Economic Burden of Renal Cell Carcinoma:

An Updated Review and Analysis

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ABSTRACT

Introduction: The economic burden of renal cell carcinoma (RCC) came into sharp focus when the UK's NICE denied coverage (later reversed) of sunitinib for metastatic RCC. We provide an updated review of RCC-related economic studies, supplemented with estimates from the latest databases that capture the utilization of several newly approved targeted agents.

Method: We performed a comprehensive literature search in PubMed for English-language studies published from January 1, 2000 to November 15, 2009. We classified articles identified from our search into three categories: cost, cost-effectiveness/cost-utility, and cost-of-illness studies. We conducted supplemental analyses using 1991-2007 SEER-Medicare and 2001-2006 MarketScan Medicare Supplemental databases, and based our estimates on a prevalent cohort of patients with RCC or kidney cancer constructed from each database. We normalized all cost estimates to 2008 US dollars.

Results: We identified 17 articles, including 5 cost, 5 cost-utility, and 7 cost-of-illness studies. In general, the studies found new surgical techniques, such as laparoscopic partial nephrectomy, to be potentially cost-saving (in the range of $175 to $5,660). Targeted agents, such as bevacizumab, sunitinib, and sorafinib, were associated with higher costs ($7,534 to $55,320) but were not necessarily cost-effective (ICER: $48,405/ QALY to $145,000/QALY). The literature reported annual estimates of the U.S. economic burden of RCC of $0.53 billion to $5.03 billion, with per-patient costs of $15,975 to $42,443. Compared to the cost of treating an elderly, non-cancer patient in the matched sample, the average cost of treating an elderly patient with RCC was $10,860 (95% CI: $10,401 - $11,320) more per year, based on our analyses of the latest

SEER-Medicare data. The annual cost to treat patients with RCC who received targeted therapies was 2.7 to 3.5 times greater than the cost to treat patients with RCC who received other therapies.

Conclusion: RCC is associated with substantial economic burden of a wide range. Comparisons among the estimates were hindered by variation in study methodology, choice of database and the associated time frame, and limitations inherent to each database. Future research is needed to understand the impact of various forces on the economic burden of RCC, such as increased disease incidence, use of minimally invasive surgical techniques, and more prevalent adoption of emerging targeted therapies.

INTRODUCTION

Kidney cancer accounted for approximately 3% of new cancer cases in the United States in 2005. (Wallen et al. 2007) In 2008, the estimated incidence of kidney cancer and associated deaths in the U.S. were 54,360 and 13,010, respectively. (Winer et al. 2009) The incidence of kidney cancer among the U.S. population is rising, increasing from 7.1 per 100,000 in 1975 to 12.0 in 2001. (Wallen et al. 2007) The increased incidence may be partly attributable to incidental findings of small renal masses as a result of more frequent use of abdominal imaging. (Jewett, and Zuniga 2008; Winer et al. 2009) At the time of diagnosis, approximately 58% of patients with kidney cancer have localized tumors, and about 19% have indications of metastasis. (SEER

2009) The prognosis of kidney cancer has improved over time, with 5-year survival rates increasing from 51% in the 1970s to 66% in the mid 1990s to early 2000s. (Winer et al. 2009)

Renal cell carcinoma (RCC), which accounts for 90% of kidney cancer diagnoses, (NCCN 2009) has an estimated annual U.S. prevalence of 109,500. (Lang et al. 2007) Risk factors of RCC include smoking, obesity, genetic mutations, and occupational exposure to certain chemicals. It is uncertain whether diet or alcohol consumption are associated with the risk of developing RCC (Hu et al. 2008; Hu et al. 2009; NCCN 2009; Zhang et al. 2004) Prognostic factors established in the literature include patient age, tumor size and grade, and the extent of metastasis, as well as other risk factors included in the Memorial Sloan-Kettering Cancer Center (MSKCC) risk classification system.(Gudbjartsson et al. 2005; Halbert et al. 2006; NCCN 2009; Scoll et al. 2009)

Surgical resection of the kidney has been the primary treatment for RCC. (Mickisch et al. 2001) The comparative efficacy of newer treatment strategies, such as nephron-sparing surgery, cryoablation, and radiofrequency ablation, has not been established in clinical trials. (Hailey 2006; NCCN 2009) Some clinicians have also considered active surveillance as a treatment strategy for select patients with localized or locally advanced RCC. (Jewett, and Zuniga 2008; NCCN 2009)

Drug therapy for metastatic RCC (mRCC) has included immunotherapeutic agents such as interleukin-2 or interferon. (McDermott, and Atkins 2004; Mickisch et al. 2001) These drugs are cytokines, an older class of immunotherapeutic agents associated with severe side effects (e.g.,

myocardial infarction, kidney damage, intestinal bleeding); thus, they have not been widely adopted for the treatment of RCC. (ACS 2009) Targeted therapies, such as bevacizumab, sorafenib, sunitinib, and temsirolimus, have increased progression-free and overall survival for individuals with RCC and have also improved their quality of life. (The Medical Letter 2007a, 2007b; Halbert et al. 2006; Motzer, and Basch 2007; Mulder, van Spronsen, and De Mulder 2007; NCCN 2009; Speca et al. 2006; Thomas et al. 2009; Cella 2009) The high cost associated with targeted agents led to an initial rejection of reimbursement from the National Institute of Health and Clinical Excellence (NICE) in the United Kingdom in 2008, which generated heated debates among concerned physicians.(Lancet editorial 2008; Drummond et al. 2009; Eisen 2008; Mayor 2009; O'Dowd 2008) Although NICE eventually reversed its decision on sunitinib as first-line therapy for patients with mRCC in early 2009, its impact on discussions about targeted agents and the economic burden of RCC resulted in the development of several related economic studies.

In this paper, we provide an updated comprehensive review of RCC-related economic studies published since 2000. We included economic studies of three types of analyses, those of cost, cost effectiveness (or cost utility), and cost of illness. In addition, we supplemented the numbers reported in the literature with the latest estimates using more recent data that reflect the period after the approval by the Food and Drug Administration (FDA) of a number of targeted therapies for RCC.

REVIEW OF ECONOMICS STUDIES OF RENAL CELL CANCER

Methods

We performed a comprehensive literature search in PubMed for English-language publications from January 1, 2000 through November 15, 2009, using the following search terms: "(renal) OR (kidney) AND (carcinoma) OR (neoplasm) AND (cost) OR (econ*) OR (burden) OR (finan*)," where * represents a wildcard. The titles and abstracts of articles identified in the search were independently reviewed by two of the authors (Chien and Shih). We selected articles for which both reviewers agreed that information related to the economic burden of RCC may be available. To focus our review on population-based estimates, we excluded articles in which cost estimates were generated based on data from a single institution. Further reviews of full-text articles and extensive manual reviews of the bibliography in these articles led to the final inclusion of 17 publications in our study.

We then classified the 17 articles into three categories: cost analysis, cost- effectiveness/utility analysis (CEA/CUA), and cost-of-illness (COI) analysis. Study characteristics and key findings for the studies in each category are summarized in Tables 1-3. We classified the analytical methods into three types, as described in the Technical Appendix of Shih and Halpern (2008): (1) a model-based analytical approach with published data from the literature (modeling approach); (2) a statistical analytic approach using patient-level data (database approach); and (3) a model-based analytical approach with published data from the literature and observational data (hybrid approach). We reported all cost estimates in 2008 U.S. dollars. For studies reporting costs in US dollars, we normalized the estimates to 2008 dollars using the medical care services component of the Consumer Price Index. (BLS 2009) For studies reporting costs in other currencies, we converted the estimates to US dollars using the purchasing power parity index. (IMF 2009) For studies that involved the use of databases and which failed to report the year of reference for the

cost estimates, we assumed the year of cost reporting to be the latest year of the database utilized in the study. For studies taking the modeling approach without specifying the year of cost reporting, we assumed the year of publication to be the reference year of cost reporting.

Results

Figure 1 depicts the flow chart of our literature search process. Our search identified seventeen publications that examined various economic aspects of RCC, including five cost studies, (Duh et al. 2009; Joudi et al. 2007; Link et al. 2006; Park et al. 2007; Tsavaris et al. 2000) five publications of CEA/CUA, (Hoyle et al. 2009a, 2009b; Pandharipande et al. 2008; Purmonen et al. 2008; Remak et al. 2008) and seven COI studies. (Burnet et al. 2005; Evans 2002; Lang et al. 2007; Wallen et al. 2007; Yabroff et al. 2007; Yabroff, and Kim 2009; Yabroff et al. 2008)

Cost Analysis

Table 1 lists the characteristics of the five costs studies of RCC published in the 2000s that we reviewed. Among those, three compared the costs of different surgical techniques for RCC, (Joudi et al. 2007; Link et al. 2006; Park et al. 2007) and two compared drug treatments for mRCC. (Duh et al. 2009; Tsavaris et al. 2000)The new surgical modalities examined in these studies included partial nephrectomy, (Joudi et al. 2007) percutaneous cryoablation, (Link et al. 2006) and laparoscopic partial nephrectomy.(Link et al. 2006; Park et al. 2007) All three studies concluded that the new surgical modality was cost-saving compared to the conventional surgical modality, with the estimated savings ranging from $175 to $5660 per patient (2008 U.S. dollars). (Joudi et al. 2007; Link et al. 2006; Park et al. 2007) In the two studies that attempted to identify cost drivers, (Link et al. 2006; Park et al. 2007) it appears that despite the high cost associated

with the new technology, cost-saving was achieve by a reduction in either hospital length of stays and/or operation room times.

The two remaining cost studies focused on the metastatic stage and compared the cost of pharmaceutical interventions. Tsavaris and colleagues compared two dosage levels of interferon-α2b (IFN- α2b): low-dose IFN- α2b in combination with vinblastine vs. high-dose IFN- α2b monotherapy. Although this conventional immunotherapy at different dosing levels yielded similar response rates and survival, the authors concluded that the average cost per patient was approximately $3,500 lower among those treated with the low-dose regimen.(Tsavaris et al. 2000) Duh and colleagues (2009) compared the costs of three emerging targeted therapies in the U.S.: sorafenib, sunitinib, and bevacizumab. The first two agents are oral medications, whereas the third agent is administered via IV infusion and was used off-label at the time of the study. (Duh et al. 2009) Results from this matched case-control study showed that bevacizumab was associated with a substantially higher cost; the average cost per patient per month for patients in the bevacizumab group was $2,889 and $2,656 (2008 $US) higher than that for those in the sorafenib and snitinib groups, respectively. The authors then extrapolated the incremental cost per patient to be $43,862, and $40,848, respectively, based on a median progression-free survival of 8.5 months, and speculated that the higher cost of bevacizumab was possibly driven by higher outpatient costs associated with IV administration.(Duh et al. 2009)

Cost-Effectiveness and Cost-Utility Analyses

Table 2 lists the five CEA/CUA studies, the majority of which (four out of five) focused on mRCC; (Hoyle et al. 2009a, 2009b; Purmonen et al. 2008; Remak et al. 2008) only one study

compared interventions for localized RCC. (Pandharipande et al. 2008) All studies took the modeling approach and used a Markov model.

Pandharipande and colleagues reported that for small renal tumors, new technology such as percutaneous radiofrequency ablation (PRFA) was preferred over nephron-sparing surgery because PRFA was associated with a minuscule reduction in QALY (2.5 days) but had a substantially lower cost (over $8,000 lower [note to authors: per what time period?]). (Pandharipande et al. 2008) Among the four CUA studies that compared treatments for patients with mRCC, two compared a targeted therapy with conventional immunotherapy as first-line treatment, (Hoyle et al. 2009b; Remak et al. 2008) and two compared a targeted therapy with the best supportive care as second-line treatment. (Hoyle et al. 2009a; Purmonen et al. 2008) Targeted therapies examined in these studies included sunitinib (Purmonen et al. 2008; Remak et al. 2008) sorafinib,(Hoyle et al. 2009a) and temsirolimus. (Hoyle et al. 2009b) All of the studies found targeted therapies to be more costly. A comparison of the ICERs shows a wide range across studies: from $48,405/QALY (Purmonen et al. 2008) to $145,812/QALY (Hoyle et al. 2009b). The two studies which concluded that the targeted therapy was cost-effective (Purmonen et al. 2008; Remak et al. 2008) were sponsored by the pharmaceutical companies that manufacture the agent.

Cost of Illness Studies

Table 3 lists the characteristics of the 7 studies that addressed various dimensions of the cost of illness (COI) associated with RCC. (Burnet et al. 2005; Evans 2002; Lang et al. 2007; Wallen et al. 2007; Yabroff et al. 2007; Yabroff, and Kim 2009; Yabroff et al. 2008) Among those, only

two provided an estimate of the overall COI, (Lang et al. 2007; Wallen et al. 2007) and another study estimated the overall COI for the elderly population. (Yabroff et al. 2008) Each of the other four studies dealt with a specific dimension of the economic burden of RCC, including follow-up surveillance, (Evans 2002) mortality cost (i.e., years of life lost), (Burnet et al. 2005) and direct non-medical cost in the context of patient time cost (Yabroff et al. 2007) as well as productivity loss for informal caregivers. (Yabroff, and Kim 2009) In 4 of the 7 studies, information on the cost of kidney cancer was included among other cancers within a large-scale research project on the economic burden of cancer or of genitourinary cancer. All studies reported the estimates of economic burden as cost or life year lost per patient; some also combined the per-patient cost with disease incidence or prevalence from cancer registries to calculate the overall economic burden of either kidney cancer or RCC. (Lang et al. 2007; Wallen et al. 2007; Yabroff et al. 2007)

All but one study reported the economic burden in the United States. All studies that combined multiple databases applied a straightforward mathematical equation to synthesize information gathered from different data sources. (Lang et al. 2007; Wallen et al. 2007; Yabroff et al. 2007; Yabroff, and Kim 2009; Yabroff et al. 2008) Because of this, we classified the approach of these studies as the hybrid approach even though no extensive decision analytic model was involved. In addition, claims data from Medicare or commercial databases were used in four studies. (Lang et al. 2007; Wallen et al. 2007; Yabroff et al. 2007; Yabroff et al. 2008)

In a study that discussed surveillance strategies for genitourinary malignancies, Evans applied a Medicare reimbursement rate retrieved from an academic medical center to follow-up

surveillance strategies recommended in the literature for prostate, bladder, renal cell, and testicular cancer. (Evans 2002) The estimated 5-year follow-up surveillance cost was in the range of $857 to $2,839 (2008 $US), depending on patients' tumor stage and the type of local treatment (radical vs. partial nephrectomy). Burnet and colleagues used data from the East Anglian Cancer Registry and the East Anglian life table to estimate the average years of life lost (AYLL) for 17 cancer sites. (Burnet et al. 2005) The authors reported that kidney cancer was associated with 12.9 AYLL in the U.K., and was one of four cancers with low research spending but high individual burden. (Burnet et al. 2005)

In a study designed to estimate patient time cost for the 11 cancer origination sites that are most prevalent in the United States, Yabroff and colleagues combined estimated "counts" for different types of medical care events (e.g., inpatient visit, outpatient visit) with the "time" associated each event to determine the patient time cost for each cancer. (Yabroff et al. 2007) The number of medical care events that occurred was estimated from the SEER-Medicare database, whereas the time associated with each event type was obtained from the National Ambulatory Medical Care Survey (for the average time spent on an office visit), the National Hospital Ambulatory Medical Care Survey – Emergency Department (for time spent on an ER visit), Medicare Current Beneficiary Survey (for time spent on outpatient surgeries), and the National Health Interview Survey (for time spent traveling and waiting to seek medical care). The authors then estimated patient time cost by multiplying patients' time in these medical care events with their wage rate. The estimated average patient time cost per patient for RCC was $3,876 (2008 $US) for those in the initial treatment phase and $5,823 (2008 $US) for those in their last year of life (i.e., terminal phase). (Yabroff et al. 2007)

In another study that addressed direct non-medical cost, Yabroff and Kim (2009) estimated the time costs associated with informal caregiving for the 10 most common cancers. They obtained information on time spent engaging in various activities by informal care givers from the American Cancer Society's Quality of Life Survey for Caregivers, and combined that information with the national median wage rate to calculate the time costs of caregiving for each cancer site. (Yabroff, and Kim 2009) For kidney cancer, the time cost of caregivers within the first two years of cancer diagnosis was $58,911 (2008 $US). (Yabroff, and Kim 2009)

Among the two studies that reported the overall economic burden of RCC, only one focused exclusively on this patient population. (Lang et al. 2007) Lang and colleagues identified patients with RCC from the SEER-Medicare database (1991-1999) and productivity loss data from the literature to estimate the COI of RCC. They reported a substantial economic burden of RCC, with an estimated annual COI of over $5 billion and respective annual direct and indirect costs per patient of $42,443 and $3,489 (2008 $US). The authors noted that because population-based claims data linked to cancer registries for non-elderly cancer patients are not currently available, they assumed that medical costs for patients with RCC who were younger than 65 years would be similar to those for the youngest age group (defined as between 65 and 69 years of age) estimated from SEER-Medicare data. The study by Wallen and colleagues extracted findings specific to kidney cancer from a large scale project called Urologic Diseases in America. (Wallen et al. 2007) That project utilized a battery of private and public databases from the 1990s to the early 2000s to quantify the burden of urologic diseases in the U.S. (Litwin et al. 2005) Wallen and colleagues reported that the annual RCC expenditure was approximately $0.58

billion, and that between 1994 and 2000, the expenditure increased 46%. (Wallen et al. 2007) That study also estimated work days lost for patients between ages 35 and 59, and found that kidney cancer was associated with more than 12 days of work absence. The authors of both studies acknowledged that the information in the databases they used was sufficiently dated so as not to accurately reflect current treatment patterns or to capture the impact of targeted therapies or less invasive local surgical interventions (e.g., cryoablation or radiofrequency ablation).

Lastly, Yabroff and colleagues used 1999-2003 SEER-Medicare data to estimate the cost of cancer care for the 18 most prevalent cancers (including kidney cancer) plus a group that combined all the remaining cancers. They also extrapolated to the long-term (5-year) cost of cancer care based on a cohort of elderly patients diagnosed with cancer in 2004. (Yabroff et al. 2008) Costs were estimated using the "incremental" approach in which a matched non-cancer control group was constructed to approximate the costs in the cohort of elderly patients with cancer had they not been diagnosed with cancer. The difference in costs between the cancer and non-cancer control groups was considered to be cancer-related. (Brown et al. 2002) Among elderly patients in three phases of living with a diagnosis of kidney cancer—the initial phase, the continuing phase, and the terminal phase (last year of life)—the mean net annual costs (in 2008 $US) for males were $32,348, $4,117, and $45,678, respectively, and those for females were $32,837, $4,241, and $44,353, respectively. The estimated 5-year total cost of care was $821 million, and the mean 5-year net cost was $43,296 and $43,010 (2008 $US) for male and female patients, respectively.

AN UPDATE OF THE COST OF ILLNESS OF RENAL CELL CANCER AMONG ELDERLY PATIENTS

As discussed previously, studies of the COI of RCC published to date were not able to capture the economic burden of emerging therapies for RCC due to the time period of databases used in the studies. In this section, we provide a brief update of the COI of RCC for elderly patients using more recent releases of two databases that had been employed in the previously published COI studies: the SEER-Medicare database (Lang et al. 2007; Yabroff et al. 2007; Yabroff et al. 2008) and the MarketScan database. (Wallen et al. 2007) The main purpose of this update is to project the potential impact of recently approved targeted therapies on the economic burden of RCC. In addition, we hope to use knowledge gained from our analyses to better understand the COI estimates generated from these databases so as to reconcile the wide range of COI estimates reported in the literature.

Methods

Data used in our analyses included those from the 1991-2007 SEER Medicare database and the 2001-2006 MarketScan Medicare Supplemental database. Briefly, the SEER-Medicare database links cancer patients in the SEER Program, an epidemiological surveillance system of population-based tumor registries containing data from 17 geographic areas in the United States, with a Medicare enrollment file to identify SEER patients who were eligible for Medicare. The recent release of the SEER-Medicare database includes persons with cancer diagnosed in 2005 and before, and Medicare claims for those patients through 2007. The dataset provides both clinical information (e.g., primary tumor site, stage at diagnosis, first course of treatment) and economic information (e.g., health resource utilization, Medicare payment) for elderly patients

with cancer. (Warren et al. 2002) The SEER-Medicare database has been the primary data source for health services research in oncology since its inception.

The MarketScan database contains proprietary data that is licensed through Thomson Healthcare. It is a nationwide employment-based database that contains information on medical claims as well as outpatient prescription drug claims for employees and their spouses and dependents. The database represents claims from approximately 45 large employers and captures insurance claims data from over 100 payers. (Medstat 2007) The MarketScan Medicare Supplemental database is built from the MarketScan database for the subset of employees who retired from one of the 45 large employers and became Medicare eligible; it includes claims for services covered by Medicare as well as employer-sponsored supplemental insurance plans. Individuals represented in the data from the SEER-Medicare and MarketScan databases cannot be identified, thus additional consent by the patients is not necessary for this study.

We identified patients with RCC from the SEER portion of the SEER-Medicare database, using the site code "kidney" and the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) histology codes indicative of RCC (8260, 8310, 8316-8320, 8510, 8959). (SEER) Because the most current year of SEER data available for review was 2005, we based our COI estimates on a prevalent cohort of elderly patients with RCC in 2005. As several targeted therapies were available in 2005 (e.g., bevacizumab, rituximab, aldesleukin), we anticipated observing the utilization of these therapies either as indicated for RCC or in an off-label use. To be included in the 2005 prevalent cohort, patients were required to have RCC that was diagnosed in 2005 or earlier and to have been alive at the beginning of 2005. We used

HCPCS codes to identify the use of non-oral targeted therapies in this cohort and applied frequency matching to construct a non-cancer control group using age group, gender, and SEER sites as the matching criterion.

For the MarketScan Medicare Supplemental database, we relied on ICD-9 codes (189.0, 198.0, and V10.52) to identify patients with kidney cancer, and could not limit our focus specifically to RCC because (unlike the SEER-Medicare database) histologic information was not available in the MarketScan data. However, the Medicare MarketScan database contained information on prescription drug claims, thus it was possible to identify oral targeted therapies such as sorafenib and sunitinib. Because sorafenib was approved by the FDA in December 2005 and sunitinib was approved in January 2006, we based our estimates on a prevalent cohort of elderly patients with RCC in 2006, anticipating that our estimate from the MarketScan Medicare Supplement database would capture the early experience of both oral targeted agents. In these data, the 2006 prevalent cohort consisted of patients with two or more claims containing kidney cancer-related ICD-9 codes on separate dates in 2006 or previous years, and who were enrolled in the employer-sponsored insurance plans at the beginning of 2006. The use of targeted therapies was identified via HCPCS codes for non-oral agents and NCD codes for oral agents.

Results

A total of 11,238 patients with RCC in 2005 were identified from the SEER-Medicare database. Among those, 911 (8.1%) were deceased in 2005. For the remaining patients, 1,973 (17.6%) were diagnosed with RCC in 2005, and 8,354 (74.3%) were diagnosed prior to 2005.

Table 4 summarizes the net mean and median costs (in 2008 $US) per patient with RCC for the entire 2005 prevalent cohort, stratified by the patients' disease phases in that year. The net costs were obtained by subtracting the costs of the matched control group from the total costs of the RCC group. Costs were quantified in two ways: Medicare payment and charges. The average Medicare payment associated with RCC was approximately $10,860, and was $23,935, $6,015, and $26,223 for those who were diagnosed in 2005, diagnosed prior to 2005, and deceased in 2005, respectively. When cost was measured in charges, much higher costs were observed. The average net cost exceeded $51,000, which is five times higher than the cost measured in the Medicare payment.

Using claims data from the SEER-Medicare database, we found a small percentage (1.2%) of patients with RCC who received targeted therapies in 2005. Among those 135 patients, the majority were treated with bevacizumab (61.8%), followed by rituximab (26.5%), and aldesleukin (11.8%). Figure 2 shows the results of our comparison of the total Medicare payment for patients with RCC who received targeted therapies versus those who did not. We used total Medicare payment instead of net Medicare payment and also did not use a non-cancer control group because we were interested in learning the "additional" economic burden attributable to targeted therapies. We conducted similar analyses using the 2006 MarketScan Medicare Supplemental database to capture the impact of oral targeted therapies that were not covered in Medicare Part B and which, therefore, were not included in the SEER-Medicare database.[†]

[†] Although oral prescription drugs are covered under Medicare Part D, the latest release of SEER-Medicare data has not yet added Part D claims to the data.

Figure 2 shows that on average, the annual Medicare payment for patients with RCC who were treated with targeted therapy was more than three times higher than that for patients with RCC who did not receive targeted therapy ($65,014 vs. $18,234). The magnitude of difference estimated from the MarketScan Medicare Supplemental database (approximately 2.7-fold) was slightly less than that from the SEER-Medicare database. In particular, the average costs were $59,951 and $21,978 for patients in the targeted therapy group and the conventional treatment group, respectively. We identified two probable reasons for the difference in the estimates produced from these databases. First, insurance coverage is likely to differ between Medicare and MarketScan Medicare Supplemental databases: the latter included claims of services covered by both Medicare and the supplemental insurance or by the supplemental insurance alone (e.g., outpatient prescription drug). Therefore, estimates from the SEER-Medicare database may be higher because they include services that were not reimbursed by supplemental insurance, such as certain medical devices, home health services, or hospice care. Conversely, the SEER-Medicare estimates could be lower as they did not include costs associated with outpatient prescription drugs, nor the copayment or deductible paid by patients' supplemental insurance or as out-of-pocket payments. Second, the two databases most likely captured different reports of the use of targeted agents. The SEER-Medicare database only captured targeted agents administered intravenously that are covered under Medicare Part B, whereas the MarketScan Medicare Supplemental database included the utilization of a mix of oral and IV targeted agents. Duh et al. suggested that targeted agents administered orally were much less costly than those administered by IV. (Duh et al. 2009) An even larger magnitude of difference was observed when comparing the medians between the groups, suggesting that what was observed based on the means was not driven primarily by extreme values in the tail of the cost distribution. In

addition, we note that because only a very small percentage of patients with RCC were treated with targeted therapies, the average annual cost for the patients as a whole was close to that for the group of patients who did not receive targeted therapy.

DISCUSSION

There is a limited number of studies in the literature that provide information on the economic burden of RCC. Our systematic review identified only 17 papers published since 2000, with the majority of the studies (12 out of 17) published in the United States. Evidence accumulated in the past decade suggests that RCC was associated with substantial economic burden. Overall, the literature suggests that new surgical techniques to treat localized RCC can potentially reduce the economic burden of this disease. Conversely, the burden is likely to increase as the use of targeted therapies for the treatment of mRCC becomes more prevalent. The cost-effectiveness of these novel agents remains inconclusive.

Two studies provided estimates of the overall economic burden. Although both studies agreed that hospitalization accounted for the majority of the economic burden of RCC in the U.S., the estimates were vastly different: $0.53 billion (Wallen et al. 2007) and $5.03 billion. (Lang et al. 2007) This large discrepancy was also noted in a recent review by Gupta et al. (2008) Several factors might account for the discrepancy. First, the estimate by Wallen et al. was based on only direct medical costs, whereas that reported by Lang et al. was based on both direct and indirect costs. Second, each study employed a different methodology to generate its estimate. Warren and colleagues obtained their estimates by aggregating medical expenditures across service sites from a variety of nationally representative surveys, whereas Lang and colleagues produced their

estimate by multiplying the per-patient net cost at each age strata with the corresponding annual prevalence. Patients may have received medical services related to RCC (e.g., treating complications of surgery) that were not billed under RCC-related ICD-9 codes. This is especially likely in survey data in which there is no or limited information on secondary diagnoses. Thus, it is possible that the economic burden estimated by Warren et al. was underestimated.

These factors still would not explain the large discrepancy in the annual cost per patient, which was found to be $15,975 among patients in the 35-59 age group by Warren et al. (2007) and $42,443 for an average patient with RCC by Lang et al. (2007). Our updated estimates, combined with those reported by Yarbroff et al. (2008) suggest that while the cost reported by Warren et al. (2007) may be an underestimation, that by Lang et al. (2007) is likely an overestimation. In fact, their estimate was more similar to ours based on charges ($51,825) and was substantially higher than our estimate using Medicare payments ($17,012). Furthermore, their annual estimate was only slightly lower than the 5-year per-patient cost ($43,193) reported by Yarbroff et al. (2008). These observations led us to speculate that either the estimate of Lang et al. was based on charges, not costs, or that calculation errors were made because the study methodology appeared to be sound.

It is difficult to project the future economic burden of RCC. Our review of the literature and our analysis of more recent data indicate that trends such as the rising incidence of RCC and expanding diffusion of targeted therapies will lead to an increase in the associated economic burden. Conversely, an increasing use of less invasive surgical techniques (which were found to be cost-saving in the literature) or more active surveillance in lieu of aggressive treatments

should result in a reduction in the associated economic burden. The net effect of both positive and negative forces has not been explored in the literature. An estimation of the future economic burden of RCC is further complicated by new treatment modalities that are likely to emerge, such as Tro Vax, a tumor antigen-targeted vaccination. (Amato et al. 2008; Hawkins et al. 2009) Much research is needed to better understand the economic burden of RCC. It is important for future studies to fully account for the inherent limitations of different databases and the associated biases resulting from the analysis of these data so as to inform policy makers of the potential direction and magnitude of biases in the estimates—something that many published studies have failed to achieve.

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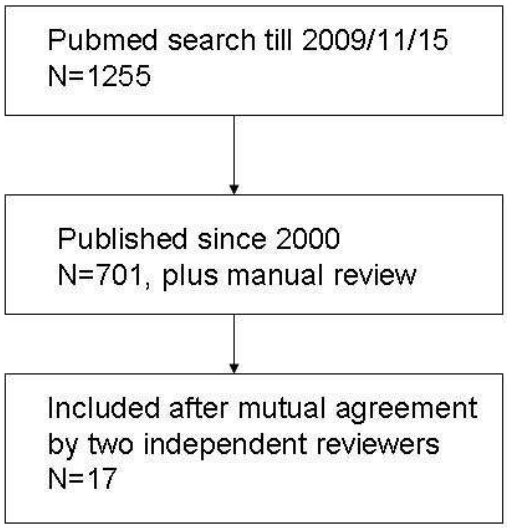
Figure 1. Flowchart of Literature Search



Inclusion: reporting economic data of Renal Cell carcinoma
Exclusion: non-English, non-full original paper, retrospective report from single institution

[note to authors: no capitalization needed in renal cell carcinoma as it appears below the figure]

Inclusion: reporting economic data of renal cell carcinoma

Figure 2: Comparison of Annual Costs (2008 $US) for Patients with RCC Who Received Targeted Therapies vs. Those Who Did Not

[note to authors: adjust figure text to state "target**ed** therapies"]

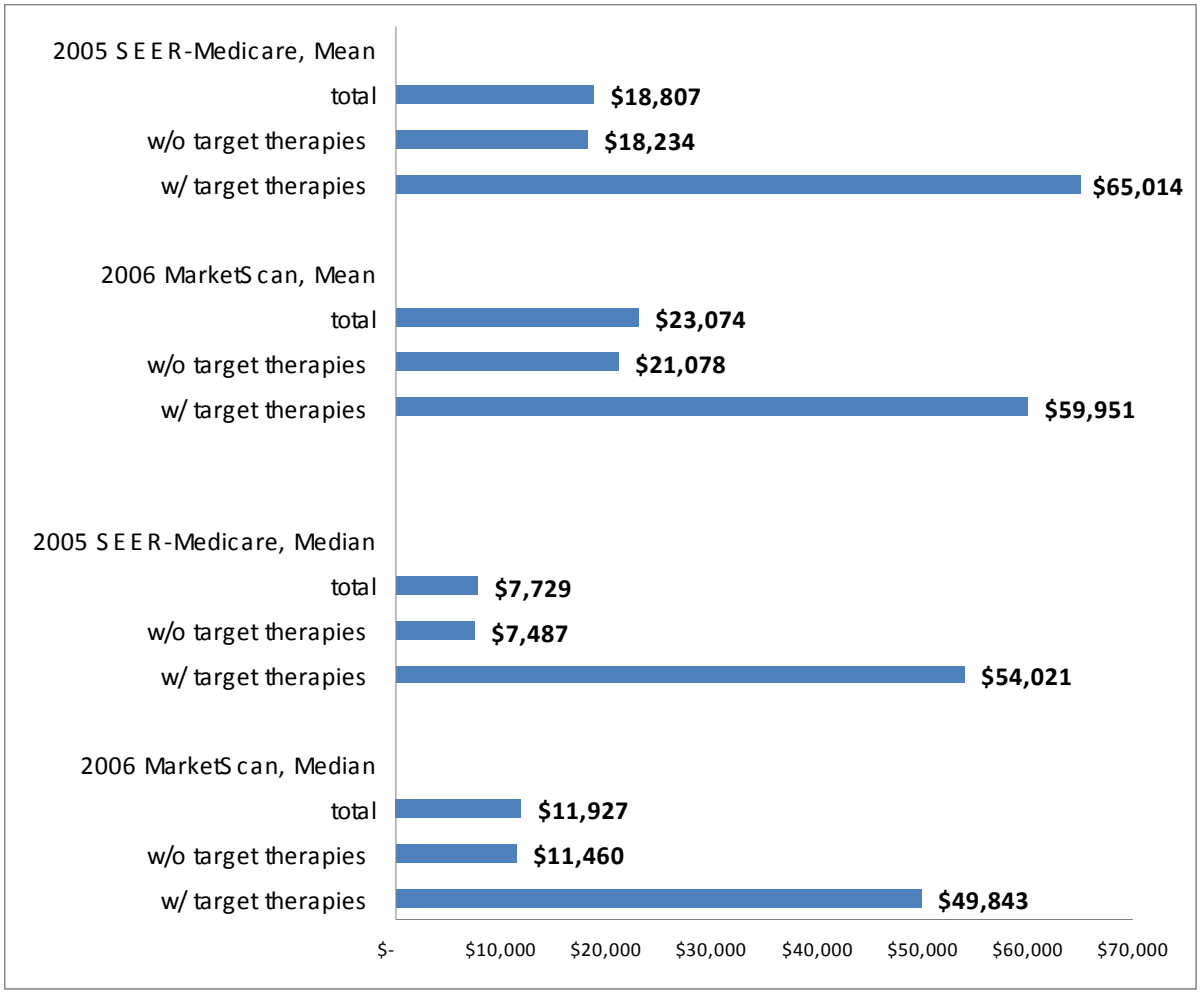


Table 1. Cost Analysis of Renal Cell Carcinoma (2008 $US)

Author (Year) Country	Approach	Cost Type Study Perspective	Reference year for cost	Data Source or model structure	Study Population	Intervention (sample size)	Results	Conclusion	Comment
Joudi et al (2007) US	Database	Direct medical Payer	2003	HCUP-NIS, 2000-2003	Kidney cancer identified from ICD-9-CM: 189	TN (N=18575) PN (N=3019)	TN: $39,886 PN: $37,605	PN was cost-saving: $2,281 per patient	Estimates based on hospital charges Primary objective was to compare complications between TN and PN
Link et al (2006) US	Hybrid	Direct medical Payer	NS, assumed to be 2006	Mathematical model, populated with data from a single institution	Patients with small renal mass, identified from retrospective chart review	OPN (N=50) LPN (N=217) LCA (N=28) PCA (N=22)	OPN: $9,074 LPN: $7,404 LCA: $7,394 PCA: $3,414	PCA has the lowest perioperative cost; cost saving ranged from $3,980 to $5,660 per patient	Major cost drivers were OR time and hospital LOS Sensitivity analysis showed that results were also sensitive to cryoprobe usage
Park et al. (2007) US	Modeling	Direct medical Payer	NS, assumed to be 2007	Decision tree model	Patients with small renal mass identified from the literature	OPN LPN Sample size varies by studies	OPN: $8,808 LPN, disposable: $8,359 LPN, reusable $8,046 LPN, hand-assisted: $8,633	Perioperative cost was lowest for LPN with reusable equipment; cost saving per patient for LPN ranged from $175 to $761	Estimates based on hospital cost data One-way sensitivity analysis showed that the results were sensitive to OR times, LOS, cost of OR equipment, and room and board charges

Tsavaris et al (2000) Greece	Database	Direct medical Payer	NS, assumed to be 2000	Randomized trial, 1988-1993	Histologically confirmed metastatic RCC	high dose IFN monotherapy (N=50) low dose IFN + VBL (N=50)	High-dose IFN: 283,411 Low-dose IFN+VBL: 109,654	Low-dose IFN+VBL was cost-saving; $3,475 per patient	Primary endpoints were response rates and toxicity, cost was one of the secondary endpoints Costs included hospital stay, intervention drugs, antibiotics and other drugs received during the 12-week study period
*Duh et al. (2009) US	Database	Direct medical Payer	2007	Market Scan database, 2004-2007	Patients with at least two claims with a primary or secondary ICD-9 of 189.0, 198.0, and treated with angiogenesis inhibitors	bevacizumab (N =109) sorafenib (N=109) sunitinib (N=109)	Cost per member per month bevacizumab: $13,916 sorafenib: $7,294 sunitinib: $8,561	On average, total medical cost per patient for bevacizumab was $40,848 and $43,862 higher than sorafenib and sunitinib, respectively	Total cost was extrapolated from a median progress-free survival of 8.5 months Matched-cohort design, frequency match by age and gender at 1:1 ratio Tobit model was used in multivariate analysis to estimate incremental costs

HCUP-NIS: nationwide inpatient sample of the healthcare cost and utilization project; ; ICD-9(-CM): International Classification of Diseases, 9th Revision (Clinical Modification); IFN: interferon; LCA: laparoscopic cryoablation ; LOS: length of stay; LPN: laparoscopic partial nephrectomy; NS: not specified; OPN: open PN; OR: operating room; PCA: percutaneous cryoablation; PN: partial nephrectomy; PPPM: per patient per month; RCC: renal cell carcinoma; TN: total nephrectomy; US: United States; VBL: vinblastine;
* study was sponsored by pharmaceutical company

Table 2. Cost-Effectiveness/Utility Analysis of Renal Cell Carcinoma (2008 $US)

Author (Year) Country	Approach	Cost Type Study Perspective	Reference year for cost	Data Source or model structure	Study Population	Intervention (sample size)	Results	Conclusion	Comment
Pandharipande et al (2008) US	Modeling	Direct medical Payer	2006	Markov model for lifetime	A hypothetical cohort of men, 65 years of age with unilateral RCC ≤ 4cm	NSS PRFA Study based on hypothetical cohort, sample size not applicable	NSS: $65,813 9.689QALY PRFA: $57,041 9.682QALY	NSS was not cost-effective; ICER of NSS vs. PRFA was $1,265,465 per QALY	Transition probabilities, costs, and utilities all obtained from the literature Costs and outcomes discounted at 3% Sensitivity analysis suggests results were robust to changes in parameters Quasi-societal perspective in which time costs were not included Estimates of colon cancer were used to approximate costs and utilities for post-treatment health states

*Remak et al (2008) US	Modeling	Direct medical Societal	2006	Probabilistic Markov model for lifetime (10 years)	A hypothetical cohort of 1,000 patients with mRCC undergoing first-line treatment	Sunitinib (S) IFN-α (IFN) IL-2 (IL) Study based on hypothetical cohort, sample size not applicable	**S**: $247,007 2.09LY/1.33QALY **IFN**: $238,735 1.98LY/1.19QALY **IL**: $250,785 1.85LY/1.13QALY	IL was dominant Sunitinib (vs. IFN- α) is cost-effective; ICER=$57,745/QALY and the prob of cost-effectiveness was 46% and 65% at WTP $50,000 and $100,000 per QALY, respectively	Transition probabilities and utility obtained from RCTs Costs & outcomes discounted at 5% Although the study took a societal perspective, the model excluded indirect costs Tornado analysis indicated results were sensitive to utility value, sunitinib and BSC costs, and time horizon
#Hoyle et al (2009) UK	Modeling	Direct medical Payer	2007/2008	"Area under the curve" decision analytic model, lifetime (10 yrs) follow-up	Hypothetical cohort of patients with poor prognosis advanced RCC receiving first-line treatment	Temsirolimus (T) IFN- α (IFN) Study based on hypothetical cohort, sample size not applicable	**T**: $44,451 1.52LY/0.77QALY **IFN**: $10,045 1.07LY/0.53QALY	Temsirolimus is effective, but not cost-effective; ICER > $145,000 and the prob. of cost-effectiveness at £30,000 per QALY was close to zero	Effectiveness obtained from RCT, utility from the literature Cost & outcomes discounted at 3.5% Both sensitivity and subgroup analyses showed that conclusion was robust

[#]Hoyle et al (2009) UK	Modeling	Direct medical Payer	2007/2008	Probabilistic Markov model, lifetime (10 yrs) follow-up	Patients with mRCC receiving second-line treatment	Sorafinib (S) BSC Study based on hypothetical cohort, sample size not applicable	**S**: $36,764 1.66LY/1.18QALY **BSC**: $5,851 1.30LY/0.91QALY	Sorafinib is clinically effective, but not cost-effective; ICER= $116,176/QALY, and the prob of cost-effectiveness at £30000 per QALY was 0.0%	Effectiveness obtained from RCT, utility from the literature Cost & outcomes discounted at 3.5% Conclusion remained even under scenarios more optimistic for sorafinib
*[#]Purmonen et al (2008) Finland	Modeling	Direct medical Payer	2005	Probabilistic Markov, five-year follow-up	Patients with mRCC seeking second-line treatment	Sunitinib (S) BSC Study based on hypothetical cohort, sample size not applicable	**S**: $36,145 (five-year cost) LY=16.4months **BSC**: $6,140 LY=3.83 – 4.98 months	Sunitinib is potentially cost-effective; ICER = $48,405/QALY, the prob. of cost-effective at €45,000 was 70%	Efficacy and utility of S from single-arm trials, efficacy of BSC from a local sample (N=39) but assumed the same utility for each health state as S Cost & outcomes discounted at 5% Results appeared to be robust to changes to modeling parameters

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; IFN: interferon; IL: interleukin; LY: life years; mRCC: metastatic RCC; NS: not specified; NSS: nephron-sparing surgery; PRFA: percutaneous radiofrequency ablation; QALY: quality-adjusted life year; RCC: renal cell carcinoma; RCT: randomized clinical trial; US: United States; UK: United Kingdom; WTP: willingness to pay;
*: sponsored by pharmaceutical company. #: cost was converted to US dollars by purchasing power parity index

Table 3. Cost of Illness of Renal Cell Carcinoma (2008 $US)

Author (Year) Country	Approach	Cost Type	Reference year for cost	Data Source or model structure	Study Population	Results	Conclusion	Comment
Evans et al (2002) US	Modeling	Direct medical Payer (Medicare)	NS, assumed to be 2002	Aggregate costs over 5 years based on published surveillance strategies	Posttherapy RCC; patients at various tumor stages and grades	Post radical nephrectomy T1N0M0 : $857 T2N0M0 : $,2745 T3N0M0: $2,745 Post partial nephrectomy T1-2N0M0: $1,422 T3N0M0: $2,839	Costs of 5-year follow-up surveillance strategies ranged from $857 to $2,839 per pt. Follow-up strategies should consider the likelihood of tumor recurrence and avoid overutilization of imaging	Primary objective: surveillance strategies for the four most common genitourinary malignancies Unit cost based on Medicare reimbursement at a medical center Surveillance cost only, cost of treating recurrence was not considered
Burnet et al (2005) UK	Hydrid	Indirect cost	Results not converted to dollars	1990-1994 East Anglian Cancer Registry	Patients with kidney cancer	AYLL: 12.8 years	The comparison between AYLL to research spending suggested that kidney cancer has high individual cancer burden but relative low research spending	Primary objective was to report AYLL for 17 cancer sites Identified four "Cinderella" cancers (i.e., high cancer burden but low research spending): CNS tumors, melanoma, cervix and kidney cancers
#Yabroff et al (2007) US	Hybrid	Direct non-medical	2002	1995-2001 SEER-Medicare, 2001 NAMCS, 2002 NHAMCS, 2001 MCBS, and 1992 NHIS	Elderly patients with renal cancer	Cost per patient by phase: Initial: $3,876 Last year of life: $5,823	Based on incidence reported in 2005, the projected time cost for renal cancer in the initial care phase was $156 million (or $4,325 per patient)	Primary objective was to estimate patient time costs for 11 most prevalent cancers, including renal Sensitivity analysis showed that point estimates from varying assumption fell within the 95% CI of base case estimates

#Yabroff et al (2009) US	Hybrid	Direct non-medical	2006	ACS Quality of Life Survey for Caregiver	Informal caregiver of renal cancer pts diagnosed between 2000 and 2003	Time cost of caregivers within the first 2 yrs of diagnosis: $58,911	Informal caregivers spent a substantial amount of time (3,352 hours cumulatively) caring for cancer patients within the first two years of their diagnosis	Primary objective was to estimate caregivers time cost for 10 most common cancer, including renal Higher caregiver burden for lung cancer, and lowest for breast Unit of analysis was caregivers, not cancer patients Sensitivity analysis: point estimates from various scenarios fell within 95% CI of base case estimates
*Lang et al (2007) US	Hybrid	Direct & Indirect	2005	SEER, 1999 SEER-Medicare	Prevalence cases of RCC in the US in 1999	Annual cost per patient: $45,932 direct costs: $42,443 indirect cost: $3,489	The annual cost of RCC was $5.03 billion; healthcare costs and lost productivity accounted for 92.5% and 7.6%, respectively.	Costs and health care utilization were estimated from SEER-Medicare using matched cohort approach Costs of pts <65 yrs were assumed to be the same as those aged 65-69 Costs of oral medications and productivity loss from the literature Healthcare costs reflected treatment pattern in 1999 Major cost drivers: cancer-related surgical procedures (11.3%) and arterial embolization (8.7), and additional hospitalization (42.1%)

Wallen et al (2007) US	Hybrid	Direct & Indirect	Vary by data sources	SEER (73-02), 5% Medicare claims (92, 95, 98, 01), HCUP, MEPS, and NHAMCS, (94, 96, 98, 00), Ingenix (02), MarketScan (99)	Kidney cancer identified from ICD-9 codes from various databases	For pts between 35-59 annual cost per pt: $15,975 annual work loss per pt: 96.6 hours	Total medical expenditures for RCC were approximately $401 million in 2000 (or $0.58 billion in 2008 $US), a 46% increase from 1994	Information extracted from the Urologic Disease in American project Major cost driver was inpatient care, accounting for 86.3% of total expenditures in 2000 Total cost reported reflects total medical expenditure; indirect cost was only reported as hours but was not converted to dollars
Yabroff et al (2008) US	Hybrid	Direct Medical	2004	SEER-Medicare (1999-2003) SEER (1998-2004)	Renal cancer (combined ICD-O & histology code)	Mean net annual cost by phase of care Male: - initial: $32,348 - continuing: $4,117 - last year: $45,678 Female: - initial: $32,837 - continuing: $4,241 - last year: $44,353	Projected 5-year cost for elderly patients with renal cancer was $821 million ($43,193 per patient or $43,296 per male patient and $43,010 per female patient)	Estimates based on disease phase specific cost from matched cohort approach (SEER-Medicare) and survival estimates (SEER) Primary objective was to estimate costs for all cancers, where 18 cancer were reported separately (including renal) Cost of elderly patients only -3% discount for 5-year cost

ACS: American Cancer Society; AYLL: average years of life lost; CI: confidence interval; Dx: diagnosis; HCUP: Healthcare Cost and Utilization Project; ICD-O: International Classification of Diseases for Oncology; MCBS: Medicare Current Beneficiary Survey; MEPS: Medical Expenditure Panel Survey; NAMCS: National Ambulatory Medical Care Survey ;NHAMCS: National Hospital Ambulatory Medical Care Survey ; NHIS: National Health Interview Survey; NS: not specified; RCC: renal cell carcinoma; SEER: ; Surveillance, Epidemiology and End Results US: United States; USD: US dollars; UK: United Kingdom;
*:sponsored by pharmaceutical company; #: time cost was inflated to year 2008 by Consumer Price Index - urban wage earners and clerical workers.

Table 4. Net Costs for Elderly Patients with RCC in the United States (2008 $US)

	Mean	(95% CI)	Median	(95% CI)
Cost measured by Medicare payment				
Total	$10,860	($10,401 - $11,320)	$5,567	($5,459 - $5,675)
Initial	$23,935	($22,958 - $24,911)	$23,571	($23,339 - $23,802)
Continuing	$6,015	($5,504 - $6,526)	$2,405	($2,289 - $2,521)
Terminal	$26,223	($24,017 - $28,428)	$22,499	($21,952 - $23,046)
Cost measured by charges				
Total	$51,825	($49,538 - $54,112)	$26,922	($26,417 - $27,427)
Initial	$99,914	($94,902 - $104,926)	$84,598	($83,517 - $85,679)
Continuing	$33,143	($30,579 - $35,706)	$13,723	($13,184 - $14,262)
Terminal	$116,390	($105,677 - $127,103)	$71,669	($69,449 - $73,890)

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