

# The Long-term Social Value of Granulocyte Colony-Stimulating Factors

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Over the past 3 decades, medical and pharmaceutical innovations have made substantial strides in many disease areas that have increased both longevity and quality of life (QOL). However, these technological advancements are often met with criticism over high prices, and, despite research showing that the benefits can outweigh the costs of new therapies, these treatments may often be underutilized.<sup>1,3</sup> For example, statins represent a huge technological breakthrough for the treatment of cardiovascular disease, and a large literature of clinical trial data and cost-effectiveness modeling demonstrates their wide-ranging cost-effectiveness, yet data still suggest that this breakthrough therapy is greatly underused.<sup>3</sup>

Similarly, prophylactic administration of granulocyte colony-stimulating factor (G-CSF) is underutilized despite guideline recommendations and literature on the cost-effectiveness of varying options.<sup>4-6</sup> G-CSF use is well established as the standard of supportive care among patients receiving myelosuppressive chemotherapy to prevent the onset of febrile neutropenia (FN; fever and infection),<sup>7-9</sup> which subsequently can lead to hospitalizations, dose reductions, and increased risk of mortality.<sup>10,11</sup> National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology guidelines recommend primary prophylactic G-CSF in patients receiving a chemotherapy regimen associated with more than a 20% risk of FN. The guidelines also suggest that G-CSF therapy should be considered for patients receiving a chemotherapy regimen with a 10% to 20% risk of FN and who have additional risk factors (eg, age  $\geq 65$  years, poor performance status, history of FN, comorbid conditions).<sup>12</sup> Despite these clear and well-respected guidelines and evidence from meta-analyses supporting the favorable benefit-risk profile of G-CSFs,<sup>13</sup> real-world use is lower than recommended. For example, only 51% of patients with breast cancer and 28% of patients with lung cancer with high risk of FN have been documented as receiving G-CSF prophylaxis.<sup>14</sup>

G-CSF prophylaxis continues to be the subject of much debate due to the rising costs of cancer care. Although previous research has noted the clinical benefits of these therapies and has demonstrated their cost-effectiveness, it has failed to completely account for

## ABSTRACT

**OBJECTIVES:** Febrile neutropenia (FN) is a life-threatening complication of chemotherapy that can lead to hospitalizations, chemotherapy dose reductions or delays, and mortality. Granulocyte colony-stimulating factor (G-CSF) prophylaxis reduces the incidence of FN, enabling patients to undergo and remain on myelosuppressive chemotherapy. We estimate the benefits of continuing current G-CSF use patterns and an alternative that aligns prophylactic G-CSF use with guideline recommendations.

**STUDY DESIGN:** Using The Health Economics Medical Innovation Simulation microsimulation, we estimated lifetime social value (SV) of prophylactic G-CSF for a nationally representative US population with breast, lung, and gynecological cancers and non-Hodgkin lymphoma.

**METHODS:** SV estimates included the cost of G-CSF, FN, chemotherapy relative dose intensity (RDI) less than 85% (RDI<85%), medical spending, and deaths for 3 scenarios: current use (current G-CSF use), targeted use (100% G-CSF use among patients with high FN risk), and reduced use (current G-CSF use reduced by 20% across all FN risk categories).

**RESULTS:** Over 10 years, current use, compared with no G-CSF use, would decrease cases of FN by 3.3 million, prevent 354,000 cases of RDI<85%, and generate \$96 billion in SV. Compared with current use, targeted use would decrease cases of FN by an additional 3.3 million, prevent 355,000 more cases of RDI<85%, and generate another \$119 billion in SV. Reduced use would increase FN and RDI<85%, lowering SV by \$18 billion compared with current use.

**CONCLUSIONS:** Current use of G-CSF prophylaxis would provide \$96 billion in SV over the next 10 years. Targeting G-CSF prophylaxis to align with guidelines would more than double SV, highlighting the substantial value of appropriate FN risk assessment and targeted G-CSF prophylaxis.

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their potential indirect benefits in the form of improved productivity and QOL.<sup>7,15,16</sup> FN can be very debilitating and often leads to inpatient hospital stays and potentially death. Although some previous studies have accounted for reductions in QOL, they have not included lost work or reductions in productivity. There has been much discussion recently about the importance of including these indirect benefits in any value calculation, and both the Second Panel on Cost-Effectiveness<sup>17</sup> and the International Society for Pharmacoeconomics and Outcomes Research's Special Task Force on Value Assessment Frameworks<sup>18</sup> recommended doing so where possible. Our study builds upon the current literature by including these indirect sources of value in our model and estimating the accumulation of value over patients' lifetimes.

Additionally, our model builds on the current literature by estimating the social value (SV) both at the US population level of current G-CSF prophylaxis use and at a level of use better aligned with NCCN guidelines. SV quantifies the resources that society would be willing to give up in order to achieve the health, QOL, and productivity benefits associated with G-CSF prophylaxis. This study represents the first comprehensive estimate of the benefit to society from G-CSF prophylaxis use that better aligns with guidelines.

## METHODS

We used The Health Economics Medical Innovation Simulation (THEMIS), an established microsimulation model based on the Future Elderly Model,<sup>19,20</sup> to predict the lifetime value associated with use of G-CSF consistent with NCCN guidelines.<sup>12</sup> A patient-level microsimulation like THEMIS allows costs and benefits to be estimated over individuals' lifetimes within a variety of subgroups while capturing the heterogeneity that would be lost in a cohort simulation. Our model focused on 4 patient populations with high rates of use of myelosuppressive chemotherapy regimens categorized as high and intermediate FN risk,<sup>12</sup> and it documented use of G-CSF prophylaxis that is not consistent with NCCN guidelines—overuse in the population at low risk of FN and/or underuse in the population at high risk of FN. Specifically, we focused on patients with breast, gynecological, and lung cancers and non-Hodgkin lymphoma (NHL) who were 25 years or older, and we simulated their health status, health spending, and mortality experience over their lifetimes.

THEMIS is based on data from the Panel Study of Income Dynamics (PSID)<sup>21</sup> and the Health and Retirement Study.<sup>22</sup> Both data sets are nationally representative panel surveys that have been ongoing since 1968 and 1992, respectively. The breast, gynecological, and lung cancer cohorts were modeled using the PSID data; however, the survey does not differentiate patients with NHL from patients

## TAKEAWAY POINTS

We modeled the benefits of prophylactic granulocyte colony-stimulating factor (G-CSF) use among patients with breast, lung, and gynecological cancers and non-Hodgkin lymphoma.

- ▶ Over 10 years, current use of G-CSF prophylaxis provides substantial benefit, reducing cases of febrile neutropenia (FN) by 3.3 million and cases of chemotherapy reduced dose intensity (RDI) less than 85% (RDI<85%) by 354,000, resulting in \$96 billion in social value (SV).
- ▶ Targeting G-CSF prophylaxis to patients at high risk of FN would increase these benefits over that period, resulting in 6.6 million fewer cases of FN, 709,000 fewer cases of RDI<85%, and an SV gain of \$215 billion.
- ▶ Appropriate FN risk assessment and targeted G-CSF prophylaxis use in patients presents an opportunity to provide substantial value to society.

with other lymphomas. Thus, we built a synthetic cohort for the NHL population based on Surveillance and Epidemiology End Results (SEER) data. A raking procedure, which adjusts the weights of the PSID cancer population to match the distributions of the NHL population in SEER, was combined with SEER NHL prevalence and incidence data and the National Cancer Institute lymphoma incidence projections to compute a population of prevalent and incident NHL cases.<sup>23-27</sup>

To estimate the potential impact of G-CSF prophylaxis on financial outcomes, we supplemented the PSID data with medical spending data from the Medicare Current Beneficiary Survey and Medical Expenditure Panel Survey, depending on the individual's Medicare eligibility. This allowed us to estimate the change in medical costs that occurs with the use of G-CSF as well as the long-term effects over the lifetime of patients. Further detail on the mechanics and implementation of the model are described in Kabiri et al.<sup>28</sup>

The risk of FN, and thus the appropriateness of G-CSF prophylaxis, depended on the toxicity of chemotherapy and other patient characteristics according to NCCN guidelines.<sup>12</sup> We stratified patients with cancer into 3 groups based on risk of FN due to chemotherapy: high risk of FN, defined as greater than 20% risk, or 10% to 20% risk with additional risk factors (eg, being  $\geq 65$  years); intermediate risk of FN, defined as 10% to 20% risk without additional patient risk factors; and low risk of FN, defined as 0% to 10% risk. We incorporated the appropriate distribution of FN risk for each cancer type according to data presented in [Table 1](#).

Simulated incident patients with cancer who received chemotherapy were at risk of developing FN and of decreased relative dose intensity (RDI) of treatment, depending on the individual's cancer type, FN risk category, and use of G-CSF prophylaxis. We based the rates of FN and RDI less than 85% (RDI<85%) on the literature (Table 1).

We assumed that each FN event reduced patients' QOL by 0.022 quality-adjusted life-years (QALYs). In addition, our model included FN mortality rates during treatment as the percentage of total deaths for each cancer type and included a calculated hazard ratio for death of 1.46 for RDI<85% across all cancer types. See the [eAppendix](#) (available at [ajmc.com](#)) for sources of model parameters and assumptions.

# POLICY

**TABLE 1.** Select Model Inputs<sup>a</sup>

Input	High Risk	Intermediate Risk	Low Risk
Percentage of patients according to FN risk categories due to chemotherapy			
Breast cancer	73.5	5.3	21.1
Gynecological cancers <sup>b</sup>	33.1	17.4	49.4
Lung cancer	12.8	28.7	58.5
NHL <sup>c</sup>	51.3	12.7	36.0
Incidence of FN without G-CSF prophylaxis <sup>d</sup>			
Breast cancer	1.12	0.73	0.24
Gynecological cancers <sup>e</sup>	1.68	1.10 <sup>f</sup>	0.36 <sup>f</sup>
Lung cancer	0.93 <sup>g</sup>	0.61 <sup>g</sup>	0.20 <sup>g</sup>
NHL	1.93 <sup>f</sup>	1.26	0.41 <sup>f</sup>
Rate of RDI<85% without G-CSF prophylaxis (%)			
Breast cancer	27	11	5 <sup>h</sup>
Gynecological cancers	57	31	5 <sup>h</sup>
Lung cancer	60	25 <sup>i</sup>	5 <sup>h</sup>
NHL	39	33	5 <sup>h</sup>
<b>G-CSF Effectiveness</b>		<b>All Risk Categories</b>	
Impact of G-CSF on the risk of FN (odds ratio)			
All cancers			0.49
Impact of G-CSF on the risk of RDI<85% (odds ratio)			
Breast, gynecological, and lung cancers <sup>j</sup>			0.73
NHL			0.70
<b>Model Costs</b>			
FN-related inpatient and outpatient encounters (2017 US\$)			
All cancers			39,050
Cost of prophylaxis per patient receiving pegfilgrastim (2017 US\$) <sup>d</sup>			
Until 2019			
Breast and gynecological cancers and NHL			25,483
Lung cancer			16,989
In 2019			
Breast and gynecological cancers and NHL			21,661
Lung cancer			14,441
In 2020 and after			
Breast and gynecological cancers and NHL			18,412
Lung cancer			12,275
Cost of prophylaxis per patient receiving filgrastim (2017 US\$) <sup>d</sup>			
Breast and gynecological cancers and NHL			16,615
Lung cancer			11,077

FN indicates febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; NHL, non-Hodgkin lymphoma; RDI<85%, relative dose intensity less than 85%.

<sup>a</sup>See eAppendix for sources of model parameters and assumptions.

<sup>b</sup>Chemotherapy risks calculated as the average across breast cancer, lung cancer, and colorectal cancer because tumor-specific data did not exist.

<sup>c</sup>High-risk chemotherapy patients estimated from the literature. Intermediate- and low-risk patients calculated using the ratio of intermediate-risk patients to low-risk patients obtained by averaging the respective categories across breast cancer, lung cancer, and colorectal cancer from the literature. See eAppendix for sources of model parameters and assumptions.

<sup>d</sup>Assumes 6 cycles of chemotherapy and G-CSF for breast and gynecological cancers and NHL; 4 cycles for lung cancer. Assumes 6 doses of filgrastim per chemotherapy cycle.

<sup>e</sup>Sources report on ovarian cancer. We assume the rate within ovarian cancer is equal to the rate within gynecological cancers.

<sup>f</sup>FN incidence calculated by using the equation:

$$FN\ incidence\ risk\ group\ i,\ cancer\ j = \frac{FN\ incidence\ intermediate\ risk\ group,\ cancer\ j}{FN\ incidence\ intermediate\ risk\ group,\ breast\ cancer} \times FN\ incidence\ i\ risk\ group,\ breast\ cancer$$

<sup>g</sup>The FN incidence for each risk group was calculated by taking the average between the FN incidence for breast cancer and the FN incidence for gynecological cancers in the respective risk groups.

<sup>h</sup>Based on the middle percentage point for FN risk rate of low FN risk category (<10%) according to National Comprehensive Cancer Network guidelines.

<sup>i</sup>Average of intermediate risk category across breast cancer, ovarian cancer, and NHL because tumor-specific data did not exist.

<sup>j</sup>The odds ratio of RDI<85% with G-CSF prophylaxis for gynecological cancers was assumed to be the same as for breast cancer because tumor-specific estimates did not exist.

**TABLE 2.** G-CSF Use (%) by Scenario and FN Risk Group<sup>a</sup>

	Coverage Scenario								
	Current Use <sup>b</sup>			Targeted Use <sup>c</sup>			Reduced Use <sup>d</sup>		
	Intermediate			Intermediate and Low Risk			Intermediate		
	High Risk	Risk	Low Risk	High Risk	Intermediate and Low Risk	High Risk	Risk	Low Risk	
Breast cancer	51.4	33.7	21.2	100	0	41.1	26.9	17.0	
Gynecological cancers <sup>b</sup>	39.5	37.5	18.3	100	0	31.6	30.0	14.6	
Lung cancer <sup>b</sup>	27.7	41.3	15.3	100	0	22.2	33.0	12.3	
NHL <sup>b</sup>	51.4	33.7	21.2	100	0	41.1	26.9	17.0	

FN indicates febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; NHL, non-Hodgkin lymphoma.

<sup>a</sup>See eAppendix for sources of model parameters and assumptions.

<sup>b</sup>Adjusted rates account for intermediate-risk patients with risk factors in the high-risk group. Lung cancer G-CSF use rates are based only on data for metastatic lung cancer. NHL rates were assumed to be the same as breast cancer rates because unadjusted rates for high-risk patients with breast cancer and NHL were very similar, according to the literature. Gynecological cancer rates were assumed to be the average of breast and lung cancer rates.

<sup>c</sup>Rates were based on National Comprehensive Cancer Network guidelines.

<sup>d</sup>Current G-CSF rates were reduced by 20%.

### G-CSF Coverage Scenarios

To model the SV of G-CSF use, we simulated 1 baseline and 3 G-CSF coverage scenarios. The baseline scenario assumed no G-CSF use, representing care in a world without G-CSF coverage. The first scenario, current use, incorporated current rates of G-CSF prophylaxis in each FN risk category, by cancer type, from the recent literature. The second scenario, targeted use, measured the SV from G-CSF coverage that aligned with the NCCN guidelines for primary prophylaxis with G-CSF. We assumed that all high-risk patients received G-CSF prophylaxis and all intermediate-risk and low-risk patients did not. Under the third scenario, reduced use, we assumed that current G-CSF use fell by 20% in each of the 3 FN risk categories, representing the potential impact of lower rates of G-CSF prophylaxis in response to cost concerns. The rates of G-CSF use by risk group and cancer type are presented in **Table 2**. The scenarios were run within each cancer population and aggregated for the results presented here. See the eAppendix for sources of model parameters and assumptions.

### Short- Versus Long-Acting G-CSF Scenario

Amid concerns over rising drug expenditures in the United States, a potential approach to minimize costs while still providing G-CSF prophylaxis could be to substitute the use of pegfilgrastim (long-acting G-CSF) with lower-cost, multidose filgrastim (short-acting G-CSF). Such a substitution would allow access to G-CSF therapies for a reduced cost. However, many studies have established the superior efficacy of pegfilgrastim over filgrastim. To test how such a strategy would affect patients, we simulated 1 additional scenario assuming a reduction in pegfilgrastim use by 20% and a corresponding increase in filgrastim use by 20%. We assumed that 6 doses of filgrastim were used per cycle, according to the median real-world utilization. We assumed that pegfilgrastim and filgrastim are associated with odds ratios of FN of 0.24 and 0.51, respectively, and that 4% and 5% of patients experience RDI < 85%, respectively. See the eAppendix for sources of model parameters and assumptions.

### Costs

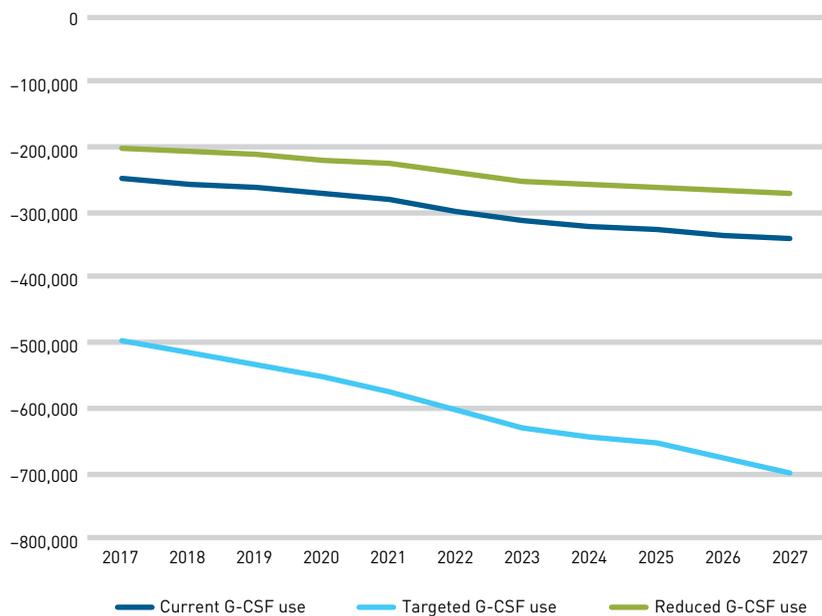
We included estimates of the cost of FN-related inpatient and outpatient encounters by cancer type from the literature and adjusted to 2017 US\$ using the Medical Consumer Price Index. We also estimated the costs of G-CSF prophylaxis assuming pegfilgrastim use in each cancer type. We assumed 6 cycles of chemotherapy and therefore 6 cycles of G-CSF prophylaxis for NHL and breast and gynecological cancers and 4 chemotherapy and G-CSF prophylaxis cycles for lung cancer. The model had a societal perspective, so the drug price represented the average price paid across all payers. We used the average wholesale acquisition cost for pegfilgrastim. To account for the introduction of biosimilar competition in the marketplace, we reduced the price of pegfilgrastim by 15% in 2019 and by an additional 15% in 2020.<sup>29</sup> All cost estimates are shown in Table 1. See the eAppendix for sources of model parameters and assumptions.

### Outcomes

We compared the incidence of FN, RDI < 85%, and death across G-CSF scenarios. Productivity was measured through additional earnings from avoided deaths and reduced caregiver burden (\$4413 per FN episode for patient and caregiver work loss).<sup>30</sup> Additionally, we calculated QALYs, total prophylaxis cost, and medical spending under each modeling scenario. This allowed us to calculate the total SV generated under each scenario estimated as QALYs gained, which were each valued at \$150,000<sup>31</sup> plus increased total earnings minus increased medical spending (including treatment cost). We used the formula:

$$SV = \sum_{i=1}^T \sum_{t=1}^N (\$QALY_{it} + \Delta Earning_{it}) - (Medical\ spending_{it} + G\text{-}CSF\ cost_{it})$$

where *i* represents individual and *t* represents each year of the simulation period. For an individual, this calculation is done over a lifetime, starting at treatment initiation. The results for G-CSF scenarios were calculated in 2017 US\$ and compared with the baseline (no G-CSF) scenario. Lifetime SV of G-CSF was estimated over a 10-year horizon, between 2017 and 2027.

**FIGURE 1.** Annual Number of FN Episodes Relative to No G-CSF Use Over 10 Years, by Scenario<sup>a</sup>

FN indicates febrile neutropenia; G-CSF, granulocyte colony-stimulating factor.

<sup>a</sup>Current G-CSF use: cancer type-specific real-world use of G-CSF in each patient population of FN risk (high, intermediate, and low). Targeted G-CSF use: 100% G-CSF use among patients with high risk of FN; 0% G-CSF use among patients with intermediate or low risk of FN. Reduced G-CSF use: current G-CSF use reduced by 20% in each FN risk group.

## RESULTS

### FN, RDI<85%, and Death

Both current and targeted use of G-CSF prophylaxis resulted in fewer annual cases of FN compared with the scenario of no G-CSF use. As seen in **Figure 1**, the benefits of G-CSF prophylaxis can be observed immediately and continue to increase over time. By 2027 (after year 10), current use and targeted use of G-CSF prophylaxis were estimated to prevent about 340,000 and 700,000 FN cases per year, respectively. The cumulative cases of FN prevented over 2 and 10 years are displayed in **Table 3**.

Similarly, occurrences of RDI<85% were reduced under both current and targeted use of G-CSF prophylaxis compared with the scenario of no G-CSF use. As shown in **Figure 2**, current use and targeted use of G-CSF prophylaxis led to an estimated 35,000 and 70,000 fewer occurrences of RDI<85%, on average, at year 10 (2027), respectively. The cumulative occurrences of RDI<85% prevented over 2 and 10 years are displayed in **Table 3**.

Reductions in both FN and RDI<85% reduced annual patient mortality. These benefits are shown as the cumulative number of deaths prevented at 2 and 10 years displayed in **Table 3**. Compared with no G-CSF use, current G-CSF use prevented more than 27,000 deaths after 2 years and more than 117,000 deaths after 10 years.

Similarly, targeted G-CSF use prevented more than 48,000 and 222,000 deaths over 2 and 10 years, respectively.

### QALYs, Prophylaxis Cost, Medical Spending, and SV

The average life expectancy gains for each of the G-CSF prophylaxis scenarios are shown in **Table 3**. Under the current G-CSF use scenario, patients treated over the next 10 years gained about 570,000 QALYs over their baseline counterparts. Targeted G-CSF use generated even greater life expectancy benefits than witnessed with current G-CSF use. Compared with no G-CSF use, patients treated under the targeted G-CSF scenario over the next 10 years generated 970,000 QALYs.

Cumulative prophylaxis costs and medical spending for each scenario over 2 and 10 years are shown in **Table 3**. Compared with no G-CSF prophylaxis, both current and targeted use of G-CSF reduced medical spending (excluding prophylaxis cost) over 10 years, such that total spending (including prophylaxis cost) was less than in the scenario of no G-CSF use. These results suggested that the cost offsets from G-CSF prophylaxis are greater than the prophylaxis costs; thus, G-CSF prophylaxis is cost-effective at all positive QALY thresholds.

Finally, we measured SV as the estimated benefits that G-CSF prophylaxis generated for society net of its costs. The components of this calculation are shown in **Table 3**. SV was positive for all G-CSF use scenarios, but targeted use generated substantially more value than current and reduced G-CSF use across all periods.

After only 2 years, we estimated that the current use of G-CSF prophylaxis would generate more than \$15 billion in value to society, or \$9700 per patient. However, if G-CSF use were targeted to patients with a high risk of FN, the value to society would more than double to almost \$40 billion, or \$16,400 per patient. After 10 years, the SV increased to \$96 billion (\$14,700 per patient) and \$215 billion (\$21,000 per patient) for current and targeted G-CSF use scenarios, respectively, compared with baseline. The per-patient SV increases over time as a result of the decrease in mortality due to G-CSF prophylaxis use.

### Reduced Pegfilgrastim Use Results

A 20% reduction in pegfilgrastim use in favor of filgrastim saved \$2.0 billion and \$3.5 billion in prophylaxis costs over 2 and 10 years, respectively, compared with current G-CSF use. However, the shift also led to an additional \$4.0 billion and \$17.0 billion in medical spending from FN events over 2 and 10 years, respectively. Ultimately, reduced use of pegfilgrastim resulted in a loss of \$2.7 billion and \$14.9 billion in SV over 2 and 10 years, respectively.

**TABLE 3.** Cumulative Health and Economic Outcomes Generated From G-CSF Use Relative to No G-CSF Use, by Treatment Scenario\*

Outcome	Over 2 Years			Over 10 Years		
	Current Use	Targeted Use	Reduced Use	Current Use	Targeted Use	Reduced Use
Number treated	1,551,360	2,404,370	1,241,650	6,502,880	10,243,100	5,208,130
Cases of FN prevented among incidence	771,690	1,542,300	619,150	3,260,120	6,582,720	2,612,960
Patients with RDI<85% prevented among incidence	94,390	197,960	76,020	353,860	708,950	280,590
Deaths avoided among incidence	27,290	48,620	22,590	117,490	222,370	94,930
QALYs gained (thousands)	104	170	90	570	970	460
Total health benefit <sup>b</sup>						
Savings in medical spending, treatment of FN events <sup>c</sup> (\$, millions)	29,330	58,640	23,520	109,370	220,670	87,670
Patient/caregiver productivity gains/earnings <sup>c</sup> (\$, millions)	6160	11,090	5060	23,190	43,650	18,800
QALYs gained <sup>c</sup> (\$, millions)	15,120	25,090	12,540	72,220	122,840	58,910
Total prophylaxis cost <sup>c</sup> (\$, millions)	35,580	55,450	28,540	108,880	171,770	87,250
Net social value <sup>d</sup> (\$, millions)	15,030	39,370	12,580	95,900	215,390	78,130

FN indicates febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; QALY, quality-adjusted life-year; RDI<85%, relative dose intensity less than 85%.  
<sup>a</sup>Current G-CSF use: cancer type-specific real-world use of G-CSF in each patient population of FN risk (high, intermediate, and low). Targeted G-CSF use: 100% G-CSF use among patients with high risk of FN; 0% G-CSF use among patients with intermediate or low risk of FN. Reduced G-CSF use: current G-CSF use reduced by 20% in each FN risk group.  
<sup>b</sup>Total health benefit includes savings in medical spending, monetized patient/caregiver productivity gains, and monetized patient QALY improvements, valued at \$150,000 per statistical life-year.  
<sup>c</sup>All costs are discounted at 3% annually.  
<sup>d</sup>Net social value is calculated as the total health benefit minus discounted prophylaxis costs.

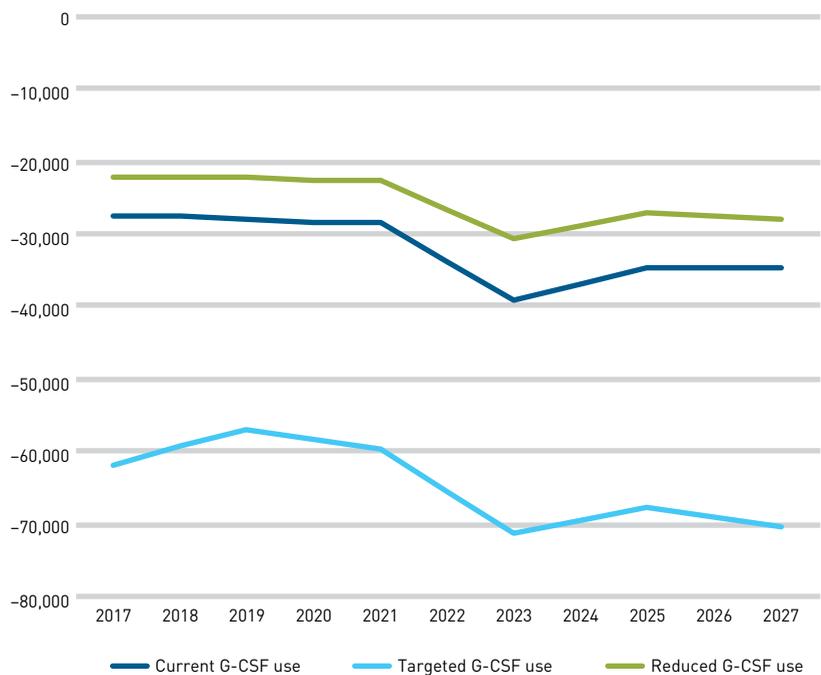
## DISCUSSION

We used a microsimulation model to examine the SV of aligning primary prophylactic G-CSF use with guideline recommendations over a 10-year period. Our model estimated that current use of G-CSF prophylaxis would decrease the total number of FN cases by 3.3 million, prevent more than 350,000 cases of RDI<85%, and generate \$96 billion in net SV over 10 years compared with a no G-CSF scenario. We estimated that the targeted use of G-CSF prophylaxis, defined according to the NCCN guidelines, would reduce the total number of FN cases and cases of RDI<85% by 6.6 million and 709,000, respectively, in addition to gaining \$215 billion in SV. Finally, our model estimated that shifting from pegfilgrastim to filgrastim would result in increased rates of FN and RDI<85%, in addition to higher medical spending and lower net SV.

We note that the large reduction in cases of FN relative to the reduction in cases of RDI<85% is due to the fact that cases of FN were estimated per cycle of chemotherapy and cases of RDI<85% were estimated per course of chemotherapy treatment.

Previous cost-effectiveness analyses of G-CSF prophylaxis have been conducted across

**FIGURE 2.** Annual Number of Patients With Relative Dose Intensity Less than 85% Relative to No G-CSF Use Over 10 Years, by Scenario<sup>a</sup>



FN indicates febrile neutropenia; G-CSF, granulocyte colony-stimulating factor.  
<sup>a</sup>Current G-CSF use: cancer type-specific real-world use of G-CSF in each patient population of febrile neutropenia (FN) risk (high, intermediate, and low). Targeted G-CSF use: 100% G-CSF use among patients with high risk of FN; 0% G-CSF use among patients with intermediate or low risk of FN. Reduced G-CSF use: current G-CSF use reduced by 20% in each FN risk group.

a variety of treatment conditions, including specific tumor types as well as solid tumors more broadly; different clinical contexts; primary versus secondary prophylaxis; and long-acting pegfilgrastim versus short-acting filgrastim. Across all of these options, primary prophylaxis with pegfilgrastim has been identified as being cost-effective at traditionally accepted thresholds for the prevention of FN in patients with cancer receiving myelosuppressive chemotherapy<sup>5,6,32-35</sup>; however, these studies have several limitations. First, they fail to fully capture the impact of FN and G-CSF prophylaxis on patient productivity. Second, they assume 100% compliance with the G-CSF prophylaxis options being evaluated, despite mounting evidence suggesting that compliance is far less.<sup>36-43</sup> Our analysis modeled increased productivity and health-related QOL due to reduced incidence of FN, which provides a more comprehensive evaluation of G-CSF prophylaxis. We also incorporated estimates of suboptimal use of G-CSF prophylaxis (specifically underuse in high-risk patients and overuse in low-risk patients) to provide an estimate of inclusive SV.

### Limitations

Our study does have limitations worth noting. First, parameters for the model were taken from the current literature. When published estimates did not exist for parameters by tumor type, we relied on reasonable assumptions and input from clinical experts. Second, the PSID data do not include information on most of the patient risk factors for FN. Thus, our FN risk group categorization relied solely on chemotherapy risk and patient age. Additionally, we were unable to account for the differential rates of FN and RDI < 85% by cancer stage and histology. Although we recognize that RDI < 85% may not equally affect survival across cancer types, disease stages, and regimens, the literature supports that RDI ≥ 85% has a favorable impact on survival.<sup>44</sup> Third, the efficacy of G-CSF prophylaxis on the risk of FN is not as well defined for intermediate- and low-risk groups. Thus, we assumed the same impact of G-CSF on the incidence of FN for all risk groups. This could potentially over- or underestimate the impact of G-CSF prophylaxis in these groups. Fourth, we did not account for the impact of newer G-CSF administration options on guideline adherence from a prescribing perspective or medication adherence at the patient level. For example, the on-body injector allows patients and caregivers to remain at home and thus avoid the caregiver burden and lost work days associated with next-day clinic visits, which have been identified as both a patient- and practice-related rationale for suboptimal prophylaxis.<sup>45,46</sup> Finally, we did not account for the evolving treatment landscape in cancer. As more targeted therapies and immunotherapies become available, chemotherapy treatment may decline, although these therapies also can be used with combinations of myelosuppressive chemotherapy.<sup>47,48</sup> Thus, we show the value gained over 2 years and over 10 years. Treatment patterns are not likely to change drastically in the next 2 years, and the introduction of newer therapies over the next decade does not change our conclusions.

## CONCLUSIONS

Our results suggest that G-CSF therapies provide tremendous value to society. Better targeting G-CSF to align with current guidelines would double this value. Rather than reducing G-CSF use or switching use to less-costly short-acting G-CSFs, efforts to support appropriate FN risk assessment in all patients receiving myelosuppressive chemotherapy, with consequent targeted G-CSF prophylaxis, could add considerable value. ■

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# THE LONG-TERM SOCIAL VALUE OF GRANULOCYTE-COLONY STIMULATING FACTORS

## Parameter Reference Appendix

“...FN events reduced patients’ QOL by 0.022.” (Naeim 2013; Fortner 2005).

“...percentage of total deaths for each cancer type...” (Dulisse 2013)

“...calculated hazard ratio for death of 1.46 for RDI<85% across all cancer types.” (Havrilesky 2015)

“...current rates of G-CSF prophylaxis in each FN risk category, by cancer type...” (Baig 2016; Wright 2013; Potosky 2011; Ramsey 2010).

“...potential impact of lower rates of G-CSF prophylaxis in response to cost concerns.” (Hershman 2012; Schnipper 2012)

“...6 doses of filgrastim were used per cycle, according to the median real-world utilization.” (Weycker 2006; Wang 2015)

“...pegfilgrastim and filgrastim are associated with odds ratios of FN of 0.24 and 0.51, respectively...” (Jansen 2011)

“...4% and 5% of patients experience RDI<85%, respectively.” (Crawford 2005)

“...cost of FN-related inpatient and outpatient encounters by cancer type from the literature.” (Michels 2012; Weycker 2008)

**Table 1.** Select Model Inputs (with Parameter References)

<b>Input</b>	<b>High Risk</b>	<b>Intermediate Risk</b>	<b>Low Risk</b>
Percentage of patients according to FN risk categories due to chemotherapy			
Breast cancer <sup>a</sup>	73.5	5.3	21.1
Gynecological cancers <sup>a*</sup>	33.1	17.4	49.4
Lung cancer <sup>a</sup>	12.8	28.7	58.5
NHL <sup>b**</sup>	51.3	12.7	36.0
Incidence of FN without G-CSF prophylaxis <sup>†</sup>			
Breast cancer <sup>c</sup>	1.12 <sup>d-f</sup>	0.73 <sup>f,g</sup>	0.24 <sup>g</sup>
Gynecological cancers <sup>‡</sup>	1.68 <sup>h,i</sup>	1.10 <sup>§</sup>	0.36 <sup>§</sup>
Lung cancer	0.93 <sup>l</sup>	0.61 <sup>l</sup>	0.20 <sup>l</sup>

NHL	1.93 <sup>§</sup>	1.26 <sup>j</sup>	0.41 <sup>§</sup>
Rate of RDI<85% without G-CSF prophylaxis (%)			
Breast cancer	27 <sup>k</sup>	11 <sup>l,m</sup>	5 <sup>**</sup>
Gynecological cancers	57 <sup>k</sup>	31 <sup>n</sup>	5 <sup>**</sup>
Lung cancer	60 <sup>k</sup>	25 <sup>¶</sup>	5 <sup>**</sup>
NHL	39 <sup>k</sup>	33 <sup>l,m</sup>	5 <sup>**</sup>
<b>G-CSF Effectiveness</b>	<b>All Risk Categories</b>		
Impact of G-CSF on the risk of FN (odds ratio)			
All cancers <sup>o</sup>	0.49		
Impact of G-CSF on the risk of RDI<85% (odds ratio)			
Breast, gynecological, and lung cancers <sup>l#</sup>	0.73		
NHL <sup>p</sup>	0.70		
<b>Model Costs</b>			
FN-related inpatient and outpatient encounters (2017 US\$)			
All cancers <sup>q-s</sup>	39,050		
Cost of prophylaxis per patient receiving pegfilgrastim (2017 US\$) <sup>†</sup>			
Until 2019			
Breast and gynecological cancers and NHL	25,483		
Lung cancer	16,989		
In 2019			
Breast and gynecological cancers and NHL	21,661		
Lung cancer	14,441		
In 2020 and after			
Breast and gynecological cancers and NHL	18,412		
Lung cancer	12,275		
Cost of prophylaxis per patient receiving filgrastim (2017 US\$) <sup>†</sup>			
Breast and gynecological cancers and NHL	16,615		
Lung cancer	11,077		

FN indicates febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; NHL, non-Hodgkin lymphoma; RDI, relative dose intensity.

Parameter references: <sup>a</sup>Ramsey 2010; <sup>b</sup>Gerlier 2010; <sup>c</sup>Kuderer 2007; <sup>d</sup>Gilbar 2014; <sup>e</sup>Martin 2005; <sup>f</sup>Younis 2012; <sup>g</sup>Perez 2002; <sup>h</sup>Rose 2003; <sup>i</sup>Swisher 1997; <sup>j</sup>Osby 2003; <sup>k</sup>Culakova 2014; <sup>l</sup>Lyman

2003; <sup>m</sup>Pettengell 2008; <sup>n</sup>Bandera 2015; <sup>o</sup>Hershman 2009; <sup>p</sup>Lyman 2004; <sup>q</sup>Federal Reserve Economic Data 2017; <sup>r</sup>Michels 2012; <sup>s</sup>Weycker 2008.

\*Chemotherapy risks calculated as the average across breast cancer, lung cancer, and colorectal cancer because tumor-specific data did not exist.

\*\*High-risk chemotherapy patients from Gerlier 2010. Intermediate- and low-risk patients calculated using the ratio of intermediate-risk patients to low-risk patients obtained by averaging the respective categories across breast cancer, lung cancer, and colorectal cancer from Ramsey 2010.

†Assumes 6 cycles of chemotherapy and G-CSF for breast and gynecological cancers and NHL; 4 cycles for lung cancer. Assumes 6 doses of filgrastim per chemotherapy cycle.

‡Sources report on ovarian cancer. We assume the rate within ovarian cancer is equal to the rate within gynecological cancers.

§FN incidence calculated by using the equation:

$$\begin{aligned} & \text{FN incidence risk group } i, \text{ cancer } j \\ &= \frac{\text{FN incidence intermediate risk group, cancer } j}{\text{FN incidence intermediate risk group, breast cancer}} \\ & \times \text{FN incidence } i \text{ risk group, breast cancer} \end{aligned}$$

||The FN incidence for each risk group was calculated by taking the average between the FN incidence for breast cancer and the FN incidence for gynecological cancers in the respective risk groups.

¶Average of intermediate risk category across breast cancer, ovarian cancer, and NHL because tumor-specific data did not exist.

\*\*Based on the middle percentage point for FN risk rate of low FN risk category (<10%) according to National Comprehensive Cancer Network guidelines.

#The odds ratio of RDI<85% with G-CSF prophylaxis for gynecological cancers was assumed to be the same as for breast cancer because tumor-specific estimates did not exist.

**Table 2.** G-CSF Use (%) by Scenario and FN Risk Group (with Parameter References)

	Coverage Scenario							
	Current Use <sup>a*</sup>			Targeted Use <sup>†</sup>		Reduced Use <sup>‡</sup>		
	High Risk	Intermediate Risk	Low Risk	High Risk	Intermediate and Low Risk	High Risk	Intermediate Risk	Low Risk
Breast cancer	51.4	33.7	21.2	100	0	41.1	26.9	17.0
Gynecological cancers*	39.5	37.5	18.3	100	0	31.6	30.0	14.6
Lung cancer	27.7	41.3	15.3	100	0	22.2	33.0	12.3
NHL*	51.4	33.7	21.2	100	0	41.1	26.9	17.0

FN indicates febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; NHL, non-Hodgkin lymphoma.

<sup>a</sup>Baig 2016

\* Adjusted rates account for intermediate-risk patients with risk factors in the high-risk group.

Lung cancer G-CSF use rates are based only on metastatic data. NHL rates were assumed to be the same as breast cancer rates because unadjusted rates for high-risk patients with breast cancer and NHL were very similar, according to the literature. Gynecological cancer rates were assumed to be the average of breast and lung cancer rates.

<sup>†</sup>Rates were based on National Comprehensive Cancer Network guidelines.

<sup>‡</sup>Current G-CSF rates were reduced by 20 percentage points.

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