is a possibility. This may indicate that the FDA outreach should target smaller hospitals or hospital unaffiliated with a larger network to help explain their decisions.

This study also provides a better understanding of a factor that influences providers' drug prescribing behavior. This is important because of the increased medication use seen in the U.S. over the past decade.[40] The Patient Protection and Affordable Care Act (ACA) signed into law on March 21, 2010 included prescription drug coverage as one of the 10 essential health benefits. In addition, Medicare Part D expanded its coverage of prescription drugs. These policy changes have helped lower medications costs for patients and may result in increased utilization.[40] The consumption of prescription drugs continues to increase making the regulation of pharmaceuticals increasingly important to public health. Within the past decade the number of people using at least one medication has increased from 44% to 48% and the number of people using two or more medications has increased from 25% to 31%.[41] The FDA has employed various tools, such as accelerated approval, to help get products to market faster when there is a population at risk with limited treatment options.[1, 21] With an increasing number of people able to access and afford these medications, it has become even more important to ensure they are safe and effective.

CONCLUSION

Overall, this study examines the impact of an advisory committee recommendation on prescribing practices. The ODAC recommendation to the U.S. FDA to withdraw Avastin received a lot of publicity. Key opinion groups like NCCN, experts, and other regulatory agencies like EMA publicly disagreed with the ODAC recommendation. Despite this, Avastin use was found to significantly decrease. This situation is not unique; as the number of drugs with an accelerated approval increases each year the FDA will continue to rely on its advisory committees to help review safety and efficacy information and provide recommendations. It is increasingly important to understand the impact of these advisory committees on prescribing practices. This is especially true for oncology. This study is the first to quantify the impact of an ODAC recommendation on prescribing here in the U.S. and uncovers potential areas for further research.

REFERENCES

1. Dagher, R., et al., *Accelerated approval of oncology products: a decade of experience.* Journal of the National Cancer Institute, 2004. **96**(20): p. 1500-9.
2. Balko, J.M., et al. *Moledular Profiling of Breast Cancer*. My Cancer Genome 2014 March 31, 2014; Available from: http://www.mycancergenome.org/content/disease/breast-cancer/.
3. Administration, U.F.a.D., *FDA Briefing Document Oncology Drug Advisory Committee Meeting Avastin (bevacizumab).*
4. McGivney, W.T., *NCCN Guidelines and Their Impact on Coverage Policy.* Journal of National Comprehensive Cancer Network, 2010. **8**(6): p. 625.
5. Broderick, J. *NCCN 2011 Guidelines for Breast Cancer: Yes on Avastin, No on CYP2D6* OncLive, 2011.
6. Riley, K., *FDA Commissioner announces Avastin decision*, in *FDA News Release*2011, U.S. Food and Drug Administration.
7. Kleinsmith, L.J., et al., in *Understanding Cancer and Related Topics Understanding Angiogenesis*, National Cancer Institute.
8. Aogi, K., et al., *First-line bevacizumab in combination with weekly paclitaxel for metastatic breast cancer: efficacy and safety results from a large, open-label, single-arm Japanese study.* Breast Cancer Res Treat, 2011. **129**(3): p. 829-38.
9. Gray, R., et al., *Independent review of E2100: a phase III trial of bevacizumab plus paclitaxel versus paclitaxel in women with metastatic breast cancer.* J Clin Oncol, 2009. **27**(30): p. 4966-72.
10. Miller, K.D., *E2100: a phase III trial of paclitaxel versus paclitaxel/bevacizumab for metastatic breast cancer.* Clin Breast Cancer, 2003. **3**(6): p. 421-2.
11. Schneider, B.P., et al., *Association of vascular endothelial growth factor and vascular endothelial growth factor receptor-2 genetic polymorphisms with outcome in a trial of paclitaxel compared with paclitaxel plus bevacizumab in advanced breast cancer: ECOG 2100.* J Clin Oncol, 2008. **26**(28): p. 4672-8.
12. Miles, D.W., et al., *Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer.* J Clin Oncol, 2010. **28**(20): p. 3239-47.
13. Robert, N.J., et al., *RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer.* J Clin Oncol, 2011. **29**(10): p. 1252-60.
14. Dawood, S., et al., *The use of bevacizumab among women with metastatic breast cancer: a survey on clinical practice and the ongoing controversy.* Cancer, 2012. **118**(11): p. 2780-6.
15. Fairman, K.A. and F.R. Curtiss, *Regulatory actions on the off-label use of prescription drugs: ongoing controversy and contradiction in 2009 and 2010*: J Manag Care Pharm. 2010 Oct;16(8):629-39.
16. Montero, A.J., et al., *Bevacizumab in the treatment of metastatic breast cancer: friend or foe?* Curr Oncol Rep, 2012. **14**(1): p. 1-11.

17. Refaat, T., et al., *Markov Model and Cost-Effectiveness Analysis of Bevacizumab in HER2-Negative Metastatic Breast Cancer.* Am J Clin Oncol, 2013.
18. Montero, A.J., et al., *A cost-benefit analysis of bevacizumab in combination with paclitaxel in the first-line treatment of patients with metastatic breast cancer.* Breast Cancer Res Treat, 2012. **132**(2): p. 747-51.
19. Dearing, J.W., *Evolution of diffusion and dissemination theory.* Journal of Public Health Management and Practice, 2008. **14**(2): p. 99-108.
20. Berwick, D.M., *Disseminating innovations in health care.* JAMA, 2003. **289**(15): p. 1969-75.
21. Johnson, J.R., et al., *Accelerated approval of oncology products: the food and drug administration experience.* Journal of the National Cancer Institute, 2011. **103**(8): p. 636-44.
22. Issa, A.M., et al., *Drug withdrawals in the United States: a systematic review of the evidence and analysis of trends.* Current Drug Safety, 2007. **2**: p. 177- 185.
23. Nemeroff, C.B.K., A.; Keller, M.B.; Charney, D.S., *Impact of Publicity Concerning Pediatric Suicidality Data on Physician Practice Patterns in the United States.* Archives of General Psychiatry, 2007. **64**(4): p. 466-472.
24. Lu, C.Y., Zhang, F., Lakoma, M.D., Madden, J.M., Rusinak, D., Penfold, R.B., Simon, G., Ahmedani, B.K., Clarket, G., Hunkeler, E.M., Waitzfelder, B., Owen-Smith, A., Raebel, M.A., Rossom, R., Coleman, K.J., Copeland, L.A., Soumerai, S.B., *Changes in antidepressant use by young people and suicidal behavior after FDA warnings and media coverage: quasi-experimental study.* BMJ, 2014. **348**.
25. Harris, G., *Study Finds Less Youth Antidepressant Use*, in *New York Times*2004.
26. Olfson, M., Marcus, S.C., Druss, B.G., *Effects of Food and Drug Administration Warnings on Antidepressant Use in a National Sample.* Archives of General Psychiatry, 2008. **65**(1): p. 94-101.
27. Cheung, A., Sacks, D., Dewa, C.S., Pong, J., Levitt, A., *Pediatric prescribing practices and the FDA Black-box warning on antidepressants.* Journal of Developmental and Behavioral Pediatrics, 2008. **29**(3): p. 2013-215.
28. Bradford, W.D. and A.N. Kleit, *Impact of Fda Actions, Dtca, and Public Information on the Market for Pain Medication.* Health Economics, 2014. **24**(10).
29. Preusser, M., et al., *Influence of the American ODAC statement on Austrian bevacizumab prescribing practice for metastatic breast cancer.* Oncologist, 2012. **17**(7): p. e13-7.
30. Harting, J., et al., *Implementation of an innovative health service a "real-world" diffusion study.* American Journal of Preventive Medicine, 2005. **29**(2): p. 113-9.
31. Nordstrom, B.L., et al., *Identification of metastatic cancer in claims data.* Pharmacoepidemiol Drug Saf, 2012. **2**: p. 21-8.
32. Whyte, J.L., et al., *An Evaluation of Algorithms for Identifying Metastatic Breast, Lung, or Colorectal Cancer in Administrative Claims Data.* Medical Care, 2013. **21**: p. 21.
33. Network, N.C.C., *NCCN Guidelines Version 3.2014 Invasive Breast Cancer.* p. 1-7.
34. Cardoso, F., et al., *International guidelines for management of metastatic breast cancer: combination vs sequential single-agent chemotherapy.* Journal of the National Cancer Institute, 2009. **101**(17): p. 1174-81.
35. Zujewski, J.A., Manrow, R.E., *Early-stage Breast Cancer Treatment: A Patient and Doctor Dialogue*, 2010, Department of Health and Human Services, Office of Women's Health.

36. *Medicare Claims Processing Manual*, in *Chapter 17 - Drugs and Biologicals*2014. p. 97.
37. HMSA *Chemotherapy Coding*. HMSA Provider Resource Center, 2013.
38. Partridge, A.H., et al., *Chemotherapy and Targeted Therapy for Women With Human Epidermal Growth Factor Receptor 2-Negative (or unknown) Advanced Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline.* J Clin Oncol, 2014.
39. Benstetter, M. *European Medicines Agency completes its review of Avastin used in breast cancer treatment*. 2010; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/12/WC500099929.pdf.
40. *What the Affordable Care Act Means for Prescription Coverage*, in *Washington Post*2014.
41. Qiuping, G., Dillon, C.F., Burt, V.L., *Prescription Drug Use Continues to Increase: U.S. Prescription Drug Data for 2007-2008.* NCHS Data Brief, 2010. **42**.