Use of Bevacizumab for Newly Diagnosed Ovarian Cancer: A National Analysis

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Abstract

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Objective**:** To describe the use patterns and costs of bevacizumab (BEV) for the upfront treatment of ovarian cancer (OC) in the US.

Methods**:** We identified women ages 18 - 65 with newly diagnosed OC from 2008 to 2016 through the Truven Health MarketScan® database. Of these, women who underwent cancer-directed surgery and platinum-based chemotherapy within 6 months of diagnosis were included (N=8109). The proportion of women receiving BEV was calculated and multivariate logistic regression was used to determine factors associated with BEV use. Total costs per cycle of BEV were calculated.

Results: About 6.4% (N=522) of new OC cases received BEV within 6 months of diagnosis. Rates of BEV use increased 1.8-fold, from 4.1% (2008) to 7.4% (2016), with peak use in 2014 (8.5%). Patients receiving BEV were less likely than those not receiving BEV to be treated with a platinum/taxane doublet (46.4% v 90.4%) and more likely to be treated with platinum monotherapy (51.3% v 5.4%) ($p<0.001$). More recent year of diagnosis, younger age, presence

of ascites or metastatic disease, treatment by a medical oncologist, and residing in the Southern US were associated with statistically higher odds of receiving BEV ($p<0.01$). The median cost of one cycle of BEV monotherapy was $6873 [IQR:$4,824–11,276] and the cost of one cycle of platinum/taxane/BEV was $ 10,897 [IQR:$7,573–18,133].

Conclusion: BEV use has increased over the years and is related to several clinical and non-clinical factors. BEV has been used with non-standard regimens (platinum/taxane) over half the time and its cost is highly variable.

Introduction

Ovarian cancer (OC) affects 1 in 78 women in their lifetime [1]. In 2018, there were an estimated 22,240 new cases and 14,070 deaths from OC in the United States (US). [2] This makes OC the fifth leading cause of cancer death among US women, and the most common cause of gynecologic cancer death [2]. The majority of women with OC have high-grade epithelial tumors, are diagnosed with advanced (Stage III or IV) disease, and are treated with a combination or surgery and platinum/taxane chemotherapy. While most patients respond to first-line treatment, 80% eventually recur [3,4]. For this reason, research has focused on therapeutic modalities that can prevent recurrence or extend the disease-free interval.

The first biologic agent to be studied for this purpose was bevacizumab (BEV), a monoclonal antibody directed against the vascular endothelial growth factor (VEGF) [5]. Between 2009 and 2015, a series of trials explored the role of BEV as an addition to standard adjuvant chemotherapy for newly-diagnosed OC [6–11]. In two landmark phase III trials, GOG-218 and ICON7, women in the experimental arms were treated with BEV concurrently with standard carboplatin and paclitaxel chemotherapy for six cycles, and continued to receive BEV-only maintenance therapy every 3 weeks for an additional 12 to 16 cycles. These trials showed an improvement in progression free survival of 2-4 months with BEV. However, neither trial was able to demonstrate a statistically significant benefit in median overall survival. An exploratory subgroup analysis of ICON7 showed that the magnitude of benefit was greatest for a "high-risk" subgroup, defined as those with Stage IV disease or inoperable or suboptimally cytoreduced Stage III disease, among whom overall survival was improved by 5 months [11]. Based on these findings, the National Comprehensive Cancer Network (NCCN) added upfront BEV to its treatment guidelines for OC as a Category 3 recommendation in November 2012 [12], defined as

major disagreement among committee members that the intervention was appropriate. This was updated to a Category 2B recommendation in the 2016 guidelines [13], based on mature overall survival data from ICON7 [11], indicating NCCN consensus that the intervention was appropriate based upon lower-level evidence. More recently, on June 13, 2018, the FDA approved BEV for patients with OC in combination with carboplatin and paclitaxel, followed by single-agent BEV, for stage III or IV disease after initial surgical resection.

Despite its approval, healthcare economics studies have suggested that BEV may not be cost-effective as a first-line treatment, finding incremental cost effectiveness ratios (ICERs) as high as 300,000-400,000 US dollars per either quality adjusted or progression-free life year saved (QALYS or PF-LYS) [14,15]. However, more favorable ICERs have been reported for "high-risk" patients, on the order of 170,000 US dollars per LYS or QALY [16–18]. These ICERs have predominantly been based on Medicare reimbursement rates, reported to be 3,064 – 3225 US dollars per cycle of Bev monotherapy, based upon ICON7 dosing of 7.5 mg/m2.

Little is known about the early uptake of BEV for upfront treatment of OC in the US. Population-level, nationally-representative studies are needed in order to characterize treatment dissemination and ensure the consistent implementation of current standards of care and curve health care costs. The objectives of this study were thus three-fold: (1) to describe time trends in use of upfront BEV for the treatment of OC in the US during the time period of its active study for this indication, (2) to determine factors associated with BEV use (3) to calculate the costs to the healthcare system of the administration of BEV for OC among the commercially insured.

Methods

Study Design and Data Source

We conducted a retrospective cohort study utilizing data from the Truven Health MarketScan® Commercial Claims and Encounters database, an administrative insurance claims database which captures the health services of over 230 million employees, dependents, and retirees under the age of 65 in the US who are insured in fee-for-service, point-of-service, or capitated health plans by over 300 large, self-insurance US employers and over 25 US health plans [19,20]. Available data included inpatient medical, outpatient medical, and outpatient pharmacy claims as well as enrollment and demographic information. Data were de-identified and deemed exempt by the University of Washington Institutional Review Board.

Study Population

We queried the database for women who were first diagnosed with primary invasive cancers of the ovary, fallopian-tube or peritoneum between January 2008 and July 2016 (ICD-9 codes 158.8-9, 183.0-2-8-9 and ICD-10 codes C48.1-2-8, C56.1-2-9, C57.00-01-02-4). To increase the probability of capturing women at the time of new diagnosis and not recurrence, only women with continuous enrollment in the health plan for 12 months before the appearance of the first OC diagnosis code were included, since most women with existing OC are seen for surveillance or treatment at least on an annual basis, if not more frequently. Additionally, we restricted our cohort to women who underwent cancer-directed surgery and platinum-based chemotherapy within six months of diagnosis, as this represents the standard treatment for newly diagnosed OC. To minimize the number of women with non-epithelial OC histologies, for whom upfront BEV would not be indicated, we excluded adolescent women (age under 18) who are

most likely to present with these histologies, as well as those treated with bleomycin or etoposide, since these are standard treatments for germ cell tumors but not upfront epithelial OC. The time window for data collection was 12 months before diagnosis and six months after diagnosis. A flowchart of patient selection is presented in **Figure 1**. A complete list of diagnosis and procedures codes used to determine eligibility are available in the supplemental **Appendix**.

Outcomes and Covariates

The primary outcome was the provision of BEV within six months after OC diagnosis. Receipt of BEV was determined by the presence of Healthcare Common Procedure Coding System (HCPCS) or National Drug Code (NDC) codes (HCPCS: J9035, C9257, S0116 and NDC: 50242006001, 50242006002, 50242006101) coinciding in date with codes for receipt of intravenous chemotherapy (**Appendix**), in order to prevent inclusion of intraocular BEV use for ophthalmologic indications. Women with a code for BEV prior to first cancer diagnosis were excluded from the study since they would have received BEV for non-OC indications.

Administrative, demographic and financial covariates available from the parent database were utilized. This included age at diagnosis, date of diagnosis, type of benefit plan, metropolitan statistical area (MSA), and geographic region of residence. For type of benefit plan, we grouped plans in categories based on similarity of care provision structures, as follows: (1) preferred provider organizations (PPO), consumer-driven health plans (CDHP) and high deductible health plans (HDHP), since the latter two are essentially PPO plans coupled with health reimbursement arrangements or savings accounts (2) health maintenance organizations (HMOs) and exclusive provider organizations (EPOs) which are both managed care structures (3) non-capitated point-of-service (POS) plans and capitated or partially-capitated POS plans and (4) comprehensive plans. We also classified plans based on similarity of payment structures into non-capitated plans

(PPO, CDHP, HDHP, EPO, non-capitated POS and comprehensive) and partially or fully capitated plans (HMO and capitated or partially-capitated POS). We used MSA values to divide patients into those residing in rural areas (<50 thousand inhabitants) and urban areas (>= 50 thousand inhabitants) based on MSA-specific population density data publically available through the 2010 US Census Bureau [21].

Comorbidity was measured during the 12 months preceding OC diagnosis using the Charlson comorbidity score and classified as 0, 1-2, or ≥3 [22]. This index is a weighed measure of comorbid medical conditions that has been validated and used extensively in health services research. We identified markers of advanced disease (ascites, pleural effusions or extra-abdominal metastases) through the presence of related procedural and diagnostic codes (**Appendix**). In addition to BEV, we tracked receipt of cytotoxic chemotherapy regimens during the six-month time period, including platinum agents, taxanes, gemcitabine, liposomal doxorubicin, topotecan and cyclophosphamide (**Appendix**).

Provider information (identification number and type) was available for a subset of patients. While descriptions of provider type were not granular enough to identify gynecologic oncologists, who are variously characterized as "oncologists", "gynecologists" or "surgeons," we mapped provider identification number to whether that provider performed surgery and/or chemotherapy. Providers who performed both services were re-classified as gynecologic oncologists and those only performing chemotherapy were re-classified as medical oncologists.

Costs

Cost data for BEV were collected per episode of BEV administration, either alone or in combination with cytotoxic drugs, per eligible enrollee. We considered total costs to the insurers

and patients (the healthcare system perspective) for the entire episode of care, which included the cost of the drug(s), as well as infusion costs and other facility fees.

Data Analysis

Women were grouped into two groups based on whether or not they received BEV as part of their frontline treatment. Baseline and treatment characteristics of BEV users and non-users were compared using t-tests for continuous data and Chi-square tests for categorical data.

The trend in the utilization rate of BEV over time was evaluated in two ways. First, the percentage of BEV users was calculated as the number of women who received at least one dose of BEV within 6 months of diagnosis out of all women diagnosed with OC that year, even if the date of first BEV administration fell in the next calendar year. So, for example, if a patient was diagnosed in November 2008 and received the first dose of BEV in January 2019, she was counted as a BEV case in 2008. Additionally, the percentage of BEV users was also calculated using, as a denominator, all cases diagnosed during successive time periods flanked by the date of presentation or publication of key research findings or national guidelines. These key events were the publication of the first Phase II trial of BEV for frontline and maintenance treatment of OC in the United States (May 2009) [6], the presentation of GOG-218 at American Society of Clinical Oncology (ASCO) annual meeting (June 2010) [23], the presentation of ICON-7 at the European Society of Medical Oncology (ESMO) annual congress (October 2010) [24], the publication of GOG-218 and ICON-7 in the same issue of the New England Journal of Medicine (NEJM) (December 2011), [8,9] the inclusion of BEV as a Category 3 recommendation for the upfront treatment of OC by the NCCN (November 2012) [12], and the publication of the final overall survival data for ICON7 (August 2015) .

Multivariable logistic regression models were fit to determine the association between all available clinical and demographic factors and receipt of BEV. Results are reported as odds ratios with 95% confidence intervals.

Cost data were analyzed at the service level among the subset of patients who received BEV, such that multiple episodes of treatment were possible per enrollee. The range of total costs per cycle of BEV monotherapy as well as per cycle of platinum/taxane/ BEV combination therapy were plotted in histograms. Median costs and interquartile ranges per cycle calculated. The cost of a cycle of platinum/taxane without Bev was calculated by subtracting the drug cost of BEV from the total cost of each platinum/taxane/ BEV encounter.

All data analyses were conducted in RStudio (Version 1.1.447). All statistical tests were two-sided. A p-value of 0.05 was considered statistically significant.

Results

A total of 8109 patients met inclusion criteria for this study. The average age of diagnosis for the entire cohort was 54. Most patients resided in urban areas (84.3%) and were relatively evenly distributed throughout the south (37%), north central (25%), northeast (19%), and western (18%) US. The majority (72%) of patients were enrolled in PPO plans with payment structures that were not capitated (85.8%). Comorbidity scores were low, with 73% of patients having Charlson scores of 0 at diagnosis. With respect to markers of advanced disease, codes for metastatic disease were present in 68%, for ascites in 44%, and for pleural effusion in 25% of patients within six months of OC diagnosis. Baseline characteristics stratified by BEV use are detailed in **Table 1**.

The overall proportion of patients receiving upfront BEV during the study period was low: 522 of 8109 patients (6.4%). Rates rose from 4.1% among those diagnosed in 2008 to 7.4 % among those diagnosed in 2016, with peak use in 2014, at 8.5% (**Figure 2A**). When grouped according to the date of key events (**Figure 2B**), rates of use rose most rapidly during the early period of dissemination of research findings, from 4.1% prior to the presentation of Phase II trials in May 2009 up to 6.8% just before the abstract presentation of ICON-7 in October 2010 (a rate of increase of 1.9% per year). Rates plateaued at 6.8% around the time that Phase III trials findings were published in peer-reviewed journals. The addition of upfront BEV to NCCN guidelines as a Category 3 recommendation led to an increase in BEV use from 6.8% to 7.6% (a rate of increase of 0.3% per year). The publication of mature overall survival data from ICON-7 was again associated with a plateau in utilization rates (7.6 to 7.5%).

Among the subgroup of patients with advanced disease, defined by the presence of diagnostic codes for ascites, metastases and/or pleural effusion (n = 6289), BEV use during the

entire study period was higher, at 8.0%. Among this subgroup, rates rose from 5.5% in 2008 to 8.9% in 2016, with a peak of 10.3% in 2014.

There was no difference between rates of primary debulking surgery versus neoadjuvant chemotherapy use between those receiving and not receiving BEV. However, rates of IP chemotherapy use were significantly lower among patient receiving BEV (6.9%) compared to those not receiving BEV (11.1%) ($p = 0.003$). Whereas the vast majority of patients who did not receive BEV received adjuvant cytotoxic chemotherapy with a platinum and taxane doublet (90.4%), patients receiving BEV were less likely to receive a platinum/taxane doublet (46.4%) and more likely to receive platinum monotherapy (51.3%) ($p < 0.001$) (**Table 2**).

Factors that predicted the use of BEV on multivariate logistic regression are summarized in **Table 3**. Increasing patient age was associated with decrease use of BEV (OR 0.98 per year; 95% CI 0.96 – 0.99, $p < 0.001$). Recency of diagnosis (OR 1.08 per year; 95% CI 1.04 – 1.12, $p < 0.001$), residing in the Southern United States (OR 1.52; 95% CI 1.16 – 2.02, $p = 0.003$), presence of ascites (OR 1.33; 95% CI 1.0 – 1.62, $p = 0.005$), and metastatic disease (OR 4.9; 95% CI 3.52 – 6.66, $p < 0.001$) were all associated with increased use of BEV.

Among the subset of patients with available provider information ($n = 1560$), treatment by a medical oncologist was associated with 1.98 greater odds of receiving BEV (95% CI 1.29 – 3.09, $p = 0.002$).

Data from 1652 unique cycles of BEV monotherapy, administered to 279 patients with newly diagnosed OC, were available for analysis. The median total cost of one cycle of BEV monotherapy was 6873 US dollars (IQR 4,824 – 11,276 US dollars) (**Figure 3A**).

Data from 935 cycles of combined therapy with a platinum agent, a taxane and BEV, administered to 241 patients, were available for analysis. The median cost of one cycle of combination therapy with a platinum, taxane and BEV was 10,897 US dollars (IQR 7,573 – 18,133 US dollars). Subtracting the drug costs of BEV from these cycles yielded an estimated median cost of 1629 US dollars (IQR 683.0 - 4,461) for platinum and taxane chemotherapy alone (**Figure 3B**).

Discussion

We found that use of BEV for the upfront treatment of OC doubled from 2008 to 2016, but remained low throughout, with peak rates of use at just 8.5% among all diagnoses and 10.3% among those with evidence of advanced disease. BEV was utilized in conjunction with a platinum/taxane doublet roughly half the time, while the other half of the time it was administered with a platinum agent alone. Clinical predictors of use included younger age and the presence of ascites or metastatic disease. Non-clinical predictors included treatment by a medical oncologist and residing in the Southern US. The median cost of one cycle of bevacizumab approached 7000 US dollars, and was highly variable.

We noted that the greatest increase in BEV use occurred following early dissemination of Phase II trial findings and preliminary results of Phase III trials in abstract form, as well as after publication of NCCN recommendations, while the actual publication of Phase III trials was associated with a plateau in utilization rates. This speaks to early enthusiasm for novel agents and to the high visibility and impact of national guidelines. However, it is important to note that the overall rates of BEV use remained low throughout the study period, even after guidelines were published. More recently, BEV received FDA approval for upfront treatment of OC in June 2018. At the time this study was being conducted, MarketScan® data were only available through the end of 2016. As such, we were not able to assess the impact this key event on BEV uptake. We would suspect rates of use have increased further, and perhaps more steeply, following FDA approval, as a result of higher rates and ease of insurance approval.

Interestingly, roughly one half of patients who received BEV received platinum-only cytotoxic therapy. This is in contrast to the regimens studied in GOG-218 and ICON-7, both of which added BEV to a backbone of platinum plus taxane cytotoxic chemotherapy [8,9]. To our

knowledge, replacing taxane with BEV in adjuvant chemotherapy for OC has not been studied, and the oncologic outcomes associated with this strategy are unknown. It is possible that providers added BEV in patients who were unable to tolerate taxane due to toxicities, though we cannot ascertain this based on the available data.

Appropriately, the presence of metastatic disease was associated with increased used of BEV, reflecting the population studied in GOG-218 and those deriving the greatest benefit in ICON-7 [8,9,11]. Similarly, the increased use of BEV among patients with ascites appears appropriate, given that angiogenesis contributes to ascites formation and anti-angiogenic agents like BEV have shown efficacy in reducing ascites [25]. The negative association between age and use of BEV may be due to higher rates of comorbidities and potential BEV contraindications among older populations that were incompletely captured by the Charlson index. The greater use of BEV among medical oncologists may reflect greater familiarity with this drug among medical oncologists during the period of study, since the use of BEV in non-gynecologic malignancies such as colorectal cancer and non-small cell lung cancer preceded its gynecologic cancer indications [26].

Previous research on the cost-effectiveness of BEV for the treatment of OC have utilized efficacy data from GOG-218 and ICON-7 paired with Medicare-based costs [15–17]. The most favorable ICER from these studies, for a US population, was $168,000 per life-year saved and was seen for the ICON-7 high risk patient subgroup [17]. However, the cost of treatment in this study was estimated at $3,225 per cycle of maintenance BEV, which is about half the median cost we observed ($6873) in a privately insured population. Irrespective of the threshold set for determining an appropriate ICER, the numbers obtained would be half as favorable when the cost of therapy doubles. Thus, it is important for clinicians to appreciate the high costs of BEV

and use it judiciously for those most likely to benefit. With respect to the high variability in costs, a small amount of this may be partially explained by patient differences in weight, dosing regimens (7.5mg versus 15 mg/kg), and facility costs (inpatient versus outpatient treatment). However, these differences are unlikely to account for all the observed variability, and idiosyncratic differences in costs based on region, health care provider, and negotiated reimbursement rates likely account for the greatest proportion of cost variation.

The main limitations of this study are those inherent to the use of administrative claims data. We cannot exclude coding inaccuracies that result in incomplete capture or misclassification of our variables. Additionally, due to the nature of the data, detailed demographic and tumor information such as stage at diagnosis and histologic subtype were not available. However, our main inclusion variable relies on the presence of a cancer diagnosis, and these codes have been noted to have sensitivities of 73-94% [27]. To identify clinical covariates, we used a combination of various diagnostic and procedural codes, thus increasing sensitivity for these variables. We applied strict inclusion criteria in order to reduce case heterogeneity and limit the cohort to newly diagnosed epithelial OC, for which BEV would be indicated. Women with germ cell histologies are unlikely to have been erroneously included in the cohort in any significant proportion, since they are typically treated with surgery only and, when receiving chemotherapy, receive bleomycin and/or etoposide containing regimens [28], which were excluded by our algorithm. We recognize that women with malignant ovarian sex cord - stromal cell tumors may be treated similarly to those with epithelial OC. However, they represent only 2% of OC cases [1], and many of these patients either do not receive chemotherapy or are treated with bleomycin / etoposide containing regimens [29]. Therefore, they are expected to represent less than 1% of our final cohort. With regard to our definition of advanced disease, the rates of

metastases (68%) and pleural effusion (25%) observed in the present study correlate well with the known stage distribution of OC, with 65% of patients presenting with Stage III/IV disease and 28% with Stage IV disease, respectively [1]. To increase the specificity of BEV use for OC treatment, we included episodes associated with intravenous administration only, thus excluding ophthalmologic BEV use. However, it is possible, though unlikely, that women received intravenous BEV in the six months immediately after OC diagnosis for the treatment of another primary cancer. We chose not to exclude women with diagnoses codes for other malignancies, since we were concerned about miscoding of OC metastatic to other tissues as primary cancers to those tissues, which would have erroneously limited the number of patients with advanced cancer in our cohort.

Generalization of our findings is limited to women under the age of 65 who are commercially insured. However, two thirds of Americans have private health insurance coverage [30], so this represents a large segment of the US population. Additionally, the average age of OC diagnosis is 63 [31], and women with *BRCA1* mutations, which represent 10% of patients with OC, are diagnosed a decade earlier [32,33], thus studying a younger population is clinically relevant.

Despite its limitations, this study is a first step toward improving our knowledge on national population trends and patterns in the use of BEV for OC that is currently lacking. Future research is needed on dissemination of use following recent FDA approval of upfront BEV.

Table and Figures

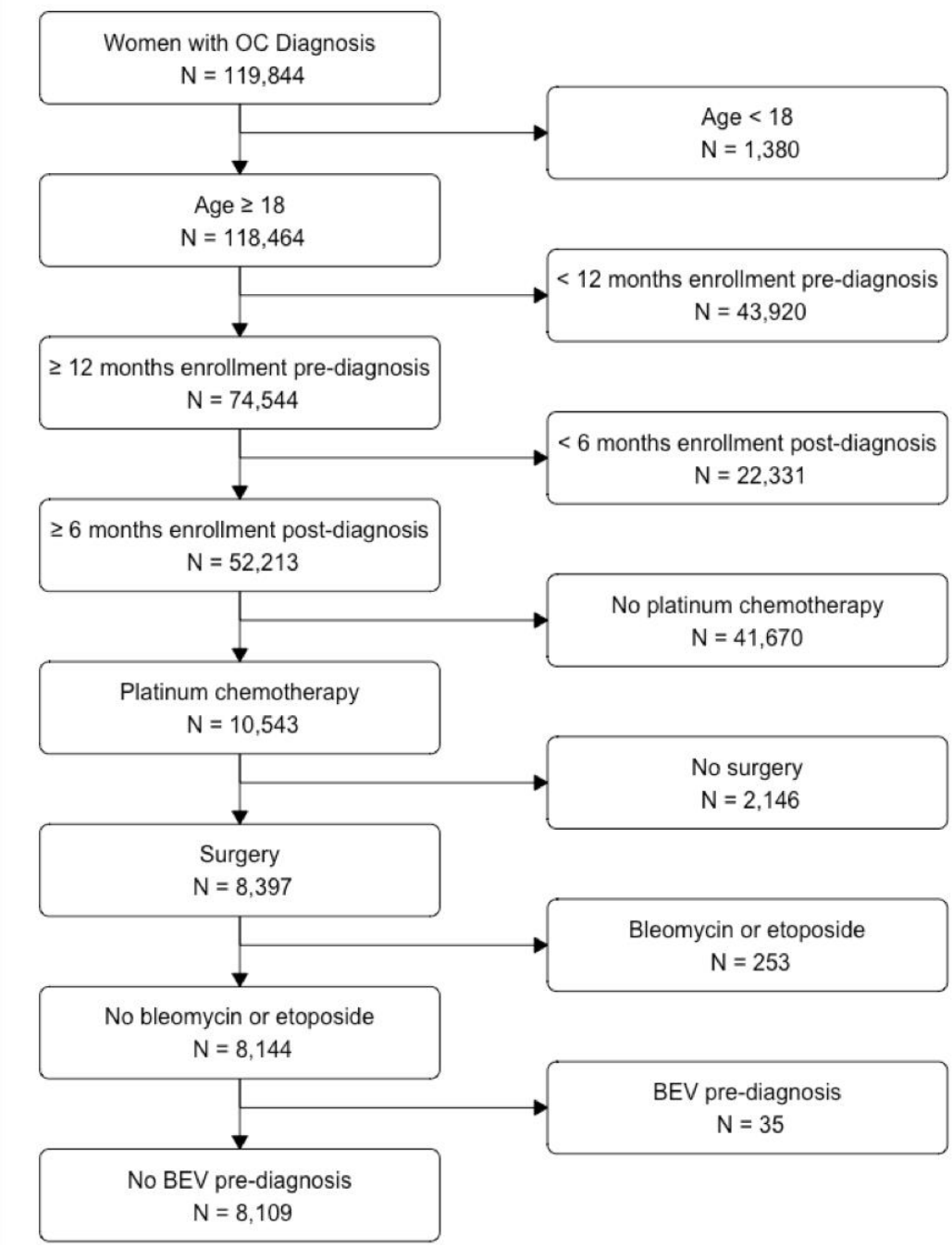

Figure 1: Flowchart of patient selection. A total of 8,109 women with OC were included in the study after applying pre-determined criteria intended to identify patients with new diagnoses and exclude those with non-epithelial histologies.

Table 1: Baseline characteristics of study cohort stratified by use of BEV.

	No BEV (n = 7587)	**BEV (n = 522)**	
	n (%)	*n (%)*	*p-value*
Age at diagnosis			
Mean (SD)	54.14 (7.43)	53.19 (8.58)	0.005
Year of diagnosis			<0.001
2008-2010	2763 (36.4)	149 (28.5)	
2011-2013	2913 (38.4)	205 (39.3)	
2014-2016	1911 (25.2)	168 (32.2)	
Geographic region			0.143
Northeast	1441 (19.0)	81 (15.5)	
North Central	1900 (25.0)	136 (26.1)	
South	2761 (36.4)	211 (40.4)	
West	1368 (18.0)	89 (17.0)	
Unknown	117 (1.5)	5 (1.0)	
Population density			0.18
Urban	6408 (84.5)	431 (82.6)	
Rural	1062 (14.0)	86 (16.5)	
Unknown	117 (1.5)	5 (1.0)	
Health plan type			0.208
PPO, CDHP, HDHP	5491 (72.4)	363 (69.5)	
EPO, HMO	948 (12.5)	75 (14.4)	
POS	651 (8.6)	39 (7.5)	
Comprehensive	322 (4.2)	28 (5.4)	
Unknown	175 (2.3)	17 (3.3)	
Payment capitation*			0.177
No	6524 (86.0)	435 (83.3)	
Yes	888 (11.7)	70 (13.4)	

Unknown	175 (2.3)	17 (3.3)	
Charlson score at diagnosis			0.041
0	5527 (72.8)	398 (76.2)	
1-2	1780 (23.5)	113 (21.6)	
3+	184 (2.4)	11 (2.1)	
Unknown	96 (1.3)	0 (0.0)	
Ascites	3260 (43.0)	294 (56.3)	<0.001
Pleural Effusion	1848 (24.4)	162 (31.0)	0.001
Metastases	5064 (66.7)	476 (91.2)	<0.001

*Health plan pays all/some services on a capitated basis.

Abbreviations: BEV – bevacizumab, CDHP – consumer-driven health plan, EPO – exclusive provider organization , HDHP – high-deductible health plan , HMO – health maintenance organization, POS – point of service, PPO – preferred provider organization, SD – standard deviation.

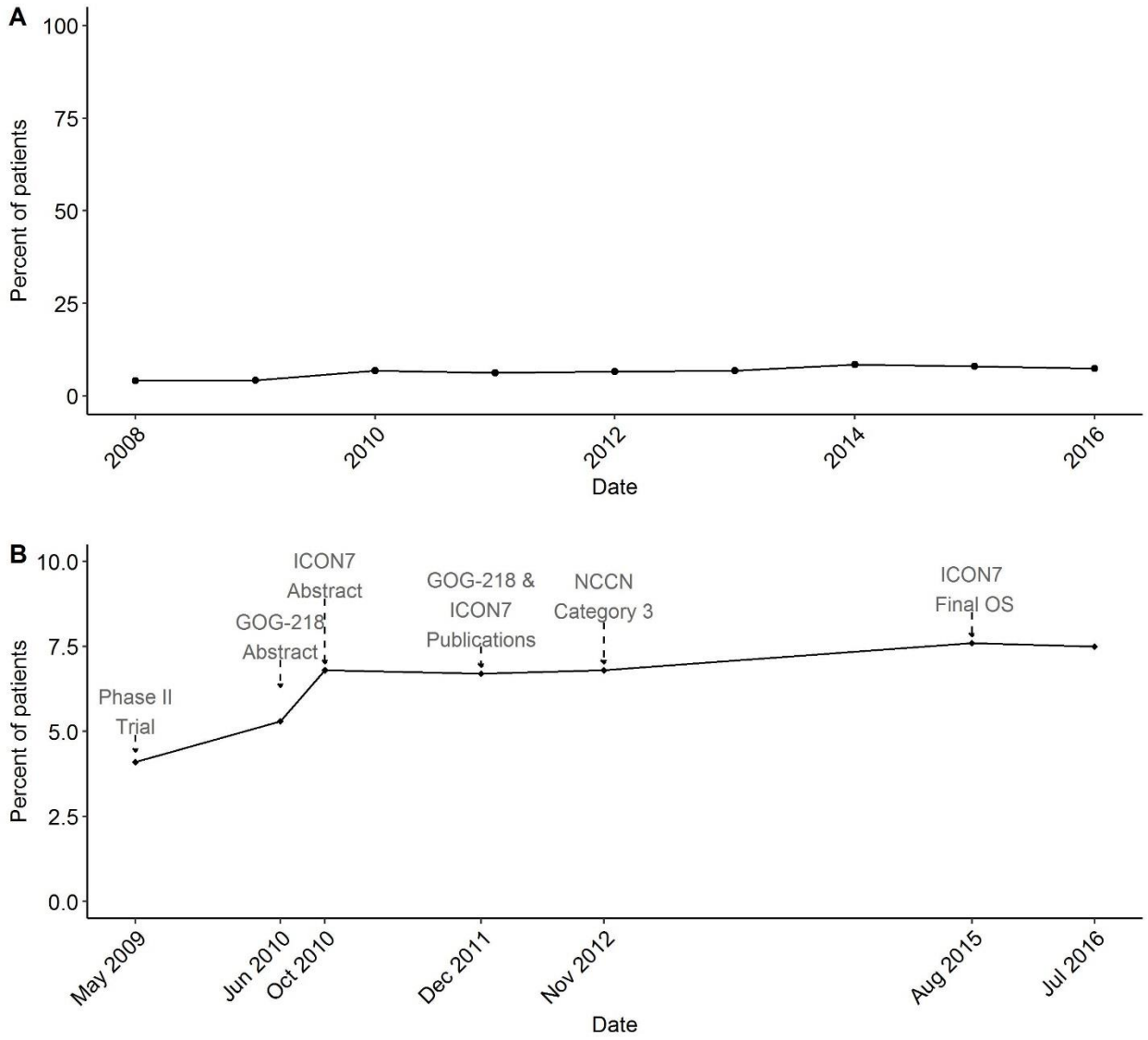

Figure 2: Early dissemination patterns of BEV for first-line treatment of OC prior to its FDA approval for this indication (2008 – 2016). **(A)** Percent of patients with newly diagnosed OC who received BEV within 6 months of diagnosis by year of diagnosis. The percent of patients receiving BEV doubled during this time period, but remained modest with a nadir of 4.1% in 2008 and a peak of 8.5% in 2014. **(B)** Percent of patients with newly diagnosed OC who received BEV within 6 months of diagnosis grouped relative to key events in upfront BEV research, including publication of Phase II trials, abstract presentations and publications of GOG-218 and ICON-7, and NCCN recommendations for the use of upfront BEV. BEV uptake was

most sensitive to publication of preliminary Phase II data and NCCN guidelines rather than publication of Phase III trials.

Table 2: Treatment patterns stratified by use of BEV.

	No BEV (n = 7587)	**BEV (n = 522)**	
	n (%)	*n (%)*	*p-value*
Primary treatment			0.275
PDS	6712 (88.5)	453 (86.8)	
NACT	875 (11.5)	69 (13.2)	
Chemotherapy route			0.003
IV	6742 (88.9)	486 (93.1)	
IP	845 (11.1)	36 (6.9)	
Cytotoxic regimen			<0.001
Platinum/Taxane Doublet	6857 (90.4)	242 (46.4)	
Platinum Monotherapy	406 (5.4)	268 (51.3)	
Platinum/Taxane + Other	236 (3.1)	4 (0.8)	
Platinum/Other Doublet	82 (1.1)	7 (1.3)	
Platinum/Taxane + 2 Others	6 (0.1)	1 (0.2)	

Abbreviations: IP – intraperitoneal, IV – intravenous, NACT – neoadjuvant chemotherapy, PDS – primary debulking surgery.

Table 3: Multivariable logistic regression models of predictors of BEV use.

	Full Cohort (n = 7706)			Provider Known (n = 1560)		
	OR	*CI*	*p-value*	*OR*	*CI*	*p-value*
Age at diagnosis (per year)	0.98	0.96 – 0.99	<0.001***	0.96	0.93 – 0.98	<0.001***
Year of diagnosis (per year)	1.08	1.04 – 1.12	<0.001***	1.12	1.02 – 1.22	0.013***
Geographic region						
Northeast		Referent			Referent	
North Central	1.35	1.00 – 1.83	0.051	1.23	0.51 – 3.27	0.655
South	1.52	1.16 – 2.02	0.003**	1.48	0.68 – 3.64	0.350
West	1.21	0.87 – 1.67	0.257	1.20	0.50 – 3.11	0.694
Rural population	1.14	0.88 – 1.47	0.295	1.67	0.99 – 2.74	0.049*
Health plan type						
PPO, CDHP, HDHP		Referent			Referent	
Comprehensive	1.42	0.92 – 2.11	0.101	3.66	0.80 – 12.19	0.054
EPO, HMO	1.18	0.63 – 2.10	0.595	0.74	0.15 – 3.51	0.717
POS	0.95	0.66 – 1.34	0.782	1.60	0.77 – 3.07	0.181
Payment capitation[+]	1.13	0.62 – 2.11	0.703	2.95	0.62 – 13.96	0.176
Charlson score at diagnosis						
0		Referent			Referent	

1-2	0.84	0.66 – 1.04	0.121	1.16	0.70 – 1.86	0.550
3+	0.79	0.39 – 1.45	0.487	1.27	0.29 – 3.85	0.708
Ascites	1.33	1.09 – 1.62	0.005**	1.50	0.96 – 2.36	0.080
Pleural Effusion	1.07	0.86 – 1.32	0.544	1.26	0.78 – 2.00	0.338
Metastasis	4.79	3.52 – 6.66	<0.001***	4.02	2.12 – 8.45	<0.001***
Medical Oncologist				1.98	1.29 – 3.09	0.002**

*p < 0.05, **p < 0.01, ***p < 0.001

[+] Health plan pays all/some services on a capitated basis.

Abbreviations: BEV – bevacizumab, CDHP – consumer-driven health plan, CI – 95% confidence interval EPO – exclusive provider organization , HDHP – high-deductible health plan , HMO – health maintenance organization, OR – odds ratio, POS – point of service, PPO – preferred provider organization.

Models were calculated for the entire cohort (for statistical robustness) as well as for the subgroup of patients (n = 1560) for whom provider information was available. Chemotherapy providers were classified as medical oncologists or gynecologic oncologists depending on whether or not they performed surgery in addition to administering chemotherapy.

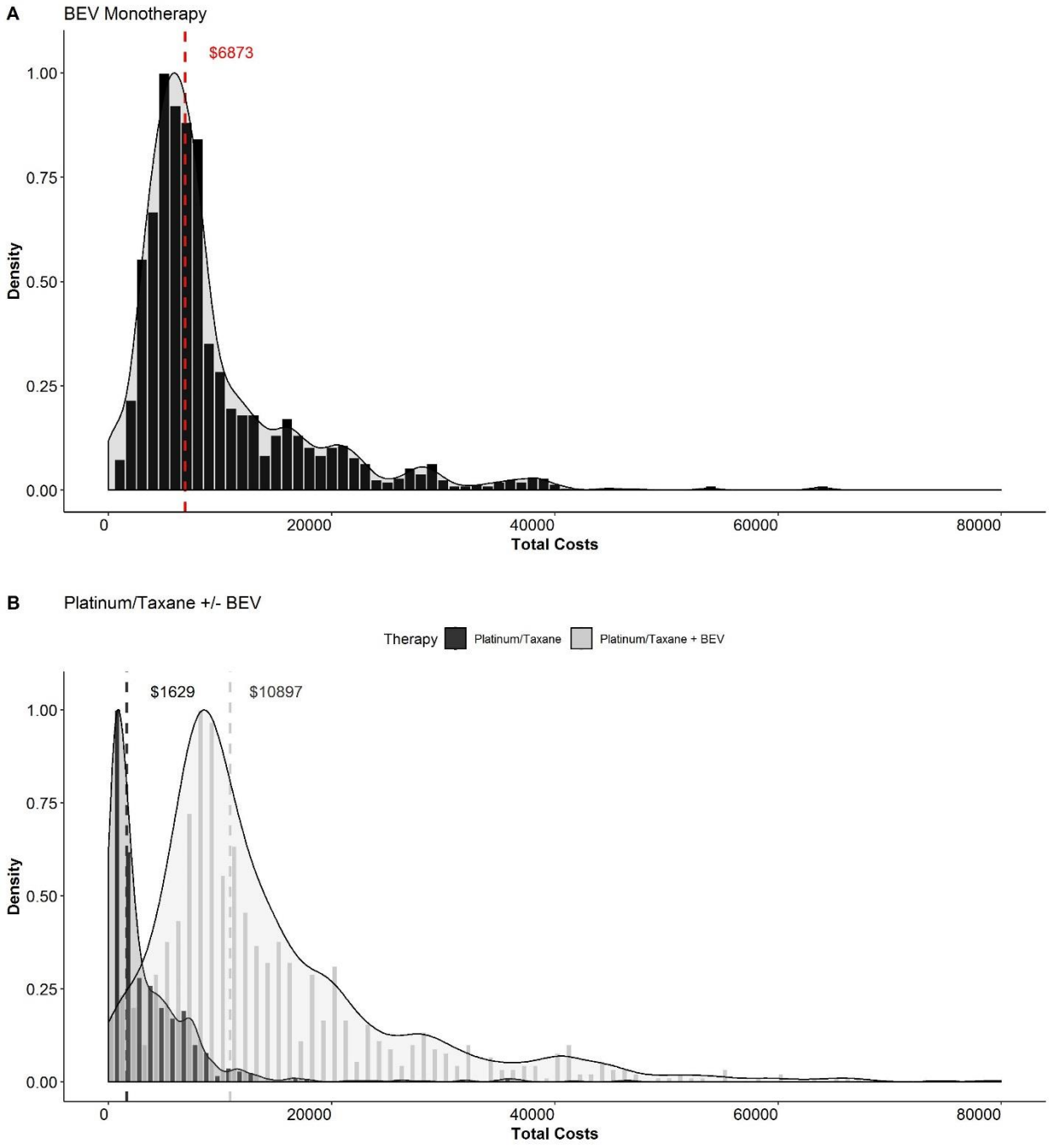

Figure 3: Relative density histograms of the cost of (A) of a single cycle of BEV monotherapy and (B) a single cycle of platinum, taxane BEV combination therapy. The cost of platinum / taxane only is calculated by subtracting the BEV drug cost from total costs.

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Appendix

List of ICD-9 and ICD-10 diagnostic and procedure codes, CPT codes, HCPCS codes and NDC codes used in identifying variables of interest

ICD-9 = Ninth revision of the International Statistical Classification of Diseases

ICD-10 = Tenth revision of the International Statistical Classification of Diseases

CPT = Common Procedural Terminology

HCPCS = Healthcare Common Procedure Coding System

NDC = National Drug Code

Variable	Description	ICD-9 diagnosis code	ICD-10 diagnosis code	ICD-9 procedure code	ICD-10 procedure code	CPT	HCPCS
Ovarian cancer	Malignant neoplasm of specified parts of peritoneum	158.8	C48.1				
	Malignant neoplasm of peritoneum, unspecified	158.9	C48.2				
	Malignant neoplasm of overlapping sites of retroperitoneum and peritoneum		C48.8				
	Malignant neoplasm of ovary	183	C56.9				
	Malignant neoplasm of right ovary		C56.1				
	Malignant neoplasm of left ovary		C56.2				
	Malignant neoplasm of fallopian tube	183.2	C57.00				
	Malignant neoplasm of right fallopian tube		C57.01				
	Malignant neoplasm of left fallopian tube		C57.02				
	Malignant neoplasm of other specified sites of uterine adnexa	183.8					
	Malignant neoplasm of uterine adnexa, unspecified site	183.9	C57.4				
Ascites	Ascites (malignant or other)	789.5*	R18.*				
	Percutaneous abdominal drainage			54.91	0D9W*		

Variable	Description	ICD-9 diagnosis code	ICD-10 diagnosis code	ICD-9 procedure code	ICD-10 procedure code	CPT	HCPCS
	Peritoneocentesis, abdominal paracentesis, or peritoneal lavage; initial					49080	
	Peritoneocentesis, abdominal paracentesis, or peritoneal lavage; subsequent					49081	
	Abdominal paracentesis (diagnostic or therapeutic); without imaging guidance					49082	
	Abdominal paracentesis (diagnostic or therapeutic); with imaging guidance					49083	
Pleural effusion	Pleurisy with effusion, with mention of a bacterial cause other than tuberculosis	511.1	J90				
	Other specified forms of pleural effusion except tuberculous	511.8*	J91.*				
	Unspecified pleural effusion	511.9					
	Thoracentesis			34.91	0B9N8ZZ	3255*	
					0B9P8ZZ	32421	
					0W9B3ZZ	32422	
					0W993ZZ		
Metastasis	Secondary and unspecified malignant neoplasm of lymph nodes	196.*	C77.*				
	Secondary malignant neoplasm of respiratory and digestive systems	197.*	C78.*				
	Secondary malignant neoplasm of other specified sites	198.*	C79.*				
	Carcinomatosis, NOS		C80.0				
Ovarian cancer surgery	Oophorectomy and Salpingectomy			65.22, 65.24, 65.25, 65.29, 65.3, 65.31, 65.39, 65.4, 65.41, 65.49, 65.5, 65.51, 65.52, 65.53, 65.54, 65.6, 65.61, 65.62, 65.63, 65.64	0UB0*, 0UB1*, 0UB2*, 0UB4*, 0UB5*, 0UB6*, 0UB7*, 0UT0*, 0UT1*, 0UT2*, 0UT4*, 0UT5*, 0UT6*, 0UT7*	38562, 38570, 38571, 38572, 44950, 44970, 4900, 49010, 49203, 49204, 49205, 49321, 58150, 58152, 58180, 58200,	

Variable	Description	ICD-9 diagnosis code	ICD-10 diagnosis code	ICD-9 procedure code	ICD-10 procedure code	CPT	HCPCS
	Hysterectomy			68.3, 68.31, 68.39, 68.4, 68.41, 68.49, 68.5, 68.51, 68.59, 68.6, 68.61, 68.69, 68.7, 68.71, 68.79, 68.9	0UT9*, 0UTC*, 0UB9*, 0UBC*	58210, 58240, 58260, 58262, 58263, 58267, 58270, 58275, 58280, 58285, 58290, 58291, 58292, 58293, 58294, 56303, 56307, 56308, 58541, 58542, 58543, 58544, 58548, 58550, 58552, 58553, 58554, 58570, 58571, 58572, 58573 58661, 58662, 58700, 58720, 58920, 58925, 58940, 58943, 58950, 58951, 58952, 58953, 58954, 58956, 58957, 58958, 58960, 58594	
	Cytoreduction			40.3, 40.5, 54.2, 54.3, 54.4, 68.8, 70.32	0UTF*, 0DT8*,0DT9*, 0DTA*, 0DTB*, 0DTC*, 0DTE*, 0DTF*, 0DTG*, 0DTH*, 0DTJ*, 0DTK*, 0DTL*, 0DTM*, 0DTN*, 0DTP*, 0DTQ*, 0DTR*, 0DTU*, 07TB*, 07TC*, 07TD*, 07TP*, 0UBF*, 0DB8*,0DB9*, 0DBA*, 0DBB*, 0DBC*, 0DBE*, 0DBF*, 0DBG*, 0DBH*, 0DBJ*, 0DBK*, 0DBL*, 0DBM*, 0DBN*, 0DBP*, 0DBQ*, 0DBR*, 0DBU*, 07BB*, 07BC*, 07BD*, 07BP*, ODBV*, ODBW*		
Chemotherapy	IV, IM or IP chemotherapy and immunotherapy	V58.1	Z51.11	54.97	3E03305	96367	G0355
		V58.11	Z51.12	99.25	3E04305	96361	G0357
		V58.12			3E0M305	96400	G0358
						96401	G0359

Variable	Description	ICD-9 diagnosis code	ICD-10 diagnosis code	ICD-9 procedure code	ICD-10 procedure code	CPT	HCPCS
						96408	G0360
						96410	G0361
						96412	G0362
						96413	G0356
						96414	
						96415	
						96417	
						96445	
						96446	
Intraperitoneal chemotherapy	IP chemotherapy only			54.97	3E0M305	96445	
						96446	

Drug	HCPCS	11 digit NDC
Bevacizumab	J9035	50242006001
	C9257	50242006002
	S0116	50242006101
Bleomycin	J9040	99999015390 99999015327 70121156701 63323013720 63323013610 61703033218 61703032322 55390000601 55390000501 54868329800 54569192900 44778017201 38779078307 6332313720 6332313610 6170333218 6170332322 5539000501 703315591 703315501 703315491 703315401 74163601 15306326 15306301 15301097 15301026 15301020 13163686 13161678
Cyclophosphomide	J8530	99999990723 99999990128 99999805201 99999085032 99999080501 99999015370 88888003601 62991162503 62991162502 62991162501 54977007899 54868521802 54868521801 54868521800 54868500501 54868500500 54569571300 54569571200 54569140000 54569037502 54569037501 54569037500 51927487100 51927442100 49452240602 49452240601 44778061801 38779050605 38779050604 38779050603 10019095711 10019095701 10019095616 10019095601 10019095550 10019095501 10019094510 10019094501 10019094450 10019094401 10019094325 10019094301 10019094210 10019094201 10019093950 10019093901 10019093825 10019093801 10019093710 10019093701 10019093650 10019093601 10019093525 10019093501 5486850051 5486850050 5192748710 5192744210 3877905065 3877905064 3877905063 1001995711 1001995701 1001995616
	J9070	
	J9080	
	J9090	
	J9091	

	J9092 J9093 J9094 J9095 J9096 J9097	1001995601 1001995550 1001995501 1001994510 1001994501 1001994450 1001994401 1001994325 1001994301 1001994210 1001994201 1001993950 1001993901 1001993825 1001993801 1001993710 1001993701 1001993650 1001993601 1001993525 1001993501 781325594 781324494 781323394 641226541 641226441 641226341 641226241 179165270 87054741 87050641 87050541 87050401 87050303 87050302 87050301 87050241 87050201 87050141 87050101 87050041 87050001 54813025 54808925 54413025 54412925 54038325 54038225 15054942 15054941 15054912 15054842 15054841 15054812 15054742 15054741 15054712 15054642 15054641 15053942 15053941 15050641 15050541 15050401 15050348 15050303 15050302 15050301 15050241 15050141 15050041 13564670 13564601 13563673 13563670 13563601 13562693 13562601 13561693 13561601 13560693 13560601
Etoposide	J9181 J9182 J8560	99737026231 68001026527 68001026526 68001026525 68001026524 68001026523 68001026522 63323010465 63323010450 63323010425 63323010405 58406071418 58406071112 55390049301 55390049201 55390049101 55390029301 55390029201 55390029101 54868535502 54868535500 54569571800 54569296300 53905029101 51927277200 51079096505 51079096501 44778069701 38779078406 38779078403 16729026231 16729011431 16729011411 16729011408 10019093002 10019093001 6800126527 6800126526 6800126525 6800126524 6800126523 6800126522 6332310450 6332310425 6332310405 5539049301 5539049201 5539049101 5539029301 5539029201 5539029101 5192727720 1672926231 1672911431 1672911411 1672911408 703566801 703566701 703565801 703565791 703565701 703565691 703565601 703565301 703564601 703564301 378326694 364302853 209309020 209308020 209307020 209306022 186157131 74566701 74565701 74565601 74565301 74564601 74564301 74148503 74148502 74148501 15340420 15309695 15309595 15309530 15309520 15309145 15308420 15306224 15306220 15306124 15306120 13736673 13735688 13735601 13734694 13734601 13733691 13733601
Gemcitabine	J9201	99999090110 68001028227 68001028226 68001028225 68001028224 68001028223 68001028222 67457046420 67457046302 67457046201 63323012600 63323012594 63323012553 63323012550 63323010294 63323010213 63323010210 55390039150 55390039110 55111068725 55111068607 47335015440 47335015340 45963063660 45963062458 45963062357 45963062060 45963061959 45963061257 25021023550 25021023410 25021020950 25021020810 23155052931 23155052831 23155048431 23155048331 23155021431 23155021331 16729011838 16729011711 16729009203 6745746420 6745746302 6745746201 6332312600 6332312553 6332312550 6332310213 5539039150 5539039110 5511168725 5511168607 4733515440 4733515340 4596361959 4596361257 2502123550 2502123410 2502120950 2502120810 2315552931 2315552831 2315548431 2315548331 2315521431 2315521331 1672911838 1672911711 1672909203 781328379 781328275 703577801 703577501 591356355 591356279 409018701 409018601 409018501 409018325 409018301 409018225 409018201 409018125 409018101 69385910 69385810 69385710 2750201 2750101
Liposomal doxorubicin (Doxil)	J9001 J9002 Q2048 Q2049	61471029512 59676096002 59676096001 47335008350 47335008250 47335005040 47335004940 17314960002 17314960001 17314096001 5967696002 5967696001 4733508350 4733508250 4733505040 4733504940

Platinum agents	Carboplatin	J9045	99999090347 67817006712 67817006612 67817006312 67817006112 67457060820 67457049461 67457049346 67457049215 67457049154 66860010201 66860010101 66860010001 66758004704 66758004703 66758004702 66758004701 63323017260 63323017245 63323017215 63323017205 63323016945 63323016915 63323016905 63323016800 63323016721 63323016720 63323016610 62991215305 62991215304 62991215303 62991215301 61703036050 61703036022 61703036018 61703033963 61703033962 61703033961 61703033956 61703033950 61703033922 61703033918 55390022201 55390022101 55390022001 55390015601 55390015501 55390015401 55390015301 55390015201 55390015101 55390015001 50111096776 50111096676 50111096576 47335030040 47335028440 47335015140 47335015040 38779078109 25021020251 25021020245 25021020215 25021020205 15210006712 15210006612 15210006312 15210006112 10139006045 10139006015 10139006005 10019091701 10019091615 10019091601 10019091501 10019091203 10019091202 10019091201 6745760820 6745749461 6745749346 6745749215 6745749154 6675804704 6332317260 6332317245 6332317215 6332317205 6332316721 6170336050 6170336022 6170336018 6170333962 6170333956 6170333950 6170333922 6170333918 4733530040 4733528440 4733515140 4733515040 2502120251 2502120245 2502120215 2502120205 703424891 703424881 703424801 703424681 703424601 703424481 703424401 703423981 703423901 703327801 703327601 703327401 703326871 703326801 703326601 703326401 703324911 703324811 703324611 703324411 591368711 591345460 591333889 591333712 591333626 591222011 591221911 409112912 409112911 409112910 15323311 15323211 15323111 15323011 15321630 15321530 15321529 15321430 15321429 15321330 15321329 15321276 15321230 15321176 15321130 15321076 15321030
	Cisplatin	J9060 J9062	68001028333 68001028332 68001028327 68001028324 67457042551 67457042410 63323010395 63323010391 63323010365 63323010364 63323010351 62991284902 62991284901 62991215405 62991215404 62991215403 62991215402 62991215401 58087034740 55390041499 55390041450 55390018701 55390011299 55390011250 55390009901 54569244500 51552107609 49452207803 49452207802 49452207801 44567051101 44567051001 44567050901 38779078206 38779078200 16729028838 16729028811 10019091002 10019091001 6745742551 6745742410 6332310365 6332310364 6332310351 6299128492 4456751001 4456750901 703574811 703574711 69008407 69008101 15322197 15322126 15322122 15322097 15322026 15322022 15307297 15307220 15307097 15307020
	Oxaliplatin	J9263	99999090127 67457047610 67457046910 67457044220 66758005302 66758005301 63323075020 63323075010 63323065027 63323065020 63323065017 63323065010 63323021220 63323021110 63323017650 63323017530 61703036322 61703036318 61703036250 61703036135 60505613207 60505613206 47335017840 47335017640 47335004740 47335004640 45963061159 45963061153 41616017840 41616017640 25021023320 25021023310 25021021250 25021021120 6745747610 6745746910 6745744220 6332375020 6332375010 6332365027 6332365020 6332365017 6332365010 6332321220 6332321110 6332317650 6332317530 6170336322 6170336318 4733517840 4733517640 4733504740 4733504640 4596361159 4596361153 2502123320 2502123310 2502121250 2502121120 955173320 955173110 955172720 955172510 781931780 781931570 781331780 781331570 703398601 703398501 69101001 69007401 69007001 69006701 24059704 24059602 24059240 24059120 24059010

Taxanes	Docetaxel	J9170 J9171	66758095004 66758095003 66758095002 66758005003 66758005002 66758005001 63739097117 63739093211 60505603706 60505603700 60505603506 60505603500 47335028641 47335028541 45963079056 45963076552 45963073474 45963073454 45963073452 43598025940 43598025811 42367012129 42367012125 42367012121 39822220001 39822218001 39822212001 25021022207 25021022204 25021022201 16729026765 16729026764 16729026763 16729023165 16729023164 16729023163 16729022850 16729012049 16714050001 16714046501 6675895004 6675895003 6675895002 6675805003 6675805002 6675805001 6373997117 6373993211 6050560376 6050560370 6050560356 6050560350 4733528641 4733528541 4596379056 4596373474 4596373454 4596373452 4359825940 4359825811 2502122207 2502122204 2502122201 1672926765 1672926764 1672926763 1672923165 1672923164 1672923163 1672912049 955102208 955102104 955102001 703573001 703572001 409036701 409036601 409020127 409020126 409020125 409020120 409020110 409020102 75800404 75800301 75800180 75800120 69914411 69914222 69914211 69914122 69914111
	Paclitaxel	J9264 J9265 J9267	99999090346 99999090297 68817013450 67457047152 67457044917 67457043451 66758004303 66758004302 66758004301 64181002300 63323076352 63323076350 63323076317 63323076316 63323076306 63323076305 61703034250 61703034222 61703034209 55390051450 55390051420 55390051405 55390031450 55390031420 55390031405 55390030450 55390030420 55390030405 55390011450 55390011420 55390011405 51079096301 51079096201 51079096101 45963061359 45963061356 45963061353 44567050601 44567050501 25021021350 25021021317 25021021305 10518010209 10518010208 10518010207 9987433501 6881713450 6745747152 6745744917 6745743451 6675804303 6675804302 6675804301 6332376352 6332376350 6332376317 6332376316 6332376306 6332376305 6170334250 6170334222 6170334209 5539031450 5539031420 5539031405 5539030450 5539030420 5539030405 5539011450 5539011420 5539011405 4596361359 4596361356 4596361353 4456750601 4456750501 2502121350 2502121317 2502121305 703476881 703476801 703476701 703476681 703476601 703476481 703476401 555198514 555198414 172375695 172375675 172375576 172375531 172375494 172375473 172375396 172375377 74433504 74433502 74433501 69007901 69007801 69007601 15347911 15347630 15347627 15347620 15347530 15347527 15347520 15345699 15345620
Topotecan		J8705 J9350 J9351	67457047404 66435041005 63323076294 63323076217 63323076210 62756002340 55390037010 50742040401 45963061556 25021082406 25021023604 25021020661 25021020606 16729015131 6745747404 6643541005 6332376294 6332376217 6332376210 6275602340 5539037010 4596361556 2502182406 2502123604 2502120661 2502120606 1672915131 703471471 703471401 409030225 409030201 78067461 78067301 69007501 7420711 7420511 7420105 7420101