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# Estimating the Population Benefits and Costs of Rituximab Therapy in the United States from 1998 to 2013 Using Real-World Data

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**Background:** Rituximab was approved in 1997 and is regularly one of the largest drug expenditures for Medicare; however, its benefits and costs have not been estimated from a population perspective.

**Objectives:** To estimate both the clinical and the economic outcomes of rituximab for its approved hematological uses at the population level.

**Research Design:** Analyses using cancer registry incidence data from the Surveillance, Epidemiology, and End Results (SEER) program, and outcomes data from SEER data linked with Medicare administrative claims (SEER-Medicare data). These results were incorporated into an epidemiological simulation model of the population over time.

**Subjects:** We modeled all United States patients from 1998 to 2013 diagnosed with diffuse large B-cell lymphoma, follicular lymphoma, or chronic lymphocytic leukemia.

**Measures:** Using this model, we estimated the life-years saved, as well as their economic benefit, in the United States population. We also estimated the incremental cost of adding rituximab to chemotherapy. All economic inputs were based on Medicare reimbursed amounts inflated to 2013 dollars.

**Results:** There were 279,704 cumulative life-years saved which were valued at $25.44 billion. The incremental direct medical cost of rituximab was estimated to be $8.92 billion, resulting in an incremental economic gain of $16.52 billion.

**Conclusions:** These analyses, based on real-world evidence, show that the introduction of rituximab into clinical practice has produced a substantial number of incremental life-years. Importantly, the economic benefit of the life-years gained greatly exceeds the added costs of treatment.

**Key Words:** lymphoma, survival, life-years, economics

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The cost of cancer therapy is considered to be very high.[1,2] Recent estimates suggest that the cost of cancer care will increase by 27% due to population changes alone.[3] Furthermore, benefits and costs may vary depending on the age and comorbidity burden in the population being treated.[4] And treatments may have heterogeneous effects in the population.[5]

Because of such variability, estimating the benefits and costs of investing in innovative therapies in the real world is complicated. While clinical trial results generate high-quality evidence, trials are limited in their ability to extend to older and sicker patients, or to predict long-term results. As a result, it may be more informative to take a retrospective look at an innovative cancer therapy to determine its benefits and costs in a real-world setting that includes a heterogeneous patient population. This is potentially a reliable approach because it leverages existing data sources and publications, as well as the known epidemiology of the disease under study.

Rituximab is an useful example because it is perennially one of the top drug expenditures for the Medicare program.[6] It was originally approved in 1997 and became the standard of care in diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL).[7] In 2010, it was also approved for use in chronic lymphocytic leukemia (CLL).[8] Rituximab plus chemotherapy (R+Chemo) compared with Chemo Alone has been shown to reduce mortality risk by 36% in DLBCL, 35% in FL, and 22% in CLL.[9–11] Importantly, because of its long use in clinical practice, the use, effectiveness, and cost of R+Chemo in the real world can be

estimated with existing data sources. Therefore, the goals of these analyses were 3-fold: (1) to estimate the clinical value of rituximab in terms of life-years saved; (2) to estimate the incremental direct medical costs to the population of adding an innovative cancer therapy (R+Chemo) to the standard of care (Chemo Alone); and (3) to compare the benefits and costs of rituximab at the United States (US) population level.

## METHODS

We developed a model of benefits and costs associated with rituximab over the first 15 years after approval (1998–2013). The analysis process was as follows: estimate the number of patients who used R+Chemo, estimate the incremental survival and the incremental cost associated with R+Chemo compared with Chemo Alone in these patients, and estimate both the incremental number and the economic value of the life-years lived by the R+Chemo patients.

Each aspect of the model is described below (Supplementary Materials Fig. 1, Supplemental Digital Content 1, http://links.lww.com/MLR/B95). All results were calculated separately for DLBCL, FL, and CLL according to the same methodology. All diagnosed patients were followed in the model for 10 years after diagnosis. While rituximab is used in other conditions, these analyses focus on rituximab in its approved oncology indications.

## Data Sources

The inputs for the model were derived from real-world, heterogenous, population-based data sources. Incidence rates were taken from the Surveillance, Epidemiology, and End Results (SEER) cancer registry data, population counts were taken from US Census data, and utilization, survival, and costs were estimated using SEER-Medicare data.[12–15]

Patients were included in the analyses of the SEER-Medicare data if their first, primary cancer was diagnosed between January 1, 1999, and December 31, 2009, and were followed through December 31, 2010. Patients with FL and DLBCL were extracted from the non-Hodgkin lymphoma (NHL) database by using the SEER-provided lymphoma re-code variables; CLL was provided as a separate file. Patients who were diagnosed in the month of death or on autopsy were excluded. To ensure complete information about therapy and outcomes, patients had to have been enrolled in both Medicare Parts A and B, with no health maintenance organization coverage after diagnosis. After diagnosis, patients were followed until death, enrollment in a health maintenance organization, development of a second primary tumor, or the last date for which Medicare claims were available. To estimate results across a broad range of age groups, there were no limitations placed on age at diagnosis in these analyses.

## Model Inputs

All model inputs were estimated by calendar year, age at diagnosis, and lymphoma type. Age was categorized using 5-year age groups from 50 to 84 years, plus age categories of <50 and >84 years.

## Epidemiology of NHL

Age group-specific, sex-specific, and year-specific incidence rates for each lymphoma type were estimated from SEER data for 1998 through 2010. Estimates for 2011–2013 were generated using SEER joinpoint–based growth rates applied to the 2010 rates.[15] Standard errors for each incidence rate were used for probabilistic analyses. These incidence rates were multiplied by the corresponding population estimates from the US Census to estimate the total number of diagnosed patients for each tumor in each year within each age, sex, and year stratum.

## Utilization of Therapy in NHL

All diagnosed patients in the SEER-Medicare data were grouped into one of the following mutually exclusive groups to estimate utilization: R+Chemo, Chemo Alone, and All Other. To align with counts of diagnosed patients from the SEER program, utilization rates for R+Chemo and for Chemo Alone were estimated as proportions of the total diagnosed population (ie, all 3 groups in the denominator). Patients receiving rituximab monotherapy were not included in the R+Chemo group.

Algorithms to identify rituximab and chemotherapy were defined as in previous studies of lymphoma using the SEER-Medicare data using relevant diagnosis and procedure codes.[16–18] Oral therapies without an intravenous equivalent (eg, chlorambucil) are not reimbursed by Medicare Part B and were not part of the data. To maximize generalizability, we did not limit the sample to the subset of patients with Part D coverage for such drugs.

Consistent with other research, infused therapies were identified by identifying the first administration after diagnosis within 6 months for DLBCL, within 12 months for FL, and within 24 months for CLL.[17–20] Individuals who did not receive infused therapy within the time window were considered to be untreated for the purposes of estimating utilization of chemotherapy and immunotherapy. All infused agents used within the first 30 days of the first administration were identified, and grouped into the remaining 3 therapy groups.

Utilization estimates were generated separately for each lymphoma type, by calendar year of diagnosis, by sex, and by age group. Estimates from patients diagnosed in 1999 used for 1998, and estimates from patients diagnosed in 2009 were used for 2010–2013. First-line utilization of R+Chemo was calculated as a proportion of all diagnosed patients in each year. Stratum-specific R+Chemo utilization estimates were multiplied by the corresponding stratum-specific patient counts based on the epidemiology calculations.

## Average Survival

To determine the additional life-years lived by patients receiving R+Chemo compared with Chemo Alone, we estimated 10-year restricted mean survival for each group using flexible parametric survival models.[21–23] These models use spline functions of time, facilitating the estimation of mean survival which is critical for estimating life-years saved. Ten-year restricted mean survival was used in these analyses,

which is the average number of life-years lived over the 10 years after therapy initiation. The final choice of model (proportional hazards, log odds, and log normal) and the number of knots was based on improvements in Akike's Information Criterion. The proportional hazards formulation with 3 knots was selected for CLL and FL, whereas 5 knots was used for DLBCL, consistent with recommendations.[23]

All models included covariates for rituximab use, age group, sex, race, anemia, presence of B-symptoms (except CLL), stage (except CLL) presence of an indicator of mobility limitations, year of diagnosis, and comorbidity score. Using this model, restricted mean survival was predicted for each individual who received R+Chemo using the R+Chemo treatment effect. Then, for these same individuals, survival was reestimated using the Chemo Alone treatment effect. The incremental treatment effect was estimated as the mean of the differences of the individual treatment effects. SEs were estimated using 1000 bootstrap samples of the estimation process.

Because there were published 10-year results in older patients with DLBCL from the Groupe d'Etude des Lymphomes de l'Adulte (GELA) study, we used these data to compare to the SEER-Medicare 10-year survival results as a validation exercise.[9,24] The Kaplan-Meier curves for the rituximab and nonrituximab groups were extracted, and the area under the curve was estimated and compared with similar results for the DLBCL population.[25]

## Costs

The model included direct medical costs but did not include any direct nonmedical costs or indirect costs. All costs were based on Medicare reimbursed amounts because a significant portion of the population is in the Medicare program. The incremental direct medical costs of R+Chemo versus Chemo Alone for each lymphoma were based on Medicare Part A and B paid amounts using inverse probability-weighted regression, accounting for censoring. Methods for this estimation have been described elsewhere.[26,27] In short, cost data were partitioned into monthly intervals, and the cumulative incremental cost of R+Chemo compared with Chemo Alone was estimated for each interval. Censoring weights were used in each interval to reweight the cumulative cost estimates in much the same way that Kaplan-Meier survival estimates are weighted, except that the roles of censoring and death are reversed. Patients who die continue to be included and have $0 cost after death. Patients who are censored are accounted for by increasing the censoring weights for the remaining patients in the sample.

Because the cost estimates are based on partitioned data, unlike parametric survival models, they cannot be readily extrapolated as part of the statistical model estimation process. And because simulation analyses suggest that results can be biased when censoring becomes substantial, cost analyses were estimated over a 6-year time horizon.[26] The model included the same covariates as the survival model described above.

The cumulative incremental cost difference between R+Chemo and Chemo Alone was adjusted to account for the different follow-up periods for survival and for cost. The incremental total direct medical cost for year 6 was applied to years 7 through 10 to extrapolate to a 10-year timeframe. We also evaluated chemotherapy costs to help determine whether the incremental cost differences were due to survival effects or to immunotherapy and chemotherapy utilization. All costs were inflated to 2013 US dollars.

To estimate the economic benefit of rituximab, we multiplied the incremental life-years by a dollar amount based on a published estimate for the value of a life-year saved ($90,941 in 2013 dollars).[28] This specific estimate was chosen because it was based on real-world data from the Medicare End-Stage Renal Disease program, and it provided estimates of parameter uncertainty.

## Model Calculations and Analyses

Monte Carlo methods were used to characterize uncertainty by sampling inputs from distributions. SEs from all models were incorporated into the model. Results are expressed as the mean with uncertainty intervals (UI) based on the middle 95% of the distribution from 1000 iterations of the model. The UI characterizes the joint effects of all parameters in the model but does not account for covariances among them.

All analyses of observational data were conducted using SAS (version 9.1.4). The model itself was constructed using Microsoft Excel 2010. Analyses of SEER incidence data were conducted using SEER*Stat.

## RESULTS

### Population Counts and Utilization

Supplementary Materials Figure 2, Supplemental Digital Content 1, http://links.lww.com/MLR/B95 shows the overall DLBCL, FL, and CLL total population counts, as well as the R+Chemo populations over time. In general, overall population counts increased over time, with DLBCL being the largest and FL the smallest. The size of the R+Chemo population also increased over time. From 2000 to 2003, the number of patients receiving R+Chemo increased substantially for DLBCL and FL, but this was not the case for CLL. Utilization of R+Chemo in the CLL population was comparatively low.

### Survival Results

Restricted mean survival did not vary by year; therefore results were pooled across all years. In addition, there were not sufficient patient counts to estimate mean survival by 5-year age groups in the population under age 65; those strata were pooled into a single "under 65" age group. The incremental survival for R+Chemo compared with Chemo Alone was longest for DLBCL and shortest for CLL. In DLBCL, the incremental survival ranged from 1.1 to 1.5 years with most estimates between 1.3 and 1.4, and older patients having longer incremental survival on R+Chemo. In FL, the range was 0.9–1.6 with older patients having much longer incremental survival on R+Chemo than younger patients. In CLL, the range was narrower, between 0.8 and 0.9 years (Supplementary Materials, Supplemental Digital Content 1, http://links.lww.com/MLR/B95).
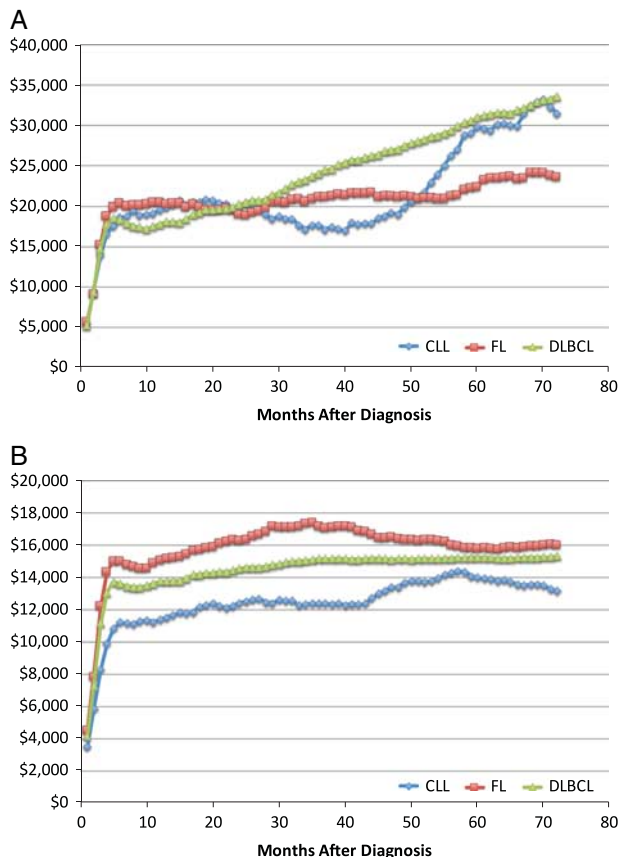
A



B



**FIGURE 1.** Cumulative incremental total direct medical costs and therapy costs associated with R+Chemo versus Chemo Alone. A, All direct medical costs. B, Only the cost of drugs for chemotherapy. Results reflect adjusted model as described in the Methods section. CLL indicates chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma.

Comparison of the DLBCL results to the GELA study showed excellent concordance. We estimated the difference in restricted 10-year mean survival in the GELA trial for rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) versus CHOP to be 493 days based on the area under the survival curves. We estimated the same outcome measure in comparable patients (stage 2 and higher, no indicators of mobility limitations, age 65–85, diagnosis before 2007) to be 478 days for R+Chemo versus Chemo Alone. For the overall DLBCL cohort, the incremental 10-year restricted mean survival was 495 days for R+Chemo versus Chemo Alone.

## Direct Medical Costs

The cost models estimated the incremental cost of R+Chemo versus Chemo Alone directly. Interactions with age group, sex, and calendar year were not significant and were not included in the final models. See Figure 1 for the incremental total direct medical cost of R+Chemo over time, and the incremental direct chemotherapy cost of R+Chemo over time for each tumor. Although the incremental cost
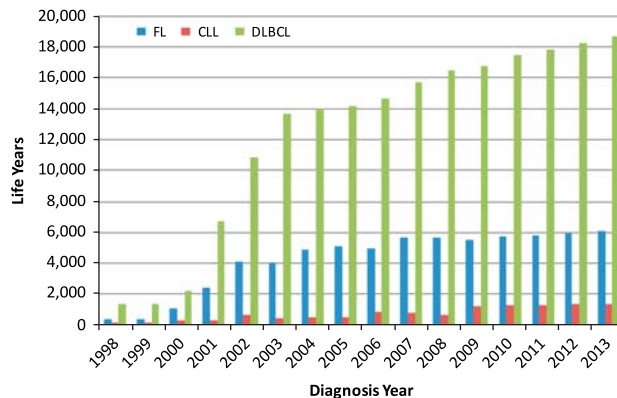


**FIGURE 2.** Life-years saved by lymphoma subtype and year. CLL indicates chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma.

increased in later years for all tumors, the cost of chemotherapy was comparatively unchanged after the initial course of chemotherapy. The incremental 6-year cumulative costs of care for R+Chemo were $33,525, $23,511, and $31,435 in DLBCL, FL, and CLL, respectively. When extrapolated to 10 years based on the mean increase over year 6, the incremental cost of R+Chemo increased to $43,899, $28,211, and $38,289, respectively (Supplementary Materials, Supplemental Digital Content 1, http://links.lww.com/MLR/B95).

## Model Results

Across all 3 lymphomas from 1998 to 2013, there were 279,704 cumulative life-years saved (95% UI, 269,136–293,345); Figs. 2, 3). For DLBCL, an estimated 151,477 patients were treated with R+Chemo. In these patients, an estimated 200,278 (95% UI, 190,558–210,678) additional life-years were lived compared with what might have occurred if Chemo Alone had been used instead. For FL, an estimated 61,520 patients were treated with R+Chemo, and an additional 68,177 (95% UI, 62,006–75,227) life-years were lived compared with Chemo Alone. For CLL, an estimated 14,083 patients were treated with R+Chemo, and an additional 12,363 (95% UI, 10,024–14,882) life-years were lived compared with Chemo Alone.

For DLBCL the cumulative incremental cost of treatment was estimated to be $6.65 billion (95% UI, $5.74–$7.61). For FL, the corresponding estimate was $1.74 billion (95% UI, $1.11–$2.57), and for CLL it was $0.54 billion (95% UI, $0.29–$0.88). Across all 3 tumors, the incremental direct medical cost of R+Chemo compared with Chemo Alone was estimated to be $8.92 billion (95% UI, $7.80–$10.28) as shown in Figure 4, and the resulting economic benefit of the life-years saved was $25.44 billion (95% UI, $11.72–$69.16) as shown in Figure 5. The net economic gain from using rituximab was therefore estimated to be $16.52 billion (95% UI, 2.27–60.44).

## DISCUSSION

The magnitude of the benefits and costs of therapy in the population depends on many factors: the size of the target
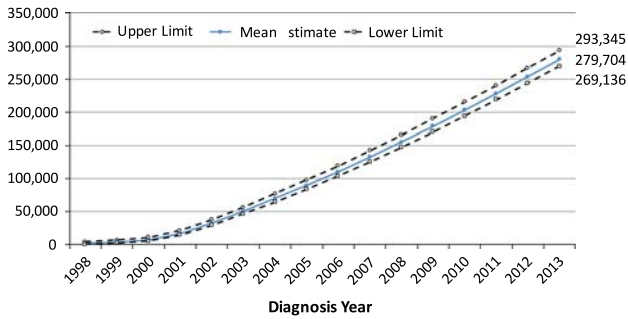
**FIGURE 3.** Cumulative life-years saved combined across DLBCL, FL, and CLL. Upper and lower uncertainty limits based on 1000 resamples. CLL indicates chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma.

population, the utilization of therapy, the real-world effectiveness of therapy, the incremental cost of therapy, and the value of the outcomes. In the case of rituximab, all of these can be estimated using data from a heterogeneous population-based cohort of patients, along with estimates of parameter uncertainty (ie, parameter SEs). When assembled, the results provide evidence about the benefits and costs of rituximab in the US population. Although focused on rituximab, these analyses present a useful framework for evaluating the population-attributable effects of therapies.

It is important to make clear that the results represent a counter-factual comparison. Real-world outcomes in patients treated with R+Chemo were reestimated assuming these same individuals had not received rituximab. The inputs used in the reestimation were based on statistical model results from patients treated with and without rituximab. Using this approach, we estimated that across DLBCL, FL, and CLL, 280,000 life-years were added to patients in the US between 1998 and 2013. The incremental direct medical cost to achieve these gains is estimated to be $8.9 billion and the resulting economic value of the life-years saved is estimated at $25.4 billion. Combined, these results in an economic gain
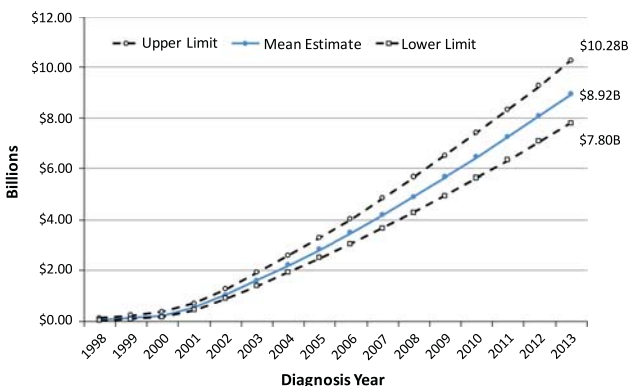


**FIGURE 4.** Cumulative incremental direct medical cost to achieve life-years saved across DLBCL, FL, and CLL. Upper and lower uncertainty limits based on 1000 resamples. CLL indicates chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma.



**FIGURE 5.** Cumulative incremental economic value of life-years saved across DLBCL, FL, and CLL. Upper and lower uncertainty limits based on 1000 resamples. CLL indicates chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma.
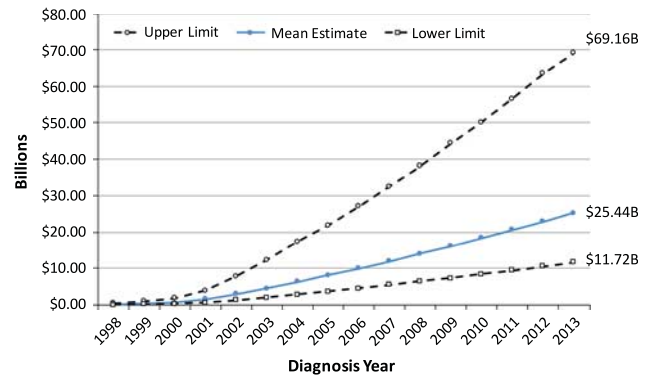
of $16.5 billion in 2013 dollars. For one of the top expenditures to the Medicare program, these results indicate a substantial benefit.

In some ways, biases in our analyses are the opposite of those from models that are traditionally constructed at the time of product approval. We used the results of sicker patients (ie, Medicare patients under 65 who generally qualify due to disability) to estimate the cost and survival inputs for all patients under 65. And we estimated benefits based on real-world use, including real-world patterns of care. Typically, economic models use healthier trial participants to model the entire population. As a result, value of rituximab in patients under age 65 might be underestimated, whereas the benefits estimated in traditional models are likely to be overestimated.

The use of "uncertainty intervals" should not be confused with confidence intervals, which would be wider. Also, we do not present 1-way sensitivity analyses because the inputs have a simple, direct effect on the outcomes (eg, a 10% increase in treatment cost, utilization, incidence rates, or population size increase the total direct medical cost by 10). Also, the width of the UI varies between the life-years reported as a count, and as a dollar value. This is due to the large variability in our estimate of the economic value of a life-year.

A number of methodological decisions deserve comment. Treatment groups were defined within 30 days of initial therapy and reflect an "intent-to-treat" approach for first-line therapy. Also, we included all patients who received at least 1 dose of therapy, including those who did not receive a full regimen, or who switched regimens. We also did not include the value of lost wages or caregiver burden and other indirect costs.

Because our inputs are based on observational data, it is possible that they are affected by selection bias. For example, patients receiving rituximab may have been sicker, or healthier, than patients who did not. This may affect some of the incremental survival and/or cost differences. To address this we included fully adjusted models to account for known confounders and we validated some of our results against

long-term trial data. In addition, other reports have shown consistent results between observational and trial treatment effects for rituximab in these populations.[17,18,29] Therefore, we believe that such bias is relatively small and not sufficient to alter the main findings in a substantive manner.

The value of a life-year is difficult to define; therefore, our estimate was data-driven, with information about uncertainty based on Medicare expenditures in the Medicare End-Stage Renal Disease program. Others have used or recommended different values.[30] In particular, Yabroff et al,[31] used $150,000 per life-year for their analyses of multiple cancer types.

We used Medicare costs for the entire population, including the subset under age 65 who were not covered by Medicare. For drugs, our Medicare costs are likely to be higher than non-Medicare costs from 1998 to 2004, when the Average Wholesale Price was used for calculating reimbursement. In 2005, Average Sales Price was introduced so that Medicare reimbursement for Part B drugs was altered to be consistent with the prices paid in the rest of the market. Therefore, while our estimates of costs for younger patients may be imperfect, they are unlikely to be substantially underestimated.

We used different times of follow-up for analyses of observational data to estimate incremental life-years and costs. We did this primarily because the current methods for estimating lifetime costs under censoring do not lend themselves well to parametric extrapolation. Therefore, to avoid assuming that the incremental cost of R+Chemo was 0 in years 7–10, we carried the cost of year 6 forward for years 7 through 10. One should be careful in interpreting these results, however, because any therapy that extends life will, by definition, increase costs. The cost of improved survival can be seen by comparing the incremental costs of chemotherapy to the incremental total direct medical costs over time, as shown in Figure 1. The differences in the patterns of each line suggest that factors other than chemotherapy treatment for cancer are adding costs in later years. Increasing cost is one economic consequence of extending life.

In conclusion, these analyses show that the introduction of rituximab into clinical practice has made substantial contributions to the population in terms of life-years gained. Importantly, the economic benefit of these gains greatly exceeds the added costs of treatment.

## ACKNOWLEDGMENTS

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