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INFLUENCE OF ONCOTYPE DX® ON CHEMOTHERAPY PRESCRIBING IN EARLY STAGE BREAST CANCER PATIENTS: A CLAIMS-BASED EVALUATION OF UTILIZATION IN THE REAL WORLD

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THESIS

A thesis submitted in partial fulfillment of the
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By

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Lexington, KY

Director: Dr. Val Adams, Associate Professor of Pharmacy

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2012

ABSTRACT OF THESIS

INFLUENCE OF ONCOTYPE DX® ON CHEMOTHERAPY PRESCRIBING IN EARLY STAGE BREAST CANCER PATIENTS: A CLAIMS-BASED EVALUATION OF UTILIZATION IN THE REAL WORLD

The decision for adjuvant therapy in women with early stage breast cancer (ESBC) has historically been guided by the presence or absence of specific biological markers (hormone and HER2 receptors), age, and extent of nodal involvement. Oncotype DX® is a validated assay that quantifies protein expression that can predict the risk of cancer recurrence. This study evaluates if the use of Oncotype DX® impacts chemotherapy prescribing in ESBC. This retrospective, cohort study identified patients with ESBC from a large commercially insured population from January 2007 through June 2009. Patients were identified as having ESBC by utilizing procedure and diagnosis codes to indicate that a sentinel lymph node biopsy had been performed. Hormone receptor status was verified by patients receiving at least one month of hormonal therapy including: tamoxifen, anastrozole, letrozole, or exemestane. Exclusion criteria will include patients less than 18 years of age, procedure codes indicating axillary lymph node dissection, or charges for trastuzumab. The administration of Oncotype DX® was not found to significantly affect a physician's decision to prescribe chemotherapy. However, there were significant regional differences in Oncotype DX® utilization by region. Future studies should be conducted at a population level to determine the effects of Oncotype DX®.

KEYWORDS: Oncotype DX® , breast cancer, early-stage, adjuvant, chemotherapy

___Kenneth Kennedy, PharmD_____

_____November 16, 2012_____

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Section 1: Background

It is estimated in 2012 in the United States that there will be approximately 227,000 new cases of breast cancer in women and approximately 40,000 deaths due to breast cancer.[1] Due to earlier detection, over 90% of breast cancers are diagnosed at an early stage.[2] Almost all women (98%) with early-stage disease can expect a five year survival with modern treatment; however, disease recurrence is still a threat to long term survival.[3] Factors that are considered by clinicians in designing treatment regimens in early-stage breast cancer (ESBC) are: age, menopausal status of the patient, stage of disease (including nodal involvement), histologic type and grade, the presence or absence of hormone receptors, mitotic figure counts, overexpression of human epidermal growth factor-2 (HER2) receptor, proliferation markers, lymphatic and vascular channel spread, and mutations in p53. [4] These patient features have been incorporated into guidelines, for example the St. Gallen[5] and the National Comprehensive Cancer Network consensus (NCCN) guidelines[6], or have been integrated into online decision tools like Adjuvant! Online.[7,8] More recently, molecular profiling of the patient's specific tumor can be performed with the use of commercially available tests like: Oncotype DX® [9] or MammaPrint[10]. These more recent molecular tests and the more historic clinicopathologic characteristics are used by clinicians to determine if the risk of recurrent disease is high enough to warrant adjuvant systemic chemotherapy for individual patients. Adjuvant therapy refers to any additional therapy offered to women after the completion of a primary therapy like surgical resection of the tumor.

Like all other medical treatments, chemotherapy carries a certain risk profile and there is a potential for serious adverse events to occur, including hospitalization and death. A study conducted in Brazil, found that 13% of patients (39 of 298 patients) admitted to an oncology unit were in connection with an adverse drug event. [11] Approximately 50% of these oncology patients (20 of 39 patients) were admitted with neutropenic fever, and unfortunately 2 of these patients

died. When focusing just on breast cancer patients in a large claims database, Hasset et al. found a lower percentage of patients admitted with infection and fever, but the number is still striking at 8.4%.[12] Other frequently encountered complications from chemotherapy were: neutropenia and/or thrombocytopenia (5.5%), anemia (2.2%), constitutional symptoms (2.2%), dehydration/electrolyte disorder (2.5%), nausea/vomiting/diarrhea (2.4%), and venous thromboembolism (1.3%). [12] Clearly, chemotherapy is not a benign experience for these women. Particularly troubling is that a breast cancer patient may be exposed to these potential complications and yet receive no added benefit from receipt of their chemotherapy. A large (n=1667) randomized trial that compared tamoxifen to chemotherapy followed by tamoxifen in node negative breast cancer reported five year disease free survival rates of 81% and 85%, respectively. Although a positive finding, it is concerning that only 1 out of 25 women treated with chemotherapy derive benefit. [13] Determining who will or will not benefit from chemotherapy as part of adjuvant treatment has been extensively studied and continues to be the focus of investigation.

Oncotype DX® was developed and marketed by Genomic Health of Redwood City, CA, and became commercially available in 2004. This 21-gene profile measures the expression of 16 cancer genes and 5 reference genes by reverse-transcriptase—polymerase-chain-reaction (RT-PCR) to output a continuous Recurrence Score (RS). Oncotype DX® was first validated using data from NSABP B-14, a large multicenter clinical trial.[9] The validation trial was conducted in node negative stage I or II patients that were hormone receptor positive and treated with tamoxifen. Patients had to have archived tumor tissue samples available. The individual RS generated by Oncotype DX® was used to group individuals into risk categories: low risk (RS <18), intermediate risk (RS 18-30), and high risk (RS >30). The assay was validated by demonstrating the low risk group (51% of patients) had a 6.8% risk of distant recurrence at 10 years, compared to 14.3% and 30.5% for the intermediate and high risk groups, respectively. [9]

Additionally, Oncotype DX® was validated in a large population-based case-control study using Kaiser Permanente data from Northern California, which showed the RS predicted 10 year death rates from breast cancer: 2.8% in the low group, 10.7% in the intermediate group, and 15.5% in the high group. [14] Next, Oncotype DX® was validated using a similar approach with archived tumor samples from the NSABP B-20, which delineated patients that would or would not benefit from adjuvant systemic chemotherapy followed by hormonal therapy. In the low risk patient population, the 10 year distant recurrence free survival (DRF) was 97% with tamoxifen alone and 96% with chemotherapy followed by tamoxifen. The intermediate group had a non-significant difference of 2%, which favored tamoxifen monotherapy; while the high risk population showed a DRF of 61% and 88% favoring the chemotherapy arm. [15] The results of this study are important because they confirmed that the test could identify the 75% of node negative, hormone receptor positive patients who will not benefit from chemotherapy. It's also interesting to note other studies of the RS from Oncotype DX® have demonstrated the ability to "downgrade" or reclassify patients into a lower risk category 40-50% of the time, as compared to initial assessment by a physician[16,17] or application of the NCCN guidelines[18], thus resulting in avoided chemotherapy.

The scientific evidence demonstrating that Oncotype DX® accurately predicts clinical outcomes in women with early-stage, node-negative, hormone receptor positive, HER2 negative disease has been answered in the previously mentioned trials. However, it is only one of a number of tools used to guide adjuvant therapy decisions. The focus of this research is to determine how the Oncotype DX® science has translated into standard practice across the United States. The primary objective of the current study is to determine how Oncotype DX® is used in a "real-world" setting to guide decision making about adjuvant chemotherapy. Secondary objectives include overall uptake of use as well as regional differences.

Section 2: Methods

This was a retrospective, population-based cohort study of ESBC patients that were diagnosed between January 2007 through June 2009. Patients were selected from a large database of commercially insured individuals that is representative of the United States. This database contains de-identified data inclusive of inpatient, outpatient, pharmacy claims, lab results, and enrollment information for an estimated 15 million unique lives. Overall, this database is representative of the non-elderly, insurance-carrying population in the US, but it also contains several hundred thousand Managed Medicaid and Medicare Advantage Members. The University of Kentucky's Institutional Review Board granted use of this de-identified database under a blanketed approval.

Early-stage, node-negative breast cancer patients were eligible if they met the International Statistical Classification of Diseases and Related Health Problems (ICD-9) and Current Procedural Terminology **(**CPT) coding criteria found in Appendix A. Briefly, this included women greater than 18 years of age, with private insurance, coded with an ICD-9 code indicative of breast cancer, who received at least one month of hormonal therapy, and underwent a sentinel lymph node injection and excision. Women had to have this "index" procedure of sentinel node injection performed between January 1, 2007 through June 30, 2009. Charges for Oncotype DX® were identified by the test's unique CPT code (S3854). After January 1, 2006, Oncotype DX® received its own unique CPT code, which occurred before the start of the the insurance claims database (personal communication with Genomic Health, Appendix A). The list of National Drug Codes (NDCs) used to define at least one month of hormonal therapy can be found in Appendix B.

Women were excluded if they received trastuzumab, which would suggest HER-2 positive disease, or if they had a more aggressive axillary lymph node dissection or mastectomy, which

might suggest node-positive disease. These CPT codes and J codes are described in Appendices A and C, respectively. These inclusion/exclusion criteria were constructed to define the population of early-stage, hormone receptor positive, node negative disease, to mirror where Oncotype DX® currently has the most data to support its use. [9,15,19]

The primary objective of this study was to determine if a difference existed in the proportion of patients receiving chemotherapy that had the Oncotype DX® test performed compared to those that did not undergo the test. Because injectable chemotherapy drugs are billed via J-codes in medical claims, a separate list of J-codes was created (Appendix C) to determine receipt of chemotherapy. Having said that, a very small percentage of chemotherapy claims were coded using NDCs in the database, so Appendix D was also developed to capture all possible chemotherapeutic agents. Secondary endpoints include: predictors of adjuvant chemotherapy use and predictors of Oncotype DX® testing. We hypothesize that age, region of the country, and year of diagnosis will influence these endpoints. The U.S. Census Bureau Regions and Divisions schema was applied to divide the patients into regions of the country (Appendix E). [20]

A question of interest to be examined in exploratory analysis is: what is the median time from diagnosis to Oncotype DX® test (for those women that had the test administered)? We hypothesize that age, region of the country, and year of diagnosis will also influence this endpoint. In particular, we hypothesize that regions of the country that have lower relative utilization of Oncotype DX® will have a longer time to ordering the test (ie. longer time from diagnosis to ordering test). Again, the U.S. Census Bureau Regions and Divisions schema was applied to divide the patients by region of the country (Appendix E). [20]

Statistical Analysis

Variables including age, region, adjuvant chemotherapy, whether the Oncotype DX® was performed, and year of diagnosis were collected and summarized for eligible women. A Chi-

squared test was used to test the primary hypothesis of the difference in proportions of patients receiving adjuvant chemotherapy based on whether Oncotype DX® was administered (yes/no).

A multivariate logistic regression, controlling for Oncotype DX®, region, age, and year of diagnosis, was utilized to study predictors of adjuvant chemotherapy use. A separate multivariable logistic regression, controlling for region, age, and year of diagnosis, was implemented to identify predictors of Oncotype DX® testing. Year of diagnosis was included in both models based on the temporal component of when Oncotype DX® became available in the US (in 2004) and the time span of the claims database (January 2007 through December 2009). Receipt of adjuvant chemotherapy was not included in the second logistic regression, as that event should occur after the Oncotype DX® test is performed, and thus should not influence the decision to order the test.

Kaplan-Meier curves were utilized to model time to administration of Oncotype DX® (for those women with a test ordered). Here, the "event" was having the Oncotype DX® test performed. The median time to Oncotype DX® was calculated as the difference between the date of Oncotype DX® claim from the date of breast cancer diagnosis (sentinel node biopsy claim). Curves were stratified by region and year of diagnosis. The log-rank test was applied to detect for a significant difference between the stratified curves. SAS version 9.1 (Cary, NC) was used to perform all statistical tests.

Section 3: Results

Based on ICD-9 codes 114,306 patients were initially identified as having breast cancer. After inclusion/exclusion criteria of CPT codes and drug classes were applied 2,475 remained with early-stage, node-negative, hormone receptor positive breast cancer. See Figure 1 for patient selection pathway. From the cohort selected, all of the patients were female with a mean age of 54.9 years and an age range of 23 to 87 years. Approximately 40% of the patients were from the South region, with the next highest percentage of 28.9% coming from the Midwest. The patients were also somewhat evenly distributed throughout the years with approximately 40% from both 2007 and 2008 and the remaining 19% from 2009. See Table 1 for Baseline Demographics when stratified by receipt of Oncotype DX® (yes/no).

Primary endpoint: Proportion receiving adjuvant chemotherapy by Oncotype DX®

From the cohort of 2,475 patients with early-stage breast cancer, 545 patients (22%) received adjuvant systemic chemotherapy. 909 patients (36.7%) from the cohort had a claim for Oncotype DX® during the prescribed time frame. Of these patients with an Oncotype DX® claim, 213 (23.4%) received adjuvant chemotherapy compared to the 332 (21.2%) patients that received adjuvant chemotherapy from the 1,566 without a claim for Oncotype DX® test (p=0.1965) (see Figure 2).

Predictors of receiving adjuvant chemotherapy

The average age for women receiving chemotherapy (51.7 years) was almost 4 years younger than those that did not receive chemotherapy (55.9 years). By region, both the South and West

received chemotherapy approximately 20% of the time. The Midwest region was noted to have the highest utilization of chemotherapy, in approximately 27% of women. The Northeast region had the lowest use of adjuvant chemotherapy in only approximately 12% of women during the study period. No differences were noted when stratified by year of diagnosis. See Table 2 for Characteristics of those receiving chemotherapy.

The results of the logistic regression for the odds of receiving chemotherapy, while controlling for Oncotype DX® administration, region, age, and year of diagnosis can be found in Table 2. The adjusted odds ratio of receiving chemotherapy based on Oncotype DX® administration, controlling for all other variables was not statistically significant at 1.06 (95% CI: 0.860 – 1.30). However, patients located in the Midwest were at a 31% increased odds (OR=1.31, 95% CI: 1.044 – 1.644) of receiving chemotherapy compared to the reference region of the South, controlling for all other variables. The odds of receiving chemotherapy for a patient in the Northeast compared to the South, while controlling for all other variables, was 53% lower (OR=0.47 95% CI: 0.33 – 0.692). There were no significant differences between the West region and the South. The adjusted odds ratio of receiving chemotherapy decreases by 5% with each additional year of age (OR=0.95, 95% CI: 0.942 – 0.963). Year of breast cancer diagnosis did not significantly impact the odds ratio of receiving chemotherapy (2008 vs 2007, OR=0.83, 95% CI: 0.66 – 1.03; 2009 vs 2007, OR=0.79, 95% CI: 0.6 – 1.04).

Predictors of receiving Oncotype DX®

A secondary objective of this study was to identify any variables that may influence the use of the Oncotype DX® test as shown in Table 3. By region, the South utilized Oncotype DX® more frequently in 40% of women, compared to approximately 36% of women in the Northeast and West, and 33% of women in the Midwest. In 2007, the test was ordered in 27.7% of women,

compared to 41.6% in 2008, to 46.7% in 2009. Again, using the South as the reference region, the adjusted odds of having the Oncotype test performed in the Midwest was decreased by 29% (OR = 0.71, 95% CI: 0.574 – 0.868), controlling for all other variables. No statistical differences were found when comparing the Northeast region or the West region to the South region. The adjusted odds of receiving the Oncotype DX® test significantly decreased by 4% with each additional year of age (OR = 0.961, 95% CI: 0.925 – 0.970). The adjusted odds of receiving Oncotype DX® was significantly increased by 1.9-fold in the year 2008 compared to 2007 (OR=1.9, 95% CI: 1.574 – 2.304) and also significantly increased by 2.4-fold in the year 2009 compared to 2007 (OR=2.419, 95% CI: 1.919 – 3.049).

Exploratory Endpoint: Impact on time to Oncotype DX®

Overall, the Kaplan-Meier estimates for the median time to having Oncotype DX® performed were 4.4%, 51.7%, 84.9%, and 93.4% at 30 days, 60 days, 90 days, and 120 days after the sentinel node procedure was performed, respectively (see Table 4). A statistically significant difference was noted when patients were stratified by region (Figure 3, p = 0.0061). In particular, women in the Northeast region had consistently lower estimates at all of the time points when compared to the overall cohort (38.9% vs 51.7% at 60 days, 77.9% vs 84.9% at 90 days). However, by 120 days women in the Northeast seemed to catch up to the overall group 91.1% vs 93.4%.

When median time to Oncotype DX® was stratified by year of breast cancer diagnosis, a significant difference was noted (Figure 4, p<0.0001). When year of breast cancer diagnosis was increased by one (2007→2008→2009), a clear correlation can be seen in a decreased median time to performing Oncotype DX®. In 2007, 3.2%, 40.6%, 76.6%, and 88.1% of patients had an

Oncotype DX® performed at 30, 60, 90, and 120 days, respectively. By year 2009, those numbers had increased to 5.9%, 61.4%, 91.4%, and 96.4%, respectively (Table 4).

Table 1. Baseline demographics

	Oncotype Yes (n=909)		Oncotype No (n=1566)		p-value
Age					
Mean (stdev)	52.9	(±7.77)	56.1	(±10.3)	<0.0001
Range (Min, Max)	23	75	28	87	
Region	*N*	*%*	*N*	*%*	
Midwest	235	32.8%	481	67.2%	0.0240
Northeast	113	36.3%	198	63.7%	
South	403	40%	605	60%	
West	158	35.9%	282	64.1%	
Year					
2007	286	27.7%	748	72.3%	<0.0001
2008	403	41.6%	567	58.5%	
2009	220	46.7%	251	53.3%	

Table 2. Characteristics of those receiving chemotherapy and logistic regression modeling the probability of receiving adjuvant chemotherapy based on administration of Oncotype DX®, region, age, year of diagnosis.

	Chemotherapy Yes (n= 545)		Chemotherapy No (n= 1930)		Adj. OR	95% CI	Adjusted p-value
Age, years					0.95	0.942 – 0.963	<0.0001*
Mean (stdev)	51.7	(8.51)	55.9	(9.67)			
Range (Min, Max)	23	82	25	87			
Region[#]							
Midwest	194	27.1%	522	72.9%	1.31	1.044 – 1.644	0.02*
Northeast	38	12.2%	273	87.8%	0.47	0.33 – 0.692	0.0001*
South	221	21.9%	787	78%	---	---	---
West	92	20.9%	348	79.7%	0.98	0.74 – 1.30	0.894
Year[$]							
2007	247	23.9%	787	76.1%	---	---	---
2008	202	20.8%	768	79.2%	0.83	0.66 – 1.03	0.085
2009	96	20.4%	375	79.6%	0.79	0.60 – 1.04	0.089
Oncotype DX® performed	213	23.4%	696	76.6%	1.06	0.86 – 1.30	0.59

Abbreviations: Adj. OR, adjusted odds ratio; 95% CI, 95% confidence interval.

* Denotes adjusted odds ratio significantly different from one at $P < .05$.

South selected as reference group.

$ 2007 selected as reference group.

Table 3. Characteristics of those that had Oncotype DX® performed and logistic regression modeling the probability of administering Oncotype DX® prior to decision of chemotherapy performed controlling for region, age, year of diagnosis

	Oncotype Yes (n=909)		Oncotype No (n=1566)		Adj. OR	95% CI	Adjusted p-value
Age					0.961	0.925 – 0.970	<0.0001*
Mean (stdev)	52.9	±7.77	56.1	±10.3			
Range (Min, Max)	23	75	28	87			
Region[#]							
Midwest	235	32.8%	481	67.2%	0.71	0.574 – 0.868	0.001*
Northeast	113	36.3%	198	63.7%	0.894	0.682 – 1.173	0.418
South	403	40%	605	60%	---	---	---
West	158	35.9%	282	64.1%	0.839	0.66 – 1.065	0.149
Year[$]							
2007	286	27.7%	748	72.3%	---	---	---
2008	403	41.6%	567	58.5%	1.904	1.574 – 2.304	<0.0001*
2009	220	46.7%	251	53.3%	2.419	1.919 – 3.049	<0.0001*

Abbreviations: Adj. OR, adjusted odds ratio; 95% CI, 95% confidence interval

* Denotes adjusted odds ratio significantly different from one at $P < .05$.

South selected as reference group.

$ 2007 selected as reference group.

Table 4. Kaplan-Meier estimates for time to utilization of Oncotype DX® by region and year of diagnosis.

	30 days (%)	95% CI	60 days (%)	95% CI	90 days (%)	95% CI	120 days (%)	95% CI
Overall	4.4	(3.2 – 6)	51.7	(48.5 – 55)	84.9	(82.5 – 87.2)	93.4	(91.7 – 94.9)
Region*								
Midwest	2.6	(1.2 – 5.6)	55.7	(49.5 – 62.2)	90.2	(86 – 93.6)	95.3	(92.1 – 97.5)
Northeast	3.5	(1.3 – 9.2)	38.9	(30.6 – 48.6)	77.9	(69.9 – 85)	91.1	(85 – 95.5)
South	6.5	(4.4 – 9.3)	51.6	(46.8 – 56.6)	81.1	(77.2 – 84.8)	91.6	(88.6 – 94)
West	2.5	(1 – 6.6)	55.1	(47.5 – 62.9)	91.8	(86.8 – 95.4)	96.8	(93.2 – 98.8)
Year of diagnosis*								
2007	3.2	(1.6 – 6)	40.6	(35.1 – 46.5)	76.6	(71.5 – 81.3)	88.1	(84.1 – 91.5)
2008	4.5	(2.8 – 7)	54.3	(49.6 – 59.3)	87.3	(83.9 – 90.4)	95.5	(93.2 – 97.3)
2009	5.9	(3.5 – 10)	61.4	(55 – 67.8)	91.4	(87.2 – 94.6)	96.4	(93.3 – 98.3)

Abbreviations: 95% CI, 95% confidence interval

* Denotes log-rank test statistically significant at $P<0.05$.

Figure 1. Pathway of inclusion/exclusion criteria.

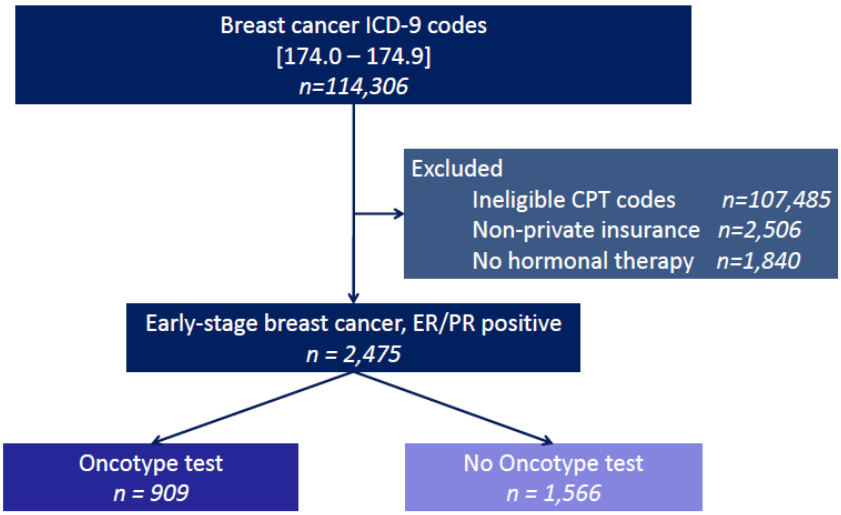


Figure 2. Proportion of patients receiving chemotherapy by Oncotype DX® yes/no

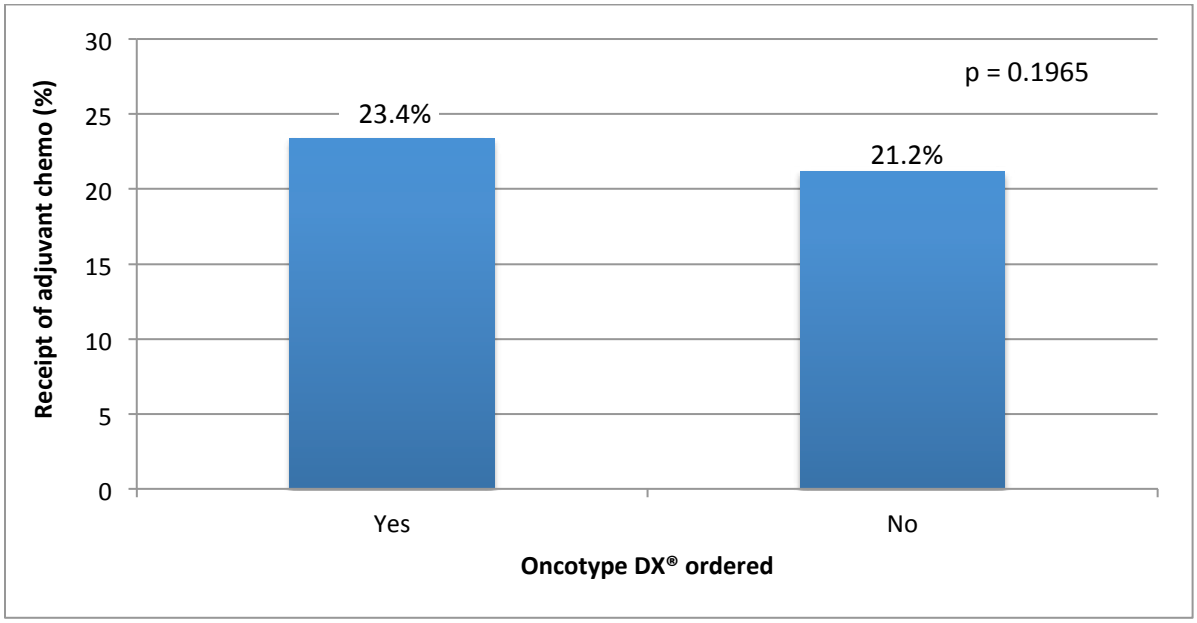


Figure 3. Kaplan-Meier curves of time to Oncotype DX® by region.

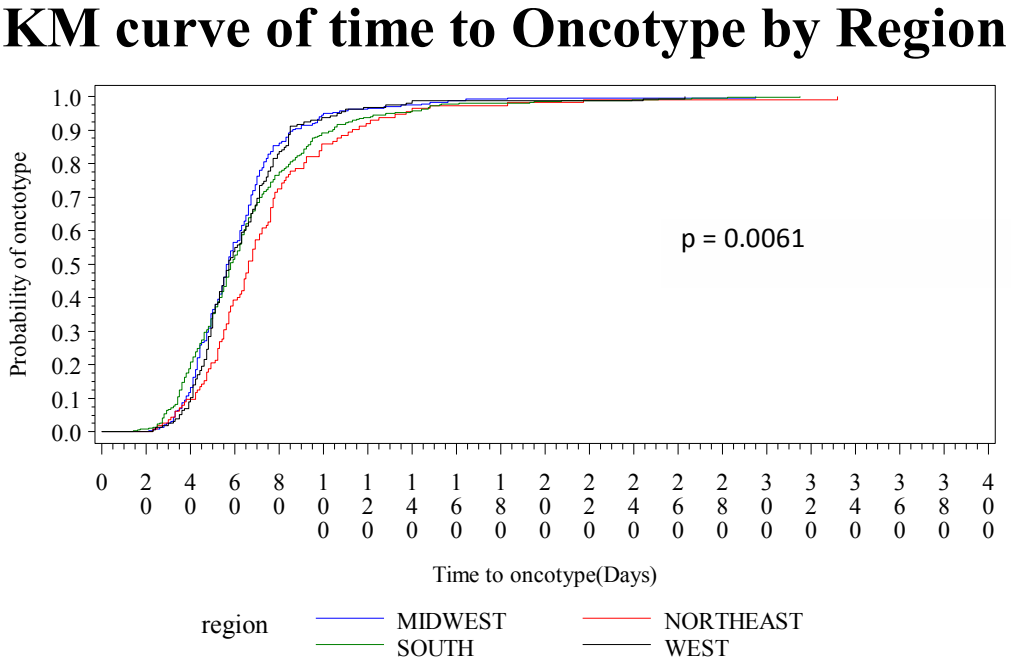
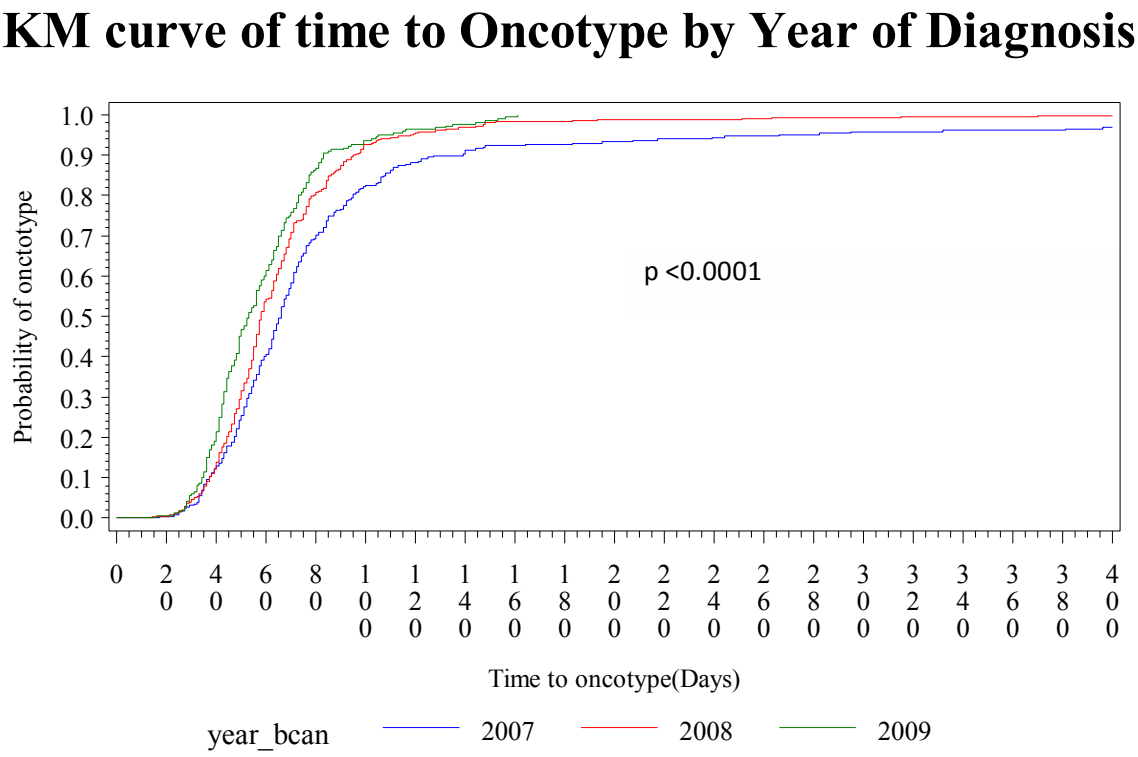


Figure 4. Kaplan-Meier curves of time to Oncotype DX® by year of diagnosis



Section 4: Discussion/Conclusions

Our hypothesis that the use of Oncotype DX® would result in fewer women receiving chemotherapy across the United States was not realized. The current study found that among women that had the Oncotype DX® test performed, 23% received adjuvant chemotherapy compared to 21% of those without an Oncotype DX® claim (p=0.1965). One potential explanation for this is that the individual RS was unknown in the claims database. A multitude of studies have answered the question of whether the RS from Oncotype DX® impacts both the clinician and/or patients' decisions for adjuvant chemotherapy. In an economic analysis from Israel, treatment decisions were collected prospectively before Oncotype DX® was ordered for 313 patients (85% of those screened). [16] Overall, adjuvant chemotherapy was recommended to 56% of patients before the RS was known, which decreased to 28% after the RS was known. The percentage of patients reported to receive adjuvant chemotherapy is in line with findings from the current study, in which 22% of patients received adjuvant chemotherapy. When Klang, et al. stratified their sample by RS risk categories, the most marked change was in the low-risk group (RS <18) where the recommendation went from 50% recommended to receive chemotherapy down to 0% actually receiving chemotherapy. [16] In another study, 89 patients and their oncologists were surveyed about their decisions for adjuvant treatment before and after the results of Oncotype DX®. Results from this study indicate that 31.5% of decisions made by medical oncologists were changed and 27% of patients changed their treatment decisions. [17] Both of these studies contrast the findings from the current study, most likely due to the individual RS available for each patient that was not available in the claims database.

The current study demonstrated a significant impact of region on a patient's odds of receiving adjuvant chemotherapy: the adjusted odds ratio for patients in the Northeast was almost half (OR = 0.47 95% CI: 0.33 – 0.692) and about 31% higher for patients in the Midwest (OR = 1.31 95% CI: 1.047 – 1.649), with the South as the reference region, controlling for all other variables. Previous research has explored regional differences in a variety of breast cancer treatments including use of granulocyte colony

stimulating factor[21], compliance with locoregional standards of care[22], rates of breast conserving therapy[23], and dose intensity of chemotherapy.[24] A similarly constructed study looked at factors associated with intentionally reduced doses of chemotherapy in breast cancer patients. [25] The authors found in their multivariate analysis that geographic region, obesity status, and level of education significantly affected when chemotherapy was "under-dosed," or intentionally prescribed at less than 85% of the recommended dose. [25] Interestingly, the geographic groups selected by these authors were very similar to those in the current study, with the exception of the Midwest being called the Central region and there were very similar distributions from each region in their study and the current study. Compared to the Northeast region (their reference), the authors found that patients in the South were 5.6 times more likely to have an intentionally reduced dose of chemotherapy. While these findings do not directly confirm or refute the findings from the current study, which was focused on factors associated with whether adjuvant chemotherapy was prescribed (i.e. Oncotype DX® , age, region, etc.) it does provide information on regional differences and the potential effect of a "local treatment culture." [26]

Factors such as race, socioeconomic status, and education can affect compliance with guideline recommendations in a variety of diseases, including breast cancer treatment. Per the most recent NCCN guidelines, Oncotype DX® has a category 2B recommendation for early-stage, node-negative, hormone receptor positive breast cancer if a patient's tumor is >0.5 cm. [6] The current study, which attempted to mirror the above population through inclusion and exclusion criteria, only noticed that 36.7% of these "appropriate" patients received the Oncotype DX® test. What are the reasons for this seemingly low uptake? One potential explanation may be the temporal issue of the time span of the claims database (January 2007 to December 2009) and when Oncotype DX® became commercially available (2004). As expected, the current study found that year of diagnosis was a significant determinant of receiving the Oncotype DX® test (OR = 1.595 95% CI: 1.424 – 1.786), controlling for all other variables. So perhaps, the effect we are seeing can be explained by a "lag time" in utilization of the test. Region did not have as much of an impact on receiving the Oncotype DX® test as it did for the receipt of chemotherapy, as the

ORs were lower. There was a significantly lower chance of receiving Oncotype DX® in the Midwest as compared to the South (OR = 0.699 95% CI: 0.568 – 0.859), controlling for all other variables.

Time from the date of diagnosis of breast cancer to utilization of Oncotype DX® was also examined in this study and yielded some interesting exploratory results. Looking at the Kaplan-Meier curve in Figure 3 provides evidence that when stratified by regions, the Midwest ordered the test sooner than other regions at a median of slightly less than 60 days after diagnosis. Compare this to the Northeast, which ordered the test around a median of 70 days after diagnosis. While this may not amount to a clinically significant difference, a statistically significant difference exists among all regions (p=0.0061). However, all regions seem to catch up with one another and approach 100% utilization of Oncotype DX® around 120 days. As expected, year of diagnosis was also significantly associated with the time to Oncotype DX® test (p<0.0001, Figure 3).

A recent, large study examined the use of Oncotype DX® and adjuvant chemotherapy in the National Comprehensive Cancer Network (NCCN) Breast Cancer Outcomes Database Project. [27] A stark contrast between that study and the current study is that the authors did not restrict their cohort to early-stage, node-negative breast cancer—they included all patients that had the test performed. The authors found a smaller proportion of patients that received the test (20.4%) compared to the current study (36.7%), while more women received adjuvant chemotherapy (50.2%) compared to the current study (22%). [27] This is likely explained by their inclusion of women with more advanced disease. Interestingly, the authors did demonstrate that chemotherapy use was lower among women that had the test performed compared to those that did not (33% vs 54.7%, p<0.01). The authors also concluded in multivariate regression that factors associated with a lower odds of receiving the test included: African American race (OR=0.70, 95% CI: 0.54 – 0.92) and an education of high school or less (OR=0.63, 95% CI: 0.52 – 0.76). [27] This previous research confirms our findings of the increased utilization of Oncotype DX® over time.

This is the first study, to the best of our knowledge, to explore the impact of exposure to Oncotype DX® —not the output of the individual RS—on utilization of adjuvant chemotherapy in early-stage breast cancer in an insurance claims-based model. This analysis provides insight on the frequency of the use of Oncotype DX®, as well as the characteristics of the women in which the test is being utilized. It also complements the work and confirms some of the findings of a larger, recent study. [27] The current study is not without its limitations, however. The major disadvantage of the current analysis is the lack of the RS. As previously mentioned, the RS has consistently shown to "downstage" patients overall and also impact both prescribers' and patients' decisions for adjuvant chemotherapy. From a policy maker's perspective the current analysis provides evidence that use of Oncotype DX® does not significantly reduce overall use of adjuvant chemotherapy. The second major weakness is our approach of using CPT codes to define our patient sample. Undoubtedly, coding terminology changes and the way in which procedures are "described" by combinations of CPT codes changes over time. Additionally, women were excluded from the cohort if they had a more aggressive axillary lymph node dissection or mastectomy. A lot of factors and personal experiences (shared family and friend experiences) go into a women's decision on primary surgical management of breast cancer. Some women opt for a more aggressive management (bilateral prophylactic mastectomy, for example) even if their disease is low risk. These decisions cannot be captured and measured reliably in a retrospective, claims-based database. The CPT definitions used are accurate to the best of our ability at the time of preparing this manuscript. To help mitigate this potential weakness, the lead author consulted with two medical oncologists specializing in breast cancer on the most common terminologies and procedures performed in ESBC patients. Another weakness of utilizing a claims database in the current analysis is the lack of clinicopathological features, such as tumor size, nodal metastasis, and pathology reports that would have provided important information in the decision for adjuvant chemotherapy. There was also limited to no demographic or comorbidity information available in the current version of the claims database. Other missing data points like comorbidity indices, race, socioeconomic status, zip code, etc. could have served as variables to help

control for confounding in the current model. Perhaps in future updates of the database this question could be posed again or in another database altogether linking more of these variables together.

In summary, Oncotype DX® does not significantly impact the number of women that are prescribed adjuvant chemotherapy in a representative cohort of women with ESBC across the United States. In multivariate analysis, significant predictors of decreasing the odds of receiving adjuvant chemotherapy were age and residing in the Northeast. Residing in the Midwest significantly increased the odds of receiving adjuvant chemotherapy. Year of diagnosis was not found to significantly affect the probability of receiving adjuvant chemotherapy. Significant predictors of decreasing the odds of receiving an Oncotype DX® test were age and residing in the Midwest. Later years of diagnosis were associated with an increased odds of receiving an Oncotype DX® test.

Appendix A. International Statistical Classification of Diseases and Health Related Problems-9 (ICD-9) /Current Procedural Terminology (CPT) used to define early-stage, node-negative breast cancer patients.

Inclusion Criteria
ICD9 codes for breast cancer = 174.0 through 174.9
CPT 38792 (injection) + CPT 38500 (excision lymph node, superficial)
CPT 38792 (injection) + CPT 38525 (excision lymph node, deep axillary)
CPT 38792(injection) + CPT 38530 (excision, internal mammary)
Exclusion Criteria
CPT 19302 (partial lumpectomy + excision axillary lymph nodes)
CPT 19162 (mastectomy, partial; with axillary lymphadenectomy)
CPT 19305 (modified radical mastectomy)
CPT 19306 (mastectomy, radical, including pectoral muscles, axillary and internal mammary lymph nodes)
CPT 19307 (mastectomy, modified radical, including axillary dissection)
CPT 38740 (superficial axillary lymphadenectomy, removal all adipose tissue)
CPT 38745 (complete axillary lymphadenectomy)

Charges for Oncotype DX® were identified by the test's unique CPT code (S3854).

Appendix B. National Drug Codes (NDCs) used to define hormonal therapy

Inclusion Criteria	
Drug name	NDCs
Anastrozole	00054016413, 00093753656, 00378603405,
	00378603477, 00781535631, 00904619546,
	16571042103, 16729003510, 38779227406,
	42043018003, 51079032301, 51079032306,
	51991062010, 51991062033, 54569619800,
	54868613000, 54868613001, 55111064730,
	60258086603, 63275993001, 63275993002,
	63323012930, 66435041530, 67877017110,
	67877017130, 68084044811, 68084044821,
	68382020906, 68382020910, 00310020130,
	00310020137, 00310020150, 35356027030,
	54569573100, 54868500000, 55175550503,
	68258903501
Exemestane	00009766304, 49999098630, 54569573200,
	54868526100
Letrozole	00078024915, 35356040930, 54569571400,
	54868415100
Tamoxifen	00310060018, 00310060025, 00310060060,
	00310060075, 00310060412, 00310060430,
	00310060490, 53002103203, 54569038200,
	54569038202, 54569853100, 55175550006,
	55289058530, 57866661501, 57866661801,
	58016065760, 60346004832, 13632012301,
	00054483121, 00054483126, 00054483413,
	00054483422, 00054883125, 00054883425,
	00093078201, 00093078205, 00093078210,
	00093078256, 00093078405, 00093078406,
	00093078410, 00093078486, 00172565649,
	00172565658, 00172565670, 00172565680,
	00172565746, 00172565755, 00172565760,
	00172565770, 00172565780, 00310073060,
	00310073130, 00378014405, 00378014491,
	00378027401, 00378027493, 00440845030,
	00440845060, 00440845092, 00440845130,
	00440845160, 00440845192, 00555044603,
	00555044605, 00555044609, 00555044663,
	00555090401, 00555090405, 00555090414,
	00591223218, 00591223260, 00591223319,
	00591223330, 38779034101, 38779034103,
	38779034104, 38779034105, 38779034108,
	49452775301, 51552083802, 51927297600,
	54569376500, 54569376501, 54569571600,
	54569860200, 54868300401, 54868300402,
	54868300403, 54868300404, 54868300405,

	54868428700, 54868428701, 54868428702,
	54868428703, 54868428704, 63304060028,
	63304060060, 63304060130, 63304060190,
	63739026910, 63739026915

Appendix C. J-codes used to define chemotherapy

Inclusion Criteria	
Drug name	J-code
Cyclophosphamide Oral 25 MG	J8530
Cyclophosphamide 100 MG Inj.	J9070
Cyclophosphamide 200 MG Inj.	J9080
Cyclophosphamide 500 MG Inj.	J9090
Cyclophosphamide 1 G Inj.	J9091
Cyclophosphamide 2 G Inj.	J9092
Cyclophosphamide Lyophilized 100 MG Inj.	J9093
Cyclophosphamide Lyophilized 200 MG Inj.	J9094
Cyclophosphamide Lyophilized 500 MG Inj.	J9095
Cyclophosphamide Lyophilized 1 G Inj.	J9096
Cyclophosphamide Lyophilized 2 G Inj.	J9097
Doxorubicin HCL 10 MG Inj.	J9000
Doxorubicin HCL LIPID 10 MG Inj.	J9001
Docetaxel 20 MG Inj.	J9170
Docetaxel 1 MG Inj.	J9171
Epirubicin HCL 2 MG Inj.	J9178
Epirubicin HCL Inj.	J9180
Fluorouracil 500 MG Inj.	J9190
Methotrexate Oral 2.5 MG	J8610
Methotrexate Sodium 5 MG Inj.	J9250
Methotrexate Sodium 50 MG Inj.	J9260
Paclitaxel Protein Bound Particle 1 MG Inj.	J9264
Paclitaxel 30 MG Inj.	J9265
Exclusion Criteria	
Trastuzumab	J9355

Appendix D. NDCs used to define chemotherapy

Inclusion Criteria	
Cyclophosphamide	00054412925, 00054413025, 00054808925,
	00054813025, 10019095501, 10019095550,
	10019095601, 10019095616, 10019095701,
	10019095711, 38779050603, 54569571200,
	54569571300, 54868500500, 54868500501,
	54868521800, 54868521801, 54868521802,
	00015050041, 00015050141, 00015050241,
	00015050301, 00015050302, 00015050401,
	00015050541, 00015050641, 00087050001,
	00015053941, 00015054641, 00015054712,
	00015054741, 00015054812, 00015054841,
	00015054912, 00015054941, 00013560693,
	00013561693, 00013562693, 00013564670,
	00013563670
Doxorubicin	55390023110, 55390023210, 55390023301,
	55390023510, 55390023610, 55390023701,
	55390023801, 00013108691, 00013109691,
	00013109694, 00013110679, 00013111683,
	54868313100, 00013113691, 00013114691,
	00013114694, 00013115679, 00013116683,
	00013117687, 00013123691, 00013124691,
	00013125679, 00013126683, 00013128683,
	00074504001, 00074504303, 00074504601,
	00186153013, 00186153101, 00186153231,
	00186153241, 00186153261, 00186153281,
	00186157512, 00469100161, 00469883020,
	00469883130, 00469883250, 00702023110,
	00702023206, 00702023301, 00702023510,
	00702023606, 00702023610, 00702023701,
	00702023801, 00703504001, 00703504303,
	00703504601, 10019092001, 10019092102,
	53905023110, 53905023210, 53905023301,
	53905023510, 53905023610, 53905023701,
	53905023801, 55390024110, 55390024210,
	55390024301, 55390024510, 55390024610,
	55390024701, 55390024801, 63323010161,
	63323088305, 63323088310, 63323088330,
	00015335122, 00015335222, 00015335322
Docetaxel	00075800120, 00075800180, 00075800301,
	00075800404
Doxorubicin HCl liposomal	17314960001, 17314960002, 61471029512
Epirubicin	00009509101, 00009509301, 00591346983,
	00591347057, 00703306711, 00703306911,
	10139006101, 10139006125, 10518010410,
	10518010411, 25021020325, 25021020351,

	55390020701, 55390020801, 59762509101,
	59762509301, 61703034735, 61703034859,
	61703035901, 61703035902, 61703035959,
	61703035991, 61703035992, 61703035993,
	63323015100, 63323015105, 63323015125,
	63323015175, 66758004201, 66758004202,
Fluorouracil	00013103691, 00013104694, 00013105694,
	00703301513, 00703301812, 00703301912,
	00066715030, 54868545000, 00004150603,
	00004170406, 00004170506, 00187320202,
	00187320210, 00187320302, 00187320310,
	00187320426, 00187320447, 54569110000,
	54569156600, 54868095100, 54868095101,
	58016201701, 00023081030, 00023081230,
	54569156500, 55045210308, 58016910601,
	00004197701, 00187395364, 10019095002,
	10139006301, 10139006310, 10139006311,
	10139006312, 10139006320, 10139006350,
	38779002501, 38779002504, 38779002505,
	38779002509, 38779002510, 38779002525,
	39769001210, 39769001290, 43547025801,
	43547025901, 49452317501, 49452317502,
	49452317503, 49452317504, 51552073301,
	51552073302, 51552073304, 51552073305,
	51672406201, 51672406301, 51672411806,
	51927108500, 61703040932, 61703040953,
	61703040967, 62991148602, 63323011710,
	63323011720, 63323011751, 63323011761,
	63370009515, 63370009525, 63370009535,
	66530024940, 66758004401, 66758004403,
	68682000431, 68682008531
Methotrexate	00013229691, 00013226691, 00013227691,
	00013228691, 38779003503, 38779003504,
	38779003506, 38779003510, 38779003511,
	38779003515, 38779003525, 49452460001,
	49452460002, 49452460003, 49452460101,
	49452460102, 49452460103, 49452460104,
	51552105401, 51552105409, 51927156500,
	62991120001, 62991120002, 63370015410,
	63370015415, 63370015425, 00005450723,
	00054455015, 00054455025, 00054855003,
	00054855005, 00054855006, 00054855007,
	00054855010, 00054855025, 00182153901,
	00182153995, 00364249901, 00364249936,
	00378001401, 00378001450, 00405464301,
	00405464336, 00536399801, 00536399836,
	00555057202, 00555057235, 00555057245,
	00555057246, 00555057247, 00555057248,

	00555057249, 00603449921, 00677161001,
	00781107601, 00781107636, 00839790506,
	00904174960, 00904174973, 00904601260,
	11845110401, 21695011100, 23490588900,
	49999038024, 49999038036, 51079067001,
	51079067005, 51079067086, 51079067087,
	51079067088, 51079067089, 51285050902,
	52959024400, 53002048720, 54569181800,
	54569181803, 54569181809, 54868382600,
	54868382601, 54868382602, 54868382603,
	54868382604, 54868382605, 54868382606,
	54868382607, 54868382608, 54868382609,
	54868479600, 55289092430, 59911587401,
	61703035038, 61703040822, 62584078201,
	62701094036, 62701094099, 63323012302,
	63323012310, 63629147201, 63629147202,
	66479013501, 66479013509, 67253032010,
	67253032036, 68115063200, 10139006202,
	10139006210, 10139006240, 54868017301,
	54868471600, 55390003110, 55390003210,
	55390003310, 55390003410, 55390014301,
	61703040841, 63323012102, 63323012104,
	63323012108, 63323012110, 63323012140,
	63323012250, 66479013611, 66479013721,
	66479013929, 66758004001, 66758004002,
	66758004008, 66758004101, 00205532526,
	00205532618, 00205532730, 00205533734,
	54569452500, 58406068312, 58406068315,
	58406068316, 58406068318, 66479013613,
	66479013619, 10019094101, 53905003110,
	53905003210, 53905003310, 53905003410,
	54569531600, 61703040707, 61703040732,
	61703040858, 10019094001, 10019094002,
	61703040804, 61703040807, 61703040813,
	61703040832, 00205455626, 00205465302,
	00205465490, 00205533834, 00205933792,
	58406067101, 58406067103, 58406068114,
	58406068117, 58406067105, 58406067301,
	00005450704, 00005450705, 00005450707,
	00005450709, 00005450791, 67253058042
	67253058043, 67253058044, 67253058045,
	67253058046, 00555092701, 00555092801,
	00555092901, 00555094501, 51285036601,
	51285036701, 51285036801, 51285036901
Paclitaxel	00015345620, 00015345699, 00015347520,
	00015347527, 00015347530, 00015347620,
	00015347627, 00015347630, 00015347911,
	00172375377, 00172375396, 00172375473,

	00172375494, 00172375531, 00172375576,
	00172375675, 00172375695, 00074433501,
	00074433502, 00074433504, 00555198414,
	00555198514, 00703476401, 00703476601,
	00703476701, 00703476801, 10518010207,
	10518010208, 10518010209, 51079096101,
	51079096201, 51079096301, 55390011405,
	55390011420, 55390011450, 55390030405,
	55390030420, 55390030450, 55390031405,
	55390031420, 55390031450, 55390051405,
	55390051420, 55390051450, 61703034209,
	61703034222, 61703034250, 63323076305,
	63323076316, 63323076350, 66758004301,
	66758004302, 66758004303
Paclitaxel Protein-Bound	68817013450
Exclusion Criteria	
Trastuzumab	50242005656, 50242013460, 50242013468

Appendix E. States used in regional breakdown

U.S. Census Bureau Regions	
Northeast	
Connecticut	New Jersey
Maine	New York
Massachusetts	Pennsylvania
New Hampshire	Vermont
Rhode Island	
Midwest	
Indiana	Nebraska
Illinois	Kansas
Michigan	North Dakota
Ohio	Minnesota
Wisconsin	South Dakota
Iowa	Missouri
South	
Delaware	Alabama
District of Columbia	Kentucky
Florida	Mississippi
Georgia	Tennessee
Maryland	Arkansas
North Carolina	Louisiana
South Carolina	Oklahoma
Virginia	Texas
West Virginia	
West	
Arizona	Alaska
Colorado	California
Idaho	Hawaii
New Mexico	Oregon
Montana	Washington
Utah	Wyoming
Nevada	

Adapted from Census Regions and Divisions of the United States. (Accessed at http://www.census.gov/geo/www/us_regdiv.pdf.)

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