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Trends in Antineoplastic Receipt after Medicare Payment Reform: Implications for Future Oncology Payment Design

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Abstract

Background—The Medicare Modernization Act (MMA) reduced reimbursement for many antineoplastics delivered in outpatient settings, altering practice patterns for some cancers. To further evaluate the MMA's effect, we focus on colon cancer, where longstanding fluorouracil-based regimens were augmented in 2004 with 3 newly-approved drugs (oxaliplatin, bevacizumab, and/or cetuximab). Staggered implementation of MMA reimbursement changes (physician offices implemented reimbursement changes in 2005 vs hospital outpatient departments(OPD) in 2006) provide a natural experiment to examine policy effects.

Methods—Using the 2000–2009 SEER-Medicare data, we examined antineoplastic use among 59,642 stage II–IV colon cancer patients. Using multivariate logistic regression models, we conducted difference-in-differences analyses to examine an interaction between time (pre-post MMA) and setting (physician offices versus OPDs) on antineoplastic receipt, adjusting for patient and cancer characteristics. A significant interaction indicates different practice patterns in physician offices versus OPD during the staggered implementation.

Results—After the reimbursement change in 2007–09 relative to 2000–03, use of fluorouracil-based therapy decreased slightly (Marginal Probability(MP): –0.07 stage II; –0.05 stage III; –0.05

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stage IV; $p < 0.01$), while use of new drugs increased substantially (MP: 0.48 stage II; 0.69 stage III, 0.79 stage IV; $p < 0.01$). The interaction between MMA implementation and physician office setting was significant when examining use of new agents for Stage IV disease only.

Conclusions—Our results indicate that providers responded to reimbursement changes after the MMA by increasing use of newly approved agents, but the magnitude of the response was small and limited to individuals diagnosed with Stage IV disease.

Keywords

Medicare Modernization Act; colon cancer; SEER-Medicare; policy; treatment

Health insurance design and reimbursement have substantial effects on individuals' utilization of healthcare, adherence with drug therapies, and health outcomes.¹⁻⁶ As the primary insurer for most cancer patients aged 65 and older, Medicare policies for reimbursement of chemotherapeutic agents and biologics (i.e., antineoplastics) may greatly influence the availability and use of recommended treatments,⁷ as demonstrated with payment changes to other Medicare services.⁷⁻⁹ The Medicare Modernization Act (MMA) of 2003 was aimed at addressing rising cancer treatment costs, substantially reducing reimbursement for many antineoplastic drugs delivered in outpatient settings, particularly generic drugs.^{10,11} Prior to the MMA, Medicare reimbursed providers for 95% of the average wholesale price or billed charges for the drug, whichever was less. As acquisition costs were often substantially lower than wholesale prices, oncologists could reap substantial net revenues. However, the relationship between acquisition costs and net revenues varied dramatically by agent, physician practice volume and other characteristics.^{7,12} Beginning in 2005 with the implementation of the MMA, Medicare instituted a new payment system where providers are reimbursed based on no more than 6% over the manufacturer's average sales price (ASP) during the previous two quarters.^{10,13} This change resulted in large reimbursement cuts for some agents. For example, the average reimbursement rate for standard monthly doses of fluorouracil declined from \$41 to \$33 from 2004 to 2009.^{7,14} At the same time, reimbursement for patented cancer drugs providing comparable or slightly improved patient survival compared to generic drugs approached \$7,000 to \$10,000 per month.^{13,15} Consequently, under the new reimbursement structure, provider gross revenues were now linked to the ASP, with greater potential net revenues for more costly drugs. Considering that prices for new chemotherapeutic agents appear to be rising faster than their associated health benefits,^{16,17} identifying the implications of MMA payment changes on treatment patterns is important for understanding the most effective future reimbursement policies for cancer care.

Prior research on the early effects of the MMA suggest that oncologists may alter chemotherapy regimens for cancer to maximize net reimbursements.^{7,18} Among a subset of lung cancer patients, one analysis indicated an increased likelihood of receiving chemotherapy after the MMA, as well as increased prescribing of more expensive, non-generic lung cancer drugs.^{7,19,20} Another study supported these findings, suggesting that individuals diagnosed with colon or lung cancer were less likely to receive drugs substantially affected by MMA reimbursement changes.¹⁸ However, these studies were limited in their ability to explore practice responses after payment reform as they do not

include data beyond the initial year of MMA implementation (2006),^{7,18,20} lack cancer-focused clinical data^{7,20} or include only a small proportion of Medicare-eligible individuals who might be impacted by reimbursement changes.¹⁸ To further understand the longer-term effect of the MMA, we focus on colon cancer treatment, where longstanding fluorouracil-based (fluorouracil (5FU) or capecitabine) regimens, with or without irinotecan, were augmented in 2004 with 3 newly-approved drugs (oxaliplatin, bevacizumab, and/or cetuximab).^{21–23} We specifically chose to evaluate the impact of the MMA on colon cancer because, unlike lung cancer, where oncologists could switch from low cost (i.e., generic paclitaxel) to high cost (i.e., brand-name docetaxel) drugs for treatment and realize larger net revenues, colon cancer regimens only allow for the addition of newer, more expensive drugs to fluorouracil-based treatments. We hypothesized that in response to payment changes, providers will change practice patterns toward newer, more expensive drugs; however, stage-based treatment recommendations^{21,24} and market entry of new drugs may influence treatment more than reimbursement. Staggered implementation of MMA reimbursement changes (physician offices implemented reimbursement changes in 2005 vs hospital outpatient departments(OPD) in 2006) allowed for a natural experiment to examine policy effects.^{25,26}

Methods

Data

We used the 2000–2009 Surveillance, Epidemiology, and End Results (SEER)-Medicare data. SEER data include information on cancer characteristics, first course of treatment and survival provided by cancer registries covering >28% of the U.S. population.²⁷ For Medicare-eligible individuals (approximately 97% of the U.S. population aged ≥65²⁸), SEER data are matched to the Medicare master enrollment file. For fee-for-service Medicare enrollees, claims for inpatient procedures are available in the MedPAR (hospitalization) and NCH (provider) files, while office visits are captured through NCH files for provider charges, Outpatient Files for facility charges and Durable Medical Equipment (DME) files for some oral antineoplastic agents.

Patients

We included 59,642 individuals who were ≥66 years at diagnosis with primary, American Joint Commission on Cancer (AJCC) 6th Edition stages II–IV colon cancer; were enrolled in Medicare Part A and B and not in a managed care plan from one year prior to six months post diagnosis or death because Medicare files do not include claims data for these enrollees; and were not diagnosed by autopsy or death certificate (because they would not be eligible for treatment).

Measures

Dependent Variables

Receipt of Antineoplastic Therapy: We defined receipt of antineoplastic therapy (yes/no) as any claims-based evidence of chemotherapy administration or drug codes in the Medicare claims (NCH, Outpatient or DME) within 6 months of diagnosis based on clinical guidelines

and previous studies evaluating chemotherapy utilization in the SEER-Medicare data.^{24,29} While antineoplastic therapy is recommended for AJCC stages III–IV, we acknowledge use of adjuvant therapy for AJCC stage II remains controversial.²⁴ Appendix 1 contains a list of all included antineoplastics.

We also created indicators for specific individual or groups of agents, based on the presence of any claim for a specific drug within 6 months of diagnosis. Indicators flagged receipt of a 1) fluorouracil-based agent (fluorouracil and/or capecitabine), 2) irinotecan, 3) new agents approved for first line therapy during the MMA reimbursement transition (oxaliplatin, bevacizumab and cetuximab)^{21–23} or 4) non-standard therapy (any antineoplastic claim for a drug not indicated for treatment of colon cancer according to NCCN guidelines).²⁴ We include use of new therapies for AJCC stages II–IV regardless of indication.

Independent variables—The SEER cancer registry data include information on the year of diagnosis (grouped as 2000–2003 (pre-MMA implementation), 2004, 2005, 2006 (individual implementation years) and 2007–2009 (post-MMA implementation), sex (male, female), race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic and Non-Hispanic Other), AJCC stage at diagnosis (II, III, IV), and cancer histology (adenocarcinoma, other). We additionally included information on Charlson comorbidity score^{30,31} (0, 1, 2, 3) based on diagnosis codes in Medicare claims in the year prior to diagnosis, as well as information on poverty status, % of population without a high school degree and % minority based on 2000 census tract data from the individual's residence at diagnosis. Finally, provider setting was defined based on predominant chemotherapy claim source (hospital outpatient vs. physician files) to account for differential timing of reimbursement changes under the MMA in physician office (2005) and hospital outpatient (2006) settings.²⁶ Antineoplastics covered under DME were assigned to the provider setting based on where the prescribing physician works.

Analysis

We first examined trends in antineoplastic use and type by stage at diagnosis (Figure 1a–c). Using multivariate logistic regression models, we conducted difference-in-differences analyses to examine an interaction between time (pre-post MMA) and setting (physician offices vs. OPDs) on receipt of any antineoplastic, and each of the distinct groups of antineoplastics, adjusting for patient and cancer characteristics. We used 2000–2003 as the reference years for all models except for newly approved agents, where 2004 was used, as this was the year of FDA-approval. All models controlled for a comprehensive set of independent patient socio-demographic and tumor characteristics identified above. Additionally, each model included an interaction term between diagnosis year and provider setting to allow for a natural experiment to examine policy effects through the staggered implementation of MMA reimbursement changes. A significant interaction would indicate different practice patterns in physician offices vs. OPD during the staggered implementation. Our marginal effects are interpreted as change in the probability of each outcome, when all other variables are set to the average for our patient population.³² Finally, we present each of our models stratified by stage at diagnosis to account for the different indications and FDA-

approval by extent of disease (e.g., bevacizumab was only FDA-approved for first and second-line treatment of metastatic colorectal cancer).²²

We performed several sensitivity analyses to evaluate if associations between diagnosis year (pre-post MMA implementation) and receipt of antineoplastics varied depending on modeling assumptions. Specifically, we evaluated this relationship using different categorizations for diagnosis year (continuous, Pre-post 2005 and pre-post 2006). In our original models, we grouped 321 individuals with an unknown source of care (i.e., antineoplastic claims from the DME claims only without an associated physician or outpatient hospital claim) with our most common practice setting, physician offices. In sensitivity analyses, we excluded those with unknown practice settings. Further, previous studies have indicated under-reporting of oral capecitabine in Medicare claims, which may have led to underestimates of fluorouracil-based therapy. In sensitivity analyses, we modeled outcomes assuming all individuals with a chemo-administration claim only were treated with fluorouracil-based therapy and then excluding those with only non-fluorouracil-based therapy from analysis.³³ Under all analyses, our main conclusions remained unchanged. Data cleaning was conducted using SAS 9.3 and analyses using StataSE 12. All statistical tests were two-sided, with an alpha=0.05. This study was approved by the Institutional Review Board.

Results

A total of 59,642 patients were diagnosed with AJCC stages II–IV colon cancer during 2000–2009, 34.1% (n=20,336) of whom received antineoplastic therapy within 6 months of diagnosis (Table 1). Treatment varied by stage at diagnosis, with 16.3% of stage II, 52.4% stage III and 39.6% stage IV colon cancer patients receiving antineoplastics. Further, those who were older at diagnosis, female, Non-Hispanic black or had a higher Charlson Comorbidity Index were less likely to receive an antineoplastic. Antineoplastic use also varied by community demographics, with patients living in communities with higher levels of poverty, a larger proportion of individuals without high school education and higher proportion of minorities less likely to receive antineoplastics as part of their care. Among those receiving antineoplastics, the majority was administered in a physician's office (78.5%) (Table 1).

Trends in Antineoplastic Use

Overall use of antineoplastics declined from 2000 to 2009 for AJCC Stages II–III, while use increased for Stage IV (Table 2; Figure 1). Among those receiving antineoplastics, the majority received fluorouracil-based therapy, which shifted from intravenous fluorouracil to oral capecitabine over time for all stages. Among newly approved agents, use of oxaliplatin and bevacizumab increased rapidly, particularly for AJCC III–IV disease (Table 2; Figure 1), consistent with FDA approval in 2004. Use of newly approved agents also increased significantly over time for those with AJCC stage II disease, regardless of indication. Further, large proportions of stage IV patients were treated with oxaliplatin, bevacizumab, and cetuximab within just a few years of approval (69.6%, 55.6%, and 4.4% in 2009). Use

of irinotecan declined over time, while use of other agents remained low (<7%) for all stages.

Changes in Antineoplastic Use over Time

After the reimbursement change in 2007–2009 relative to 2000–2003, stages II (marginal probability (MP)=−0.045, (99% Confidence Interval:−0.057;−0.033) and III (MP=−0.026(−0.052;−0.000)) patients saw small but significant decreases in any antineoplastic use, while stage IV patients saw increased use (MP=0.079(0.048;0.104) (Table 3; Figures 1a–c). While use of fluorouracil-based therapy slightly decreased after reimbursement changes across all stages in 2007–2009 relative to 2000–2003 (stage II(MP=−0.071); stage III(MP=−0.047); stage IV(MP=−0.049), use of newly approved agents increased substantially (stage II(MP=0.334), stage III(MP=0.417), stage IV(MP:0.231) relative to 2004, when the drugs were approved (Table 3). Use of irinotecan-based therapy decreased significantly after the reimbursement changes in 2007–2009 relative to 2000–2003 for stages III and IV and remained stable for stage II (Table 3).

In multivariable models including an interaction term between diagnosis year and provider setting (Table 3), we found no significant differences in use of fluorouracil-based therapy, irinotecan or non-standard therapy by provider setting during MMA implementation ($p > 0.05$). However, we found a significantly higher use of newly approved agents in physician offices relative to OPD in 2005 ($p=0.001$) for stage IV colon cancer, indicating different practice patterns during the staggered implementation of the MMA (Table 3; Figure 1c).

Discussion

In this large scale, clinically-based study of the impact of the MMA on antineoplastic use for older adults with colon cancer, we found minor substitution away from inexpensive fluorouracil-based therapy, but found evidence of increased adoption of newly approved agents for individuals with stage IV disease associated with the reimbursement change. Specifically, we found increased use of newly approved agents throughout the period, but found that adoption accelerated in physician offices relative to OPD settings in 2005, which implemented the payment changes one year earlier than OPDs; although the specific effects of the MMA are likely small relative to increased utilization associated with availability of the newly approved therapies. Our results reinforce earlier findings concerning provider response to changes in chemotherapy reimbursement, and suggest that reimbursement cuts through the federal budget agreement of 2013 may create similar incentives to add more expensive chemotherapy regimens for stage IV patients.

Overall, we find a more nuanced effect of payment reform on physician practices several years after implemented changes and highlight the need to place practice changes in context with other practice-changing policies such as FDA-approval of new drugs.^{21–23} Specifically, we identify slightly earlier increases in use of higher-margin (i.e., newly approved) drugs in physician offices for stage IV patients, where payment changes were implemented before hospital outpatient facilities. However, the MMA-related change in utilization was small relative to increases in utilization directly after FDA-approval and NCCN guideline

development for these new drugs (Figures 1a–c) and, importantly, this effect was only seen in stage IV patients, demonstrating a localized impact.

Previous studies have suggested that physicians may alter practice patterns in response to Medicare reimbursement policies in oncology settings.^{7,18,20,34} The intent of the MMA was to more closely align reimbursement with drug acquisition costs for oncology drugs.¹¹ This change may incentivize providers to prescribe higher-cost and, therefore, higher-margin drugs. Jacobsen et al. demonstrated that among a sample of Medicare-eligible lung cancer patients, the MMA increased the likelihood that individuals received chemotherapy; however, they were also more likely to receive treatment with higher-margin drugs.^{7,20} Hornbrook et al. partially supported these findings in a sample of newly diagnosed lung and colon cancer patients from the Cancer Care Outcomes Research Surveillance Consortium, finding that lung cancer patients experienced significant increases in use of the most-profitable drugs after the MMA while colon cancer patients experienced declining use of the most-profitable drugs.¹⁸ In contrast, Colla et al. found that among a sample of Medicare beneficiaries at the end of life, use of chemotherapy significantly decreased after the MMA in physician offices but not in hospital outpatient facilities; however they do not evaluate changes in utilization of individual drugs, making conclusions about changing practice patterns challenging.³⁴ While Jacobsen and Hornbrook, respectively, demonstrate some effect of the MMA by increasing utilization of higher-margin drugs, our large population-based analyses extend these policy evaluations to include practice patterns several years after the policy implementation,^{7,18,20} comprehensive cancer-focused clinical data to place treatment in context,^{7,20} and a large Medicare population with diverse clinical and demographic characteristics.¹⁸

Our study presents several implications for future policy modifications targeting reimbursement of oncology services as well as Medicare services more broadly. First, our study highlights the difficulty of assessing the impact of reimbursement policies in rapidly changing clinical and regulatory environments, particularly in the Medicare program where most changes are implemented nationally. For example, these reimbursement changes were implemented during significant practice changes, including the approval of three high-profile drugs (oxaliplatin, bevacizumab, and/or cetuximab) as well as guideline changes for Stage II disease (e.g., ASCO announced there was not enough evidence to support adjuvant therapy unless patients had “high risk disease”).²⁴ Without clinical context and knowledge about the changing practice environment for oncology services, practice changes may be inappropriately attributed to specific policies. Control groups could greatly benefit our ability to tease apart the effects of specific policy changes and new drugs entering the market. Second, our results demonstrate differential changes by stage of disease, highlighting disparate effects of these policies across settings and populations. Finally, these findings suggest that despite significant reimbursement changes for oncology drugs under the MMA, the overall impact on practice patterns for colon cancer was relatively small. This may have significant implications as the CMS implements new payment models under its Oncology Demonstration Projects as well as reduction in reimbursement as a result of sequestration policies and the Affordable Care Act.³⁵

While our findings demonstrate the effect of the MMA several years after the payment changes in a large, population-based sample of Medicare beneficiaries with colon cancer, one of the most common cancers in the US, we acknowledge certain limitations. First, some concern has been raised that SEER regions, which currently represent >28% of the US population,²⁷ may respond differently to policy changes than the US as a whole.¹⁹ While we recognize that our estimates may be conservative, the relative MMA impact we identify is likely small compared to changing practice patterns due to new treatment options. Additionally, while the staggered implementation of MMA payment changes allowed for evaluation of practice patterns at the time of change, reimbursement changes applied to all Medicare beneficiaries so no true control group exists to examine practice patterns in the absence of policy. Despite these limitations, we demonstrate a significant effect of the MMA payment changes on treatment patterns for Medicare-eligible colon cancer patients. The identifiable effects of the MMA are relatively small, but highlight the responsiveness of providers to changes in reimbursement, and the need to integrate new drugs into existing payment schema.

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Appendix 1

Type and Frequency of Claims of Colon Cancer Patients (Stage II, III or IV) who Received Chemotherapy, SEER Medicare 2000–2009 (N=20,336)

Claim Type	Number of Patients with Claim	Percent (%)
ARSENIC TRIOXIDE	<11	<4.00
ASPARAGINASE	<11	<4.00
AZACITIDINE	<11	<4.00
BCG	<11	<4.00
BEVACIZUMAB	2,283	11.23
BLEOMYCIN	<11	<4.00
BORTEZOMIB	<11	<4.00
CAPECITABINE	2,271	11.17
CARBOPLATIN	141	<4.00
CARMUSTINE	<11	<4.00
CETUXIMAB	159	<4.00
CISPLATIN	47	<4.00
CLADRIBINE	<11	<4.00
CYCLOPHOSPHAMIDE	61	<4.00
CYTARABINE	<11	<4.00
DACARBAZINE	<11	<4.00
DACTINOMYCIN	<11	<4.00
DAUNORUBICIN	<11	<4.00
DECITABINE	<11	<4.00
DENILEUKIN DIFTITOX	<11	<4.00
DOCETAXEL	30	<4.00
DOXORUBICIN	47	<4.00
EPIRUBICIN	<11	<4.00
ETOPOSIDE	63	<4.00
FLOXURIDINE	64	<4.00
FLUDARABINE	64	<4.00
FLUOROURACIL	16,997	83.58
FULVESTRANT	<11	<4.00
GEMCITABINE	48	<4.00
GOSERELIN	54	<4.00
IFOSFAMIDE	<11	<4.00
INTERFERON ALFA-2A	<11	<4.00
INTERFERON ALFA-2B	19	<4.00
INTERFERON ALFACON-1	<11	<4.00

Claim Type	Number of Patients with Claim	Percent (%)
IRINOTECAN	2,076	10.21
IXABEPILONE	<11	<4.00
LEUPROLIDE	52	<4.00
MECHLORETHAMINE	<11	<4.00
MEDROXYPROGESTERONE	<11	<4.00
METHOTREXATE	36	<4.00
MITOMYCIN	42	<4.00
MITOXANTRONE	<11	<4.00
OXALIPLATIN	6,166	30.32
PACLITAXEL	82	<4.00
PANITUMUMAB	<11	<4.00
PEMETREXED	12	<4.00
PLICAMYCIN	<11	<4.00
RITUXIMAB	23	<4.00
TOPOTECAN	<11	<4.00
TRASTUZUMAB	10	<4.00
TRIMETREXATE GLUCURONATE	12	<4.00
TRIPTORELIN	12	<4.00
VALRUBICIN	<11	<4.00
VINBLASTINE	<11	<4.00
VINCRIStINE	26	<4.00
VINORELBINE	<11	<4.00

a

b

c

Figure 1.
Trends in Antineoplastics Use in AJCC Stages II–IV Colon Cancer Patients, SEER-Medicare 2000–2009; New Drugs=Oxaliplatin, Cetuximab and/or Bevacizumab

Table 1

Socio-demographic and Cancer Characteristics of Patients Diagnosed with AJCC Stages II–IV Colon Cancer, 2000–2009 SEER-Medicare Data

	Total Column %, (#)	Received Antineoplastics Row %	p-value
# of Patients	59,642	20,336 (34.1%)	
Socio-demographic Characteristics			
Age at Diagnosis			
65–69	14.6% (8,733)	56.3%	<0.01
70–74	20.6% (12,266)	49.4%	
75–79	22.9% (13,673)	39.3%	
80–84	21.2% (12,640)	23.8%	
85	20.7% (12,330)	8.1%	
Sex			
Male	43.4% (25,905)	37.2%	<0.01
Female	56.6% (33,737)	31.7%	
Race/Ethnicity			
NH White	84.2% (50,210)	34.3%	<0.01
NH Black	9.8% (5,828)	30.1%	
Hispanic	1.4% (803)	37.1%	
NH Other	4.7% (2,801)	38.9%	
Place of Residence			
Metropolitan Area	81.8% (48,788)	34.1%	0.90
Non-Metro Area	18.2% (10,854)	34.0%	
% Below the Poverty Threshold, CT 2000 ^I Mean [StD]			
	11.7 [9.8]	11.2 [9.4]	<0.01
% aged 25+ Without a High School Degree, CT 2000 ^I Mean [StD]			
	19.7 [13.0]	19.4 [13.0]	<0.01
% Minority, CT 2000 ^I Mean [StD]			
	25.0 [25.2]	24.1 [24.6]	<0.01
Cancer Characteristics			
AJCC Stage at Diagnosis			
II	42.0% (25,051)	16.3%	<0.01
III	33.7% (20,088)	52.4%	
IV	24.3% (14,503)	39.6%	
Charlson Comorbidity Index ²			
0	26.7% (15,927)	46.9%	<0.01
1	25.6% (15,245)	38.6%	
2	19.0% (11,350)	32.5%	
3	28.7% (17,120)	23.6%	
Histology			
Adenocarcinoma	75.9% (45,243)	34.6%	<0.01

	Total Column %, (#)	Received Antineoplastics Row %	p-value
Other	24.1% (14,399)	32.7%	
Antineoplastic Provider Setting			
Hospital Outpatient Department	-	19.9%	
Physician's Office	-	78.5%	
Unknown	-	1.6%	
Diagnosis Year			
2000–2003(Pre-MMA)	43.4% (25,871)	35.5%	<0.01
2004	10.8% (6,467)	34.0%	
2005	10.3% (6,116)	33.2%	
2006	9.6% (5,732)	31.4%	
2007–2009(Post-MMA)	25.9% (15,456)	33.1%	

Notes:

¹ p-value using ANOVA, all other p-values represent Chi-squared tests

² Based on comorbidities treated <1yr prior to cancer diagnosis.

AJCC=American Joint Committee on Cancer

CT=Census Tract

Table 2

Antineoplastic Use in Patients Diagnosed with AJCC Stages II–IV Colon Cancer between 2000–2009, SEER-Medicare Data

	All Years	Year of Diagnosis									OR (p-value) ^f	
		2000	2001	2002	2003	2004	2005	2006	2007	2008		2009
Stage II												
Any Chemotherapy Yes	16.3%(4,072)	21.1%	19.0%	18.5%	17.3%	15.8%	14.2%	14.8%	14.2%	12.0%	12.7%	0.93(<0.01)
Type of Antineoplastic Fluorouracil	83.4%(3,397)	96.9%	94.8%	94.4%	91.4%	84.1%	69.4%	72.4%	64.2%	65.3%	65.4%	0.72(<0.01)
Capecitabine	9.5% (387)	-	<4.0%	<4.0%	5.4%	7.7%	17.0%	18.0%	26.4%	22.8%	22.5%	1.49(<0.01)
Irinotecan	<4.0%(117)	<4.0%	<4.0%	<4.0%	<4.0%	4.1%	<4.0%	<4.0%	<4.0%	<4.0%	<4.0%	0.97(0.33)
Oxaliplatin	16.5%(672)	-	-	-	<4.0%	15.4%	29.0%	39.5%	43.0%	42.1%	43.8%	1.70(<0.01)
Bevacizumab	<4.0%(116)	-	-	-	<4.0%	<4.0%	5.6%	5.8%	7.2%	9.3%	10.4%	1.65(<0.01)
Cetuximab	<4.0%(<11)	-	-	-	-	<4.0%	-	<4.0%	-	<4.0%	<4.0%	1.75(<0.01)
Other Agents	4.8% (197)	4.9%	4.6%	<4.0%	5.0%	6.5%	6.1%	4.7%	5.2%	<4.0%	5.0%	1.00(0.92)
Unknown	<4.0%(112)	<4.0%	<4.0%	<4.0%	<4.0%	<4.0%	7.2%	<4.0%	<4.0%	<4.0%	<4.0%	1.11(<0.01)
Stage III												
Any Chemotherapy Yes	52.4%(10,519)	54.5%	53.4%	54.6%	57.0%	51.9%	50.8%	48.1%	51.6%	49.9%	49.9%	0.97(<0.01)
Type of Antineoplastic Fluorouracil	86.5%(9,098)	98.7%	98.2%	96.5%	95.2%	85.7%	76.3%	77.5%	73.4%	75.3%	75.6%	0.73(<0.01)
Capecitabine	10.3%(1,078)	<4.0%	<4.0%	<4.0%	<4.0%	9.6%	19.1%	16.4%	21.4%	20.3%	20.3%	1.41(<0.01)
Irinotecan	4.9% (510)	6.5%	6.9%	7.7%	5.8%	4.1%	4.5%	<4.0%	<4.0%	<4.0%	<4.0%	0.87(<0.01)
Oxaliplatin	30.3%(3,245)	-	-	-	5.4%	30.3%	49.7%	63.1%	63.8%	65.9%	68.6%	1.86(<0.01)
Bevacizumab	<4.0%(392)	-	-	-	-	<4.0%	7.2%	9.9%	8.4%	7.8%	7.1%	1.46(<0.01)
Cetuximab	<4.0%(27)	-	-	-	-	<4.0%	<4.0%	<4.0%	<4.0%	<4.0%	<4.0%	1.44(<0.01)
Other Agents	<4.0%(279)	<4.0%	<4.0%	4.2%	<4.0%	<4.0%	<4.0%	<4.0%	<4.0%	<4.0%	<4.0%	0.90(<0.01)
Unknown	<4.0%(139)	<4.0%	<4.0%	<4.0%	<4.0%	<4.0%	<4.0%	<4.0%	<4.0%	<4.0%	<4.0%	1.07(0.02)

	Year of Diagnosis										OR (p-value) ^I
	All Years	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Any Chemotherapy											
Yes	39.6%(5,745)	38.5%	38.0%	38.5%	38.4%	39.6%	40.6%	38.4%	40.0%	42.4%	42.3%
Type of Antineoplastic											
Fluorouracil	78.3%(4,502)	94.1%	90.6%	84.7%	79.5%	76.2%	76.7%	70.4%	68.9%	70.4%	72.2%
Capecitabine	14.0%(806)	<4.0 %	6.7%	11.9%	13.9%	13.0%	14.4%	17.0%	21.9%	19.3%	21.4%
Irinotecan	25.2%(1,449)	35.0%	40.1%	41.4%	37.2%	21.0%	17.8%	14.6%	14.8%	14.8%	15.8%
Oxaliplatin	39.2%(2,249)	-	-	-	16.4%	51.2%	57.4%	64.3%	62.7%	68.6%	69.6%
Bevacizumab	30.9%(1,775)	-	-	-	<4.0%	20.5%	59.6%	61.4%	57.5%	55.4%	55.6%
Cetuximab	<4.0%(126)	-	-	-	<4.0%	<4.0%	<4.0%	5.2%	4.5%	4.3%	4.4%
Other Agents	5.3%(307)	7.0%	7.0%	6.9%	5.9%	5.6%	4.9%	4.8%	<4.0%	<4.0%	4.6%
Unknown	<4.0%(105)	<4.0 %	>4.0%	<4.0%	<4.0%	<4.0%	<4.0%	<4.0%	<4.0%	<4.0%	<4.0%

Notes:

^I Odd Ratios(OR) and p-values from unadjusted logistic regression with year as independent variable; Categories not mutually exclusive except "unknown" , "-"=No patients with this antineoplastic; AJCC=American Joint Committee on Cancer

Table 3

Change in Probability of Antineoplastic Use Associated with MMA-related Reimbursement Changes in Patients Diagnosed with AJCC Stages II–IV
Colon Cancer between 2000–2009, SEER-Medicare Data

	Received Antineoplastics* MP(99%CI)	Fluorouracil-based Therapy MP(99%CI)	Newly-Approved Agent Therapy MP(99%CI)	Irinotecan Therapy MP(99%CI)	Non-Standard Therapy MP(99%CI)
Stage II⁺					
2000–2003	Ref.	Ref.	–0.145 (–0.190;–0.010)	Ref.	Ref.
2004	–0.027 (–0.043;–0.010)	–0.040 (–0.073;–0.006)	Ref.	0.010 (–0.015;0.035)	0.017 (–0.013;0.047)
2005	–0.034 (–0.051;–0.018)	–0.097 (–0.143;–0.050)	0.151 (0.074;0.228)	0.007 (–0.019;0.032)	0.014 (–0.017;0.045)
2006	–0.032 (–0.049;–0.016)	–0.072 (–0.115;–0.029)	0.262 (0.180;0.344)	–0.006 (–0.027;0.016)	–0.002 (–0.026;0.031)
2007–2009	–0.045 (–0.057;–0.033)	–0.071 (–0.101;–0.042)	0.334 (0.269;0.399)	–0.007 (–0.023;0.008)	–0.003 (–0.023;0.016)
HOD Setting*2000–2003 [#]			1.202, NS		
HOD Setting*2004		–0.985, NS		–0.119, NS	–0.103, NS
HOD Setting*2005		–0.618, NS	0.376, NS	–1.363, NS	–0.168, NS
HOD Setting*2006		–1.032, NS	0.251, NS	NE	–0.432, NS
HOD Setting*2007–2009		–0.161, NS	0.546, NS	NE	0.630, NS
Stage III⁺					
2000–2003	Ref.	Ref.	–0.275 (–0.311;–0.240)	Ref.	Ref.
2004	–0.027 (–0.062;0.008)	–0.044 (–0.063;–0.025)	Ref.	–0.025 (–0.042;–0.009)	–0.009 (–0.022;0.003)
2005	–0.045 (–0.081;–0.009)	–0.050 (–0.070;–0.030)	0.235 (0.180;0.291)	–0.021 (–0.039;–0.003)	–0.007 (–0.021;0.007)
2006	–0.059 (–0.096;–0.021)	–0.066 (–0.090;–0.042)	0.386 (0.329;0.442)	–0.036 (–0.053;–0.020)	–0.017 (–0.029;–0.004)
2007–2009	–0.026 (–0.052;–0.000)	–0.047 (–0.059;–0.034)	0.417 (0.373;0.460)	–0.038 (–0.050;–0.026)	–0.017 (–0.026;–0.008)
HOD Setting*2000–2003 [#]			0.091, NS		
HOD Setting*2004		–0.583, NS		0.307, NS	0.367, NS
HOD Setting*2005		–0.614, NS	–0.184, NS	0.157, NS	0.531, NS
HOD Setting*2006		0.147, NS	–0.220, NS	–0.209, NS	0.261, NS
HOD Setting*2007–2009		0.142, NS	0.274, NS	–0.085, NS	–0.424, NS
Stage IV⁺					
2000–2003	Ref.	Ref.	–0.562 (–0.615;–0.510)	Ref.	Ref.

	Received Antineoplasics* MP(99%CI)	Fluorouracil-based Therapy MP(99%CI)	Newly-Approved Agent Therapy MP(99%CI)	Irinotecan Therapy MP(99%CI)	Non-Standard Therapy MP(99%CI)
2004	0.029 (-0.008;0.066)	-0.069 (-0.105;-0.033)	Ref.	-0.176 (-0.224;-0.128)	-0.011 (-0.036;0.014)
2005	0.039 (0.000;0.077)	-0.051 (-0.086;-0.016)	0.195 (0.129;0.262)	-0.206 (-0.253;-0.160)	-0.018 (-0.042;0.007)
2006	0.019 (-0.019;0.058)	-0.075 (-0.114;-0.035)	0.221 (0.155;0.288)	-0.239 (-0.284;-0.194)	-0.018 (-0.043;0.007)
2007-2009	0.076 (0.048;0.104)	-0.049 (-0.072;-0.025)	0.231 (0.174;0.288)	-0.227 (-0.262;-0.191)	-0.027 (-0.044;-0.010)
HOD Setting*2000-2003 [#]			-0.052, NS		
HOD Setting*2004		-0.417, NS		0.022, NS	-0.186, NS
HOD Setting*2005		-0.394, NS	-1.138, p-value:0.001	-0.114, NS	-0.623, NS
HOD Setting*2006		0.263, NS	-0.280, NS	-0.072, NS	-0.644, NS
HOD Setting*2007-2009		0.111, NS	-0.249, NS	-0.204, NS	-0.196, NS

Notes: MP: Marginal Probability; NE: Not Estimable; NS: Non-significant, with P>0.05. HOD: Hospital Outpatient Department

First-line treatment: Fluorouracil and/or Capecitabine; Newly approved drugs:Oxaliplatin, Bevacizumab and/or Cetuximab;

Non-standard therapy: Drugs not including first-line, newly approved therapy or irinotecan;

[†] Marginal Probabilities adjusted for: provider setting, age, sex, race/ethnicity, non-metropolitan area, % living below federal poverty threshold, % minority, % aged 25 and without a high school degree/ GED, Charlson Comorbidity Index, cancer histology;

* Not adjusted for provider setting;

[#] Models adjusted for all main model variables plus an interaction term for time period and provider setting, estimates and p-values