Estimating the Social Value of G-CSF Therapies in the United States

Jacqueline Vanderpuye-Orgle, PhD; Alison Sexton Ward, PhD; Caroline Huber, MPH; Chelsey Kamson, BS; and Anupam B. Jena, MD, PhD

ABSTRACT

OBJECTIVES: To provide a comprehensive estimate of the total social value (TSV) delivered by granulocyte-colony stimulating factor (G-CSF) therapies in the United States in 2014.

STUDY DESIGN: Estimation of the TSV of G-CSF, based on a targeted literature review of pivotal studies.

METHODS: A literature review was conducted to obtain estimates of the adverse outcomes associated with myelosuppressive chemotherapy-induced febrile neutropenia (FN) and the positive impacts of G-CSFs. We monetized each outcome into a set of mutually exclusive value components that were aggregated to estimate the TSV. To estimate the share of TSV captured by manufacturers, we estimated 2014 profits from G-CSF using measures of industry revenues and operating costs.

RESULTS: In 2014, approximately 314,440 patients received G-CSFs. Compared with what they would have experienced without G-CSFs, these patients were less likely to be hospitalized or die from FN, incur reductions in chemotherapy relative dose intensity, receive antibiotics, miss work, or experience reduced health-related quality of life. We estimated the social value from fewer FN hospitalizations to be $770 million; from fewer FN-related deaths, $2.65 billion; from fewer deaths due to higher effective chemotherapy doses, $4.83 billion; from reductions in antibiotics, $2.3 million; from reductions in indirect costs, $230 million; and from improvements in health-related quality of life, $1.9 million. The estimated 2014 US TSV of G-CSFs was $8.5 billion. Industry profits associated with G-CSFs were estimated at $1.3 billion, accounting for approximately 15% of the TSV.

CONCLUSIONS: Based on our calculations, the TSV generated by G-CSFs in the United States in 2014 was substantial, with the majority of this value accruing to patients.

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Despite major advances in cancer treatment, neutropenia is a life-threatening complication of chemotherapy.[1-3] Severe neutropenia is a below-normal count of neutrophils in the blood (less than 500 per mm), which impairs the body's ability to combat opportunistic infections.[4] Neutropenia can progress to febrile neutropenia (FN) when accompanied by a temperature of 38˚C (100.4˚F) or higher, and can lead to hospitalizations, mortality, and chemotherapy dose reductions or delays, all of which adversely affect patient outcomes[4-7] and medical costs.[3,8] The risk of FN is determined by the chemotherapy regimen (CR) and patient factors, such as age and comorbidities.[9]

For patients with solid tumors or nonmyeloid malignancies, granulocyte-colony stimulating factors (G-CSFs) can enable them to undergo and remain on myelosuppressive chemotherapy with lower risk of FN and infection. Despite well-established clinical benefits of G-CSFs,[10-14] these therapies have been the subject of recent concern due to large variation in their utilization. Research has indicated that G-CSFs may be overprescribed for patients at a low risk of FN (≤20%) and underprescribed for high-risk (≥20%) patients.[15,16]

Several studies have evaluated the cost-effectiveness of G-CSFs in particular tumor types, from a payer's perspective[1,17-21]; however, these studies may understate the value of G-CSFs from a societal perspective. For example, reductions in lost workdays or disability provide tremendous value to society, but may be excluded from existing studies.[11,22] Therefore, a better understanding of the total social value (TSV) of G-CSFs is needed to appropriately determine the cost-effectiveness and value afforded to patients and others affected by chemotherapy-induced neutropenia. In this study, we estimated the TSV of G-CSFs delivered to patients with cancer in the United States in 2014 by combining various components of value derived from the literature.

METHODS

Targeted Literature Review

To identify evidence on the value of G-CSFs, we conducted a targeted literature review of pivotal studies. Specifically, we limited

the search to articles published between 1991 (the year G-CSFs were approved in the United States) and 2014 that examined both adverse outcomes associated with myelosuppressive chemotherapy-induced FN, as well as the impacts of G-CSFs on these outcomes.

The searches yielded 77 potentially relevant articles that were narrowed to 58 for data extraction (**Table 1** summarizes the articles by type of analysis). Articles were selected if they investigated patients with nonmyeloid cancers at risk of the clinical definition of chemotherapy-induced FN who were treated with G-CSFs. We focused on studies that compared outcomes for patients who received G-CSFs with patients who did not.

TAKE-AWAY POINTS

Granulocyte-colony stimulating factors (G-CSFs) can significantly reduce the risk of febrile neutropenia (FN) among certain patients receiving chemotherapy. FN is associated with significant clinical and nonclinical complications. This study provides a comprehensive analysis of the total social value of G-CSFs, accounting for the nonclinical, as well as clinical benefits captured by these therapies.

- In 2014, approximately 314,440 patients received G-CSFs, and compared with individuals who did not, they were less likely to be hospitalized or die from FN, incur chemotherapy dose reductions, receive antibiotics, miss work, or experience reduced health-related quality of life.
- The estimated 2014 US total social value of G-CSFs was $8.5 billion.

Outcomes

Our literature review provided information on 6 clinical outcomes: FN hospitalization, neutropenia events, length of hospital stay, reductions in relative dose intensity of chemotherapy, overall mortality, and antibiotic use. To associate these outcomes with savings or social value (SV), we mapped them to 4 clinical value components: savings from reductions in FN hospitalizations, reductions in FN mortality, reductions in mortality due to the ability to deliver higher-dose chemotherapy, and reductions in antibiotic use. Then, using cost estimates from the literature, along with clinical improvements, we estimated the SV for all 4 components and, in aggregate, the TSV of G-CSFs.[23-26]

Using the limited literature on nonclinical outcomes associated with G-CSFs, we collated information on productivity loss and quality of life.[27,28] These outcomes were mapped into similar SV components: savings from reduced indirect costs (productivity loss) and improved quality of life. Again, we calculated the value for each component and in total for the nonclinical SV of G-CSFs.[23-26]

The TSV of G-CSFs was calculated as the sum of all clinical and nonclinical value components. All reported estimates were adjusted to 2014 US dollars using the Medical Care Consumer Price Index, which is a measure of changes in the price level of medical care commodities and services.[29] To maintain the integrity of the outputs derived from the literature and to facilitate replication of our study methods, we kept all decimal places of the estimates, recognizing that the level of precision implied by our estimates is less than should be expected of our modeling exercise.

G-CSF Population

In both the United States and the European Union, G-CSFs are indicated for patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy associated with a clinically significant (≥20%) risk of FN. They also may be considered for patients with a 10% to 20% risk and certain individual factors, such as age or stage of cancer.[11,22] We derived an estimate of this population using the Surveillance, Epidemiology, and End Results (SEER) program, which estimated the overall cancer incidence in 2014 at 1,665,540 cases.[30] To account for patients with myeloid malignancies who fall outside the approved indication, we used an incidence rate of 0.015% (15 individuals with myeloid malignancies per 100,000 population), as reported by the 2014 World Trade Center Health Program.[31] Subtracting the myeloid malignancies from the SEER all-cancer incidence suggests that, in 2014, there were approximately 1,617,665 individuals diagnosed with nonmyeloid malignancies in the United States. Given that not all of these individuals would receive a CR associated with a significant risk of FN, we applied a G-CSF usage rate of 19.4%, as reported in Naeim et al (2013), to estimate a 2014 population of patients eligible for GSCFs of 314,442.[32]

RESULTS

Clinical SV

FN hospitalization. The occurrence of FN often results in immediate hospitalization to treat the associated infection.[33] Crawford et al (2008) used medical claims data to estimate that 10.7% of patients with breast, lung, colorectal, and ovarian cancers, as well as lymphoma, develop FN in the first 3 cycles of chemotherapy.[34] We found that patients with nonmyeloid malignancies receive 6 cycles of chemotherapy on average. Thus, we used the growth rate in incidence of FN from cycles 1 to 2 and cycles 2 to 3, reported in Crawford et al, to predict the growth rate from cycles 3 to 4, 4 to 5, and 5 to 6 in order to estimate a 6-cycle incidence rate (I_{FN}) of 22%.[34]

Further, many trials have demonstrated that, when used prophylactically, G-CSFs significantly reduce the incidence of FN. Cooper et al (2011) and Kuderer et al (2007) both reviewed randomized controlled trials and reported relative risk ratios (RRs) for developing FN (RR_{FN}) for all solid tumor patients receiving primary G-CSFs of 0.51 and 0.44, respectively.[35,36] We applied the average of these RRs (0.48) to our calculated incidence measure to estimate that G-CSFs reduce the incidence of FN to 10%. Using cost estimates from Dulisse et al (2013), we used the following equation to estimate that G-CSFs prevented 35,988 FN hospitalizations in 2014, thus creating $768 million in SV derived from avoided FN hospitalizations[24]:

TABLE 1. Types of Articles Included

	Used	Not Used	Total
Systematic reviews	4	4	8
Clinical trials	8	4	12
Retrospective (claims data/EHRs)	9	8	17
Cost-effectiveness	3	5	8
Other (review, opinion articles)	2	11	13

EHR indicates electronic health record.

$$\text{FN Hospitalizations Value} = [\{I_{FN} - (I_{FN} \times RR_{FN})\} \times \text{GCSF Population}] \times \text{Cost}_{FN} = \$768{,}000{,}000$$

$$\text{FN Hospitalizations Value} = [\{0.22 - (0.22 \times 0.48)\} \times 314{,}442] \times \$21{,}341 = \$768{,}000{,}000$$

FN mortality. In addition to hospitalizations, FN is also associated with high mortality. Using claims data, Dulisse et al (2013) found that the inpatient mortality rate (MR) for patients with breast cancer, lung cancer, colorectal cancer, ovarian cancer, non-Hodgkin lymphoma, and Hodgkin lymphoma with FN was 10.6%.[24] Similarly, Kuderer et al (2006) and Caggiano et al (2005) reviewed discharge data for all patients with cancer with FN and reported mortality (MR_{FN}) rates of 8.3% and 6.8%, respectively.[3,8] We used the average of all 3 rates (8.6%) to estimate that in the absence of G-CSFs, there would have been 5872 FN-related deaths in the United States in 2014.

G-CSFs reduce the chances of developing FN and the probability of death among patients who develop FN. In their systematic review of the G-CSF literature, Kuderer et al (2007) estimated a 0.55 RR of FN-related mortality (RR_{FNM}) with G-CSFs.[36] Applying this estimate to the reduced FN population derived above, we calculated that G-CSFs prevented approximately 4171 deaths in 2014.

To calculate the SV generated from the reduction in FNM, we estimated the average value of each life saved. Specifically, we used estimates of average life expectancy from diagnosis for several types of cancers.[37] Weighting these values using patient populations provided in Dulisse et al (2013) and Caggiano et al (2005), we estimated that, on average, a patient who dies because of FN has lost 8.81 years of life (LYL).[3,24] Valuing each year of life (VLY) in perfect health at $100,000[25,26] and adjusting it to account for the average long-term quality-adjusted life-years (QALYs) weight of 0.72 for patients with cancer,[38] we used the following equation to estimate a total annual value of reduced FN deaths of $2.65 billion:

$$\text{FNM Value} = [\{([I_{FN} - (I_{FN} \times RR_{FN}\, M)] \times \text{GCSF Population}) \times [MR_{FN} \times (1 - RR_{FN}\, M)]\} \times \text{LYL FNM}] \times \text{VLY} = \$2{,}645{,}923{,}449$$

$$\text{FNM Value} = [\{([0.22 - (0.22 \times 0.55)] \times 314{,}442) \times [0.086 \times (1 - 0.55)]\} \times 8.81] \times 100{,}000 = \$2{,}645{,}923{,}449$$

Mortality Due to Reduced Chemotherapy Relative Dose Intensity

Many patients receiving chemotherapy do not achieve their planned relative dose intensity (RDI) because of treatment toxicity complications. Lower RDI has been associated with adverse clinical outcomes, including reduced life expectancy.[39] We identified several studies that estimated an incidence of chemotherapy dose reductions (I_{DR}) greater than 15% among some cancer types, including an estimate of 40% based on a systematic literature review by Kuderer et al (2007) in a robust cancer population.[36]

Several studies have also found that G-CSFs significantly reduce a patient's risk of a chemotherapy dose reduction. Although our literature review identified 3 separate estimates of the odds ratio of a dose reduction (OR_{DR}) from 2 different systematic literature reviews, these were all based on very select populations.[7,20] Assuming that patients in our population would experience similar reductions in risk, we calculated the average of all 3 reported estimates (0.63). This estimate suggests that G-CSFs reduced the number of patients requiring chemotherapy dose reductions (I_{DR}) by approximately 45,979 patients in 2014, or nearly 25% of our total G-CSF population.

To value survival gains associated with avoided chemotherapy dose reductions, we used estimates from Havrilesky et al (2014) who found that an RDI greater than 85% was associated with increased survival for patients with breast and lung cancers.[40] Using population weights from Naeim et al (2013), we calculated an average survival gain (S_{DR}) of 17.5 months per G-CSF patient, attributable to chemotherapy dose reductions avoided.[32] We then used an estimate of the average cost of CRs ($24,392) calculated from data provided in Naeim et al to account for higher treatment costs associated with this increased dosing (assuming a 15% increase).[32] Clinical experts suggested these increased costs should only apply to the roughly 50% of patients receiving chemotherapy from multi-use vials. Applying the value of a cancer-adjusted life-year at $72,000, we used the following equation to estimate the value of lowering the incidence of chemotherapy dose reductions (dose-related mortality [DRM value]) to be $4.8 billion, annually:

$$\text{DRM Value} = [\{([I_{DR} - (I_{DR} \times OR_{DR})] \times \text{GCSF Population}) \times S_{DR}\} \times \text{VLY}] - [(CR \times 0.15) \times ([I_{DR} - (I_{DR} \times OR_{DR})] \times \text{GCSF Population})] = \$4{,}827{,}749{,}599$$

$$\text{DRM Value} = \{([0.4 - (0.4 \times 0.63)] \times 314{,}442) \times 1.46\} \times 100{,}000 - [(\$24{,}392 \times 0.15) \times [0.4 - (0.4 \times 0.63)] \times 314{,}442] = \$4{,}827{,}749{,}599$$

Antibiotic Use

Myelosuppressive chemotherapy is associated with antibiotic use (AU) to fight infection. According to a randomized controlled trial published by Vogel et al (2005) and a claims analysis by Almenar et al (2009), 10% of patients with breast cancer receive antibiotics.[41,42] Our literature review did not provide estimates of the incidence of AU (I_{AU}) for other cancer types; therefore, to derive a proxy estimate, we assumed that other patients with nonmyeloid malignancies receive antibiotics at a similar rate. The estimate would be that 31,444 patients received antibiotics in our 2014 population.

TABLE 2. Annual Total Social Value of G-CSFs

Value Component	Social Value	
	Amount	Percent of Total
Annual social value of G-CSFs due to clinical outcomes		
FN hospitalizations	$768,000,000	9.32%
FN mortality	$2,645,923,449	33.21%
Increased chemotherapy intensity	$4,827,749,599	59.83%
Antibiotic use	$2,297,596	0.02%
Total clinical social value	*$8,243,970,645*	*100%*
Annual social value of G-CSFs due to nonclinical outcomes		
Indirect costs avoided	$230,087,690	99%
HRQoL improvements	$1,930,031	1%
Total nonclinical social value	*$232,017,721*	*100%*
Annual total social value of G-CSFs		
Total clinical social value	$8,243,970,645	97%
Total nonclinical social value	$232,017,721	3%
Total social value	*$ 8,475,988,366*	*100%*

FN indicates febrile neutropenia; G-CSF, granulocyte-colony stimulating factor; HRQoL, health-related quality of life.

G-CSFs have been estimated to reduce the use of antibiotics substantially. We identified 3 studies that reported relative RRs for AU (RR_{AU}) from randomized controlled trials of 0.64 for patients with small cell lung cancer,[39] and 0.80 for patients with breast cancer receiving G-CSFs.[41,42] Assuming all tumor types respond similarly, the average of these 2 estimates (0.72) suggests that G-CSFs prevented antibiotic use in roughly 8837 patients in 2014, an incidence rate of 7%. Using the equation below and the cost of AU ($Cost_{AU}$) reported in Elder-Lissai (2008), we estimated G-CSFs generated $2.3 million in value due to fewer patients receiving antibiotics[23]:

$$\text{AU Value} = [\{I_{AU} - (I_{AU} \times RR_{AU})\} * \text{GCSF Population}] \times Cost_{AU} = \$2,297,596$$

$$\text{AU Value} = [\{0.1 - (0.1 \times 0.72)\} \times 314,442] \times \$260 = \$2,297,596$$

Total Clinical SV

Table 2 reports the estimated total clinical SV of G-CSFs in 2014. The annual value for each component ranged from $2.3 million for AU to $4.8 billion for reduction in mortality related to chemotherapy dose reductions avoided, summing to a total value of $11 billion.

Nonclinical SV

Indirect costs. Our literature review identified 1 article that analyzed the ICs associated with neutropenia events. Calhoun et al (2001) define total ICs (TICs) as the sum of patient work loss, caregiver work loss, and payments for caregivers.[27] Using a sample of patients with ovarian cancer, they estimated the cost of each component was, on average, $4038, $1185, and $1170 per patient per event, respectively, for a TIC of $6393 per patient. We multiplied this by the reduction in FN events due to G-CSFs using the following equation to estimate a total value of $230 million:

$$\text{IC Value} = [\{I_{FN} - (I_{FN} \times RR_{FN})\} \times \text{GCSF Population}] \times TIC = \$230,087,690$$

$$\text{IC Value} = [\{0.22 - (0.22 \times 0.48)\} \times 314,442] \times 6393 = \$230,087,690$$

Quality of life. Few studies have measured how FN and G-CSF usage affect patients' health-related quality of life (HRQoL). Our review identified 1 study that used the difference in Short Form Health Survey 36 (SF-36) scores for a group of patients with neutropenia in the last 7 days and a control group. Fortner et al (2005) found the only significant difference in responses between the groups was for bodily pain.[28]

To associate this difference in SF-36 scores with a dollar value, we used a published algorithm to calculate the equivalent QALY reduction.[43] Using a QALY value of $100,000,[25,26] we estimated that neutropenia and FN are associated with an $85 reduction in HRQoL per FN event ($HRQoL_{FN}$). Multiplying this amount by the reduction in FN events due to G-CSFs, we used the following equation to estimate a total annual value of $1.9 million:

$$\text{HRQoL Value} = [\{I_{FN} - (I_{FN} \times RR_{FN})\} \times \text{GCSF Population}] \times HRQoL_{FN} = \$1,930,031$$

$$\text{HRQoL Value} = [\{0.22 - (0.22 \times 0.48)\} \times 314,442] \times \$85 = \$1,930,031$$

Nonclinical SV

Although literature on the nonclinical value of G-CSFs was limited, we used all available data to create what can be viewed as a conservative estimate of the nonclinical SV from G-CSF use.[27,28] Table 2 shows that the indirect costs avoided account for 99% of our estimates, with an annual savings of $232 million.

Total Social Value

Table 2 presents the estimated TSV of G-CSFs used prophylactically as indicated in 2014. The vast majority of the SV stems from the clinical, rather than nonclinical, benefits of G-CSFs.

DISCUSSION

Value to Society Versus to Manufacturers

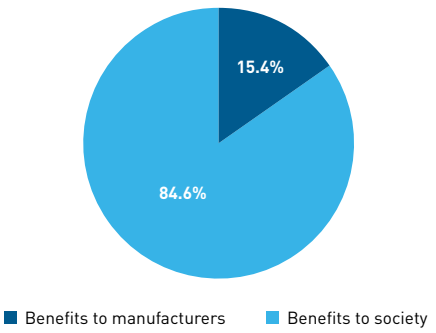
An important question in the debate about G-CSFs, and expensive medical technologies more broadly, is how the value created by these therapies is divided between pharmaceutical manufacturers and patients. For manufacturers, value is represented as profits, and for patients, it is "consumer surplus"—an economic concept that reflects the difference between what individuals are willing to pay for a therapy and what they actually pay. To evaluate this

TABLE 3. 2014 US G-CSF Profits

Product	Estimate
Pegfilgrastim US sales ($M)[a]	3649
Filgrastim US sales ($M)	982
Total G-CSF sales ($M)	4631
Manufacturer profit margin	28.2%
2014 Profits ($M)	**1306**

$M indicates dollars in millions; G-CSF, granulocyte-colony stimulating factor.
[a]Amgen 2014 US sales of filgrastim and pegfilgrastim were used assuming 83% and 100% market shares, respectively.

FIGURE 1. Benefits to Society Versus to Manufacturers (%)



question, we estimated the 2014 profits accruing to G-CSF manufacturers in the United States.

The US G-CSF market is dominated by 2 Amgen products: filgrastim, which maintains around 83% market share despite patent expiration in the United States in 2013; and pegfilgrastim, with patent expiration in October 2015.[44] Thus, we based our cost and revenue estimates on Amgen's 2014 annual report scaled to represent the entire market.[45,46] Revenues were reported for their G-CSFs; however, the only cost data available were for all products and included all operating costs. We therefore applied the all-product profit margin to filgrastim and pegfilgrastim revenues to estimate 2014 G-CSF profits of $1.306 billion (see **Table 3**). Compared with our estimate of $8.5 billion in TSV created by G-CSFs, manufacturer profits account for approximately 15% (**Figure 1**). This low rate of producer surplus is not surprising when considering the monopolistic form of competition that happens across branded drugs and therapies.

Sensitivity Analysis

When possible, the parameters used in the baseline analysis were based on an average (weighted when appropriate) of estimates from multiple studies. However, 2 stronger assumptions were required to translate the mortality benefits associated with G-CSFs into monetary values. For each FN-related death that G-CSFs prevented, we developed an average number of life-years gained using estimates of life expectancy at diagnosis reported in Liu et al (2013).[37]

On average, the number of life-years gained in the baseline model assumed FN is a random event among patients with cancer receiving myelosuppressive chemotherapy; however, in practice, older and weaker patients may be more susceptible. These patients likely have below-average life expectancies, which bias our baseline estimate toward longer survival. To test the sensitivity of our results, we recalculated the TSV of G-CSFs assuming the average life-years gained was 50% lower (4.4 instead of 8.8 years). This reduction decreased the TSV estimate by $1.8 billion (**Figure 2**).

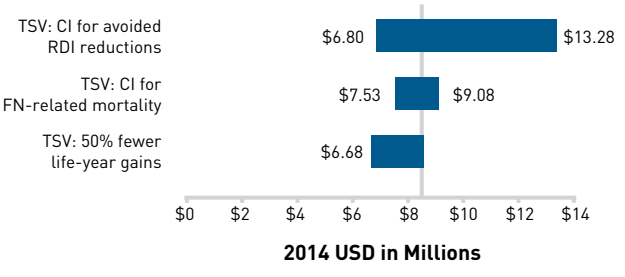
Additionally, the 2 largest drivers of SV in our model are the reduction in FN-related mortality (33%) and the value of avoiding chemotherapy RDI reductions (60%). We performed additional sensitivity analyses using confidence intervals (CIs) presented in the literature for these parameters. For example, Kuderer et al (2007) provided a CI of 0.33 to 0.90 for their estimate of the RR of FN-related mortality with G-CSFs (0.55). The lower end of this interval would add $603 million to the TSV estimate, and the upper end of the interval would reduce the TSV by $945 million. Similarly, Kuderer et al (2007) also provide a CI of 0.30 to 0.65 for their estimate of the incidence of dose reductions (0.4). Our sensitivity analysis suggests that the lower end of the CI would reduce the TSV by almost $1.68 billion, but the upper end of the CI would increase the TSV by almost $4.8 billion.

Limitations

This study had a number of limitations. First, TSV estimates were limited by the lack of available research, particularly on nonclinical burdens imposed by FN. For example, by reducing the likelihood of chemotherapy dose reductions, G-CSFs may provide patients with less anxiety about complications.

Second, previous research on the value of G-CSFs has been constrained by the limited scope of the study population considered. When possible, we based our SV estimates on results from studies with large sample populations that covered all, or most, of the malignancies for which G-CSFs are typically indicated; however, there were limited data for several SV components. For these value

FIGURE 2. Tornado Diagram of Sensitivity Analyses



CI indicates confidence interval; FN, febrile neutropenia; RDI, relative dose intensity; TSV, total social value; USD, US dollars.

components, our estimates were based on more select samples, and we assumed the outcomes would, on average, be similar across other tumor types. Additionally, prior studies focus almost exclusively on patients for whom G-CSFs are indicated (as previously described), making it impossible to generate estimates of SV for patients for whom G-CSFs are not indicated and for whom TSV would be expected to be lower.

Third, our modeling exercise relied on parameter estimates drawn from the literature. Our findings, therefore, reflect uncertainty stemming from the various study designs on which parameter estimates that populate our model were drawn.

CONCLUSIONS

This study estimates that 314,442 patients with cancer were potential candidates for prophylactic G-CSFs in the United States in 2014. Based on the parameters and assumptions used in our calculations, G-CSFs generated a total of almost $8.5 billion in SV. More than 97% of this value was attributable to estimated improvements in clinical outcomes. Importantly, reductions in overall mortality from both reduced FN hospitalizations and chemotherapy dose reductions avoided accounted for $10 billion in SV. Since we found few studies that investigated improvements in nonclinical outcomes associated with G-CSFs, our SV estimate of $232 million may be a conservative lower bound for the total nonclinical value.

By considering all possible benefits of G-CSFs, our study results suggest these therapies provide substantial value for society, particularly for patients. The portion of value accruing to manufacturers in the form of profits is approximately 15%. These estimates are similar to previous work that suggests that between 5% and 19% of the value generated by gains in cancer survival have been appropriated by manufacturers in the form of profits.[47] Our analysis further demonstrates the need to evaluate the cost-effectiveness of medical innovations in a way that incorporates broader impacts to society, such as nonclinical benefits. Failure to include these components can significantly underestimate the economic value of medical innovations and the value to patients.

Author Affiliations: Precision Health Economics (JV-O, ASW, CH, CK), Los Angeles, CA; Harvard Medical School, Department of Health Care Policy (ABJ), Boston, MA.

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Address Correspondence to: Anupam B. Jena, MD, PhD, Harvard Medical School, Department of Health Care Policy, 180 Longwood Ave, Boston, MA 02115-5899. E-mail: jena@hcp.med.harvard.edu.

REFERENCES

1. Aarts MJ, Grutters JP, Peters FP, et al. Cost effectiveness of primary pegfilgrastim prophylaxis in patients with breast cancer at risk of febrile neutropenia. *J Clin Oncol.* 2013;31(34):4283-4289. doi: 10.1200/JCO.2012.48.3644.

2. Wang X-J, Lopez S-E, Chan A. Economic burden of chemotherapy-induced febrile neutropenia in patients with lymphoma: a systematic review. *Crit Rev Oncol Hematol.* 2015;94(2):201-212. doi: 10.1016/j.critrevonc.2014.12.011.

3. Caggiano V, Weiss RV, Rickert TS, Linde-Zwirble WT. Incidence, cost, and mortality of neutropenia hospitalization associated with chemotherapy. *Cancer.* 2005;103(9):1916-1924.

4. Schilling MB, Parks C, Deeter RG. Costs and outcomes associated with hospitalized cancer patients with neutropenic complications: a retrospective study. *Exp Ther Med.* 2011;2(5):859-866.

5. De Naurois J, Novitzky-Basso I, Gill M, Marti FM, Cullen MH, Roila F; ESMO Guidelines Working Group. Management of febrile neutropenia: ESMO clinical practice guidelines. *Ann Oncol.* 2010;21(suppl 5):v252-v256. doi: 10.1093/annonc/mdq196.

6. Rajan SS, Lyman GH, Carpenter WR, Stearns SC. Chemotherapy characteristics are important predictors of primary prophylactic CSF administration in older patients with breast cancer. *Breast Cancer Res Treat.* 2011;127(2):511-520. doi: 10.1007/s10549-010-1216-1.

7. Shayne M, Crawford J, Dale DC, Culakova E, Lyman GH; ANC Study Group. Predictors of reduced dose intensity in patients with early-stage breast cancer receiving adjuvant chemotherapy. *Breast Cancer Res Treat.* 2006;100(3):255-262.

8. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. *Cancer.* 2006;106(10):2258-2266.

9. Smith TJ, Bohlke K, Lyman GH, et al; American Society of Clinical Oncology. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol.* 2015;33(28):3199-3212. doi: 10.1200/JCO.2015.62.3488.

10. Crawford J, Ozer H, Stoller R, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. *N Engl J Med.* 1991;325(3):164-170.

11. Aapro MS, Cameron DA, Pettengell R, et al; European Organisation for Research and Treatment of Cancer (EORTC) Granulocyte Colony-Stimulating Factor (G-CSF) Guidelines Working Party. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. *Eur J Cancer.* 2006;42(15):2433-2453.

12. Lieschke GJ, Burgess AW. Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor. *N Engl J Med.* 1992;327(1):28-35.

13. Dale DC. Colony-stimulating factors for the management of neutropenia in cancer patients. *Drugs.* 2002;62(suppl 1):1-15.

14. Freyer G, Ligneau B, Trillet-Lenoir V. Colony-stimulating factors in the prevention of solid tumors induced by chemotherapy in patients with febrile neutropenia. *Int J Antimicrob Agents.* 1998;10(1):3-9.

15. Barnes G, Pathak A, Schwartzberg L. G-CSF utilization rate and prescribing patterns in United States: associations between physician and patient factors and G-CSF use. *Cancer Med.* 2014;3(6):1477-1484. doi: 10.1002/cam4.344.

16. Waters GE, Corrigan P, Gatesman M, Smith TJ. Comparison of pegfilgrastim prescribing practice to national guidelines at a university hospital outpatient oncology clinic. *J Oncol Pract.* 2013;9(4):203-206. doi: 10.1200/JOP.2012.000662.

17. Flynn TN, Kelsey SM, Hazel DL, Guest JF. Cost effectiveness of amphotericin B plus G-CSF compared with amphotericin B monotherapy. treatment of presumed deep-seated fungal infection in neutropenic patients in the UK. *Pharmacoeconomics.* 1999;16(5, pt 2):543-550.

18. Whyte S, Cooper KL, Stevenson MD, Madan J, Akehurst R. Cost-effectiveness of granulocyte colony–stimulating factor prophylaxis for febrile neutropenia in breast cancer in the United Kingdom. *Value Health.* 2011;14(4):465-474. doi: 10.1016/j.jval.2010.10.037.

19. Silber JH, Fridman M, Shpilsky A, et al. Modeling the cost-effectiveness of granulocyte colony-stimulating factor use in early-stage breast cancer. *J Clin Oncol.* 1998;16(7):2435-2444.

20. Wildiers H, Reiser M. Relative dose intensity of chemotherapy and its impact on outcomes in patients with early breast cancer or aggressive lymphoma. *Crit Rev Oncol Hematol.* 2011;77(3):221-240. doi: 10.1016/j.critrevonc.2010.02.002.

21. Aarts MJ, Peters FP, Mandigers CM, et al. Primary granulocyte colony-stimulating factor prophylaxis during the first two cycles only or throughout all chemotherapy cycles in patients with breast cancer at risk for febrile neutropenia. J Clin Oncol. 2013;31(34):4290-4296. doi: 10.1200/JCO.2012.44.6229.

22. Myeloid growth factors. National Comprehensive Cancer Network website. http://www.nccn.org/professionals/physician_gls/PDF/myeloid_growth.pdf. Accessed September 4, 2013.

23. Eldar-Lissai A, Cosler LE, Culakova E, Lyman GH. Economic analysis of prophylactic pegfilgrastim in adult cancer patients receiving chemotherapy. *Value Health.* 2008;11(2):172-179. doi: 10.1111/j.1524-4733.2007.00242.x.

24. Dulisse B, Li X, Gayle JA, et al. A retrospective study of the clinical and economic burden during hospitalizations among cancer patients with febrile neutropenia. *J Med Econ.* 2013;16(6):720-735. doi: 10.3111/13696998.2013.782034.

25. Braithwaite RS, Meltzer DO, King Jr JT, Leslie D, Roberts MS. What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule? *Med Care.* 2008;46(4):349-356. doi: 10.1097/MLR.0b013e31815c31a7.

26. Weinstein MC. How much are Americans willing to pay for a quality-adjusted life year? *Med Care.* 2008;46(4):343-345. doi: 10.1097/MLR.0b013e31816a7144.

27. Calhoun EA, Chang C-H, Welshman EE, Fishman DA, Lurain JR, Bennett CL. Evaluating the total costs of chemotherapy-induced toxicity: results from a pilot study with ovarian cancer patients. *Oncologist.* 2001;6(5):441-445.

28. Fortner BV, Tauer KW, Okon T, Houts AC, Schwartzberg LS. Experiencing neutropenia: quality of life interviews with adult cancer patients. *BMC Nurs.* 2005;4:4.

29. Consumer Price Index—all urban consumers [2014]. Bureau of Labor Statistics website. http://data.bls.gov/timeseries/CUUR0000SAM?output_view=pct_12mths. Accessed November 17 2014, 2014.

30. SEER stat fact sheets: cancer of any site. National Cancer Institute website. http://seer.cancer.gov/statfacts/html/all.html. Accessed November 5, 2014.

31. Howard J. WTC Health Program: myeloid malignancies. CDC website. https://www.cdc.gov/wtc/pdfs/WTCHP_PP_MyeloidMalignancies_02012014.pdf. Published February 1, 2014. Accessed September 2016.

32. Naeim A, Henk HJ, Becker L, et al. Pegfilgrastim prophylaxis is associated with a lower risk of hospitalization of cancer patients than filgrastim prophylaxis: a retrospective United States claims analysis of granulocyte colony-stimulating factors (G-CSF). *BMC Cancer.* 2013;13:11. doi: 10.1186/1471-2407-13-11.

33. Flowers CR, Seidenfeld J, Bow EJ, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol.* 2013:31(6):794-810. doi: 10.1200/JCO.2012.45.8661.

34. Crawford J, Dale DC, Kuderer NM, et al. Risk and timing of neutropenic events in adult cancer patients receiving chemotherapy: the results of a prospective nationwide study of oncology practice. *J Natl Compr Canc Netw.* 2008;6(2):109-118.

35. Cooper KL, Madan J, Whyte S, Stevenson MD, Akehurst RL. Granulocyte colony-stimulating factors for febrile neutropenia prophylaxis following chemotherapy: systematic review and meta-analysis. *BMC Cancer.* 2011;11:404. doi: 10.1186/1471-2407-11-404.

36. Kuderer NM, Dale DC, Crawford J, Lyman GH. Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. *J Clin Oncol.* 2007;25(21):3158-3167.

37. Liu PH, Wang JD, Keating NL. Expected years of life lost for six potentially preventable cancers in the United States. *Prev Med.* 2013;56(5):309-313. doi: 10.1016/j.ypmed.2013.02.003.

38. Ko CY, Maggard M, Livingston EH. Evaluating health utility in patients with melanoma, breast cancer, colon cancer, and lung cancer: a nationwide, population-based assessment. *J Surg Res.* 2003;114(1):1-5.

39. Trillet-Lenoir V, Green J, Manegold C, et al. Recombinant granulocyte colony stimulating factor reduces the infectious complications of cytotoxic chemotherapy. *Eur J Cancer.* 1993;29A(3):319-324.

40. Havrilesky LJ, Reiner M, Morrow PK, Watson H, Crawford J. A review of relative dose intensity and survival in patients with metastatic solid tumors. *Crit Rev Oncol Hematol*. 2015;93(3):203-210. doi: 10.1016/j.critrevonc.2014.10.006.

41. Almenar D, Mayans J, Juan O, et al. Pegfilgrastim and daily granulocyte colony-stimulating factor: patterns of use and neutropenia-related outcomes in cancer patients in Spain—results of the LEARN Study. *Eur J Cancer Care (Engl).* 2009;18(3):280-286. doi: 10.1111/j.1365-2354.2008.00959.x.

42. Vogel CL, Wojtukiewicz MZ, Carroll RR, et al. First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled phase III study. *J Clin Oncol.* 2005;23(6):1178-1184.

43. Nichol MB, Sengupta N, Globe DR. Evaluating quality-adjusted life years estimation of the Health Utility Index (HUI2) from the SF-36. *Med Decis Making.* 2001;21(2):105-112.

44. Stanton D. Amgen prepped to compete in US filgrastim market post Sandoz's Zarxio launch. BioPharma-Reporter website. http://www.biopharma-reporter.com/Markets-Regulations/Amgen-prepped-to-compete-in-US-filgastrim-market-post-Zarxio-launch. Published July 31, 2015. Accessed April 5, 2016.

45. Amgen Inc. 2014 annual report and 10-K. http://bit.ly/2d4ZlgA. Accessed December 8, 2015.

46. Research and markets: filgrastim & pegfilgrastim biosimilars & biosuperiors 2015 - a G-CSF & GM-CSF competitor analysis [press release]. Dublin, Ireland: Business Wire; September 1, 2015. http://www.businesswire.com/news/home/20150901005894/en/Research-Markets-Filgrastim-Pegfilgrastim-Biosimilars-Biosuperiors-2015. Accessed October 23, 2015.

47. Lakdawalla DN, Sun EC, Jena AB, Reyes CM, Goldman DP, Philipson TJ. An economic evaluation of the war on cancer. *J Health Econ.* 2010;29(3):333-346. doi: 10.1016/j.jhealeco.2010.02.006. ■

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