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Estimation Of G-CSF effectiveness in reducing neutropenia hospitalization among non-Hodgkin's Lymphoma (NHL)patients treated with anthracycline-based chemotherapy

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ESTIMATION OF G-CSF EFFECTIVENESS IN REDUCING NEUTROPENIA HOSPITALIZATION AMONG NON-HODGKIN'S LYMPHOMA (NHL) PATIENTS TREATED WITH ANTHRACYCLINE-BASED CHEMOTHERAPY

by

Xiaoyun Pan

An Abstract

Of a thesis submitted in partial fulfillment
of the requirements for the Doctor of
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ABSTRACT

The objective of this research was to estimate prophylactic G-CSF effectiveness among patients on the extensive margin, whose treatment decisions are most likely to be affected by policy changes intended to alter the G-CSF treatment rate.

Using the national Surveillance, Epidemiology and End Results (SEER)-Medicare Linked Database, we studied patients 66 years or older diagnosed with Non-Hodgkin's Lymphoma (NHL) and on anthracycline in one of the 13 SEER registry areas from 1994-2002. Prophylactic G-CSF use was designated if a patient had a G-CSF claim within the first five days of the first chemotherapy cycle. The dependent variable of neutropenia hospitalization (NH) was identified within 6 months of diagnosis and was further specified as NH incidence within 21, 42, 63 and 126 days after anthracycline initiation in sensitivity analyses. Multivariate regression estimates were used to examine whether treated patients actually benefited from G-CSF. Instrumental variable estimates using local area prophylactic G-CSF treatment rates as instruments were used to estimate whether increases in the G-CSF utilization rate could lead to further reductions in the rate of neutropenia hospitalization.

We found only 9.85% of study patients had prophylactic G-CSF. After adjustment for patient demographic and clinical risk factors, multiple regressions indicated prophylactic G-CSF significantly reduced NH events within six months of diagnosis date for the patients who received G-CSF (OR=0.595, 95% CI=0.384-0.922). This estimate of G-CSF's effect may be biased low from the true values of Average Treatment effect on the Treated (ATT) because patients may be selected into treatment based on unobservable risk factors. Chow F-statistics showed our instrumental variable of area prophylactic G-CSF treatment rate described a statistically significant portion in the variation of G-CSF use ($F=60.46$, $P<0.0001$). In the base-case analysis, we found instrumental variable estimates of prophylactic G-CSF benefits within 6 months of diagnosis date among marginal patients. The estimated benefits varied with different instrument specifications,

regardless of the level of statistical significance. In the sensitivity analyses, the exclusion criteria for the inability to calculate an area reimbursement variable in base-case analysis were removed. We found substantial G-CSF benefits available within first cycle of chemotherapy among marginal patients and the instrumental variable estimates were statistically significant.

Among elderly NHL patients on anthracycline-based chemotherapy, our multiple regression estimates suggest that patients treated with prophylactic G-CSF reduced their neutropenia risk within six months of diagnosis date. The effect of prophylactic G-CSF on neutropenia hospitalization among marginal patients whose choices varied with local area G-CSF treatment rate was negative. Substantial G-CSF treatment benefits within the first cycle of chemotherapy were available for patients on the extensive margin. Higher treatment rates may be guaranteed to improve patient short-term benefits from G-CSF.

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CERTIFICATE OF APPROVAL

PH.D. THESIS

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The objective of this research was to estimate prophylactic G-CSF effectiveness among patients on the extensive margin, whose treatment decisions are most likely to be affected by policy changes intended to alter the G-CSF treatment rate.

Using the national Surveillance, Epidemiology and End Results (SEER)-Medicare Linked Database, we studied patients 66 years or older diagnosed with Non-Hodgkin's Lymphoma (NHL) and on anthracycline in one of the 13 SEER registry areas from 1994-2002. Prophylactic G-CSF use was designated if a patient had a G-CSF claim within the first five days of the first chemotherapy cycle. The dependent variable of neutropenia hospitalization (NH) was identified within 6 months of diagnosis and was further defined as NH incidence within 21, 42, 63 and 126 days post anthracycline initiation in the sensitivity analyses. Multivariate regression estimates were used to examine whether treated patients actually benefited from G-CSF. Instrumental variable estimates using local area prophylactic G-CSF treatment rates as instruments were used to estimate whether increases in the G-CSF utilization rate could lead to further reductions in the rate of neutropenia hospitalization.

We found only 9.85% of study patients had prophylactic G-CSF. After adjustment for patient demographic and clinical risk factors, multiple regressions indicated prophylactic G-CSF significantly reduced NH events within six months of diagnosis date for the patients who received G-CSF (OR=0.595, 95% CI=0.384-0.922). This estimate of G-CSF effect may be biased low from the true values of Average Treatment effect on the Treated (ATT) because patients may be selected into treatment based on unobservable risk factors. Chow F-statistics showed our instrumental variable of area prophylactic G-CSF treatment rate described a statistically significant portion in the variation of G-CSF use ($F=60.46$, $P<0.0001$). In the base-case analysis, we found prophylactic G-CSF benefits within 6 months of diagnosis date among marginal patients. The estimated

benefits varied with different instrument specifications, regardless of the level of statistical significance. In the sensitivity analyses, the exclusion criteria for the inability to calculate an area reimbursement variable in the base-case analysis were removed. We found substantial G-CSF benefits available within first cycle of chemotherapy among marginal patients and the instrumental variable estimates were statistically significant.

Among elderly NHL patients on anthracycline-based chemotherapy, our multiple regression estimates suggest that patients treated with prophylactic G-CSF reduced their neutropenia risk within six months of diagnosis date. The effect of prophylactic G-CSF on neutropenia hospitalization among marginal patients whose choices varied with local area G-CSF treatment rate was negative. Substantial G-CSF treatment benefits within the first cycle of chemotherapy were available for marginal patients. Higher treatment rates may be guaranteed to improve patient short-term benefits of G-CSF.

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CHAPTER I INTRODUCTION

Background

Non-Hodgkin's Lymphoma (NHL) is a type of cancer that starts in lymphocytes or white blood cells, which are part of the immune system (American Cancer Society 2009). According to US cancer statistics, the incidence rate of NHL is 19 per 100,000 persons, which is one of the highest cancer incidence rates (National Cancer Institute 2010; USCS). The National Cancer Institute (NCI) estimates that 65,540 new NHL cases will be diagnosed in 2010 (National Cancer Institute 2010). Currently, one of the primary types of treatment for NHL is chemotherapy, which may kill the cancer cells or stop the cells from dividing (National Cancer Institute 2010). Anthracycline-based chemotherapy (ABC) is the most common and effective type of cancer drug therapy used in NHL patients (Lymphoma Information Network). Typical agents of anthracycline include Daunorubicin, Doxorubicin, Epirubicin, Idarubicin and Mitoxantrone. For example, CHOP (Cyclophosphamide, Doxorubicin, Vincristine and Prednisone), which contains an anthracycline agent (Doxorubicin), is the standard treatment for patients with advanced-stage intermediate-grade NHL (Coltman, Dahlberg, and Jones 1986; Dorr and Von Hoff January 30, 1994; Fisher et al. 1993; McKelvey et al. 1976; Tirelli et al. 1998).

Although anthracycline-based chemotherapy is commonly used, it is toxic. One of the most serious side effects of this treatment is febrile neutropenia (FN). Febrile neutropenia, which is defined as an absolute neutrophil count (ANC) of less than 1000 cells/μL or <500 cells/μL with a temperature of more than 100.6°F, is a life-threatening condition (Lyman and Kuderer 2003). The consequences of FN are febrile neutropenia hospitalization (FNH), incompleteness and delays in chemotherapy. It was reported that among intermediate-grade NHL patients, CHOP caused febrile neutropenia hospitalization in 28% of patients 65 years or older (Chrischilles et al. 2002). A study estimated the average total cost of neutropenia hospitalization (NH) for each NHL patient

was $2,124, with an average daily cost of $1,078 per neutropenia hospitalization day (Chrischilles et al. 2005).

The management of febrile neutropenia involves the use of Granulocyte Colony Stimulating Factor (G-CSF). As the most common type of Colony Stimulating Factors (CSFs), G-CSF stimulates bone marrow to produce neutrophils, the infection-fighting white blood cells. The indication of this drug is to prevent and treat febrile neutropenia among cancer patients who use myelosuppressive chemotherapy (Amgen 2007). G-CSF has been a covered expense by Medicare for this indication since 1994, which is the year the sample period of this study began.

Statement of the Problem

The 1994 American Society of Clinical Oncology (ASCO) guidelines recommend that cancer patients with high risk of FN (40% or greater) should receive prophylactic G-CSF. This guideline suggests that being "elderly", causes greater than a 40% risk of FN (ASCO 1994). This indicates that the appropriate G-CSF rate in patients with ASCO guideline-defined conditions should be 100%. However, in practice, G-CSF utilization rates among NHL patients are low. A pilot SEER-Medicare data analysis of elderly Diffuse Large B-cell (DLC) NHL patients treated with ABC from 1994 to 2002 indicates the rate of prophylactic G-CSF use was only 11.9% (Link et al. 2008). DLC NHL patients were found to have the highest neutropenia hospitalization incidence rates when compared to NHL patients with other histology types (Chrischilles et al. 2005). The substantial deviation of G-CSF use from guideline recommendation elicits the question: "Why might rates be so low?" This question cannot be well answered without an understanding of the reasons underlying treatment variation and the factors incorporated into patient-physician decision-making (Langley, Minkin, and Till 1997).

Hunink et al. provide a useful construct to consider this question (Hunink and Glasziou 2001). They theorize that patients along with their physicians choose treatments

with the highest expected utility. The expected utility of a treatment option is defined as the sum of values placed on all consequences (benefits and costs) associated with the treatment option, weighted by the probability of experiencing each consequence (Hunink and Glasziou 2001). Under the theoretical construct of expected utility, patients weigh the expected treatment benefits and costs and would choose to be treated if the net expected utility of the treatment relative to watchful waiting is positive.

With regard to G-CSF, treatment options are assumed to be either prophylactic G-CSF or watchful waiting. Given current low treatment rates, under Hunink's theoretical construct, it must be that for most patients, their perceived treatment costs associated with G-CSF are greater than perceived benefits of G-CSF. Generally, perceived treatment benefit is defined as a patient's beliefs in the positive consequences of an intervention (e.g. the effectiveness of treatment in reducing risk) (Glanz, Rimer, and Lewis 2002). In this research, perceived treatment benefit is assumed to be a function of the values a patient places on positive consequences weighted by the probability leading to these consequences. Perceived treatment cost is defined as a patient's beliefs in the tangible and intangible (psychological) costs of the intervention (Glanz, Rimer, and Lewis 2002). In this research, perceived treatment cost is assumed to be a function of the values a patient places on negative consequences weighted by the probability leading to these costs.

A clinical balance sheet as seen in Table I-1 is a good approach to summarize the benefits and costs of G-CSF treatment. Potential treatment benefits include G-CSF's effect in reducing neutropenia risk, neutropenia hospitalization cost savings, increase in oncologist income, and improvement of oncologist reputation. Potential treatment costs include treatment side effects, discomfort of daily injection, out-of-pocket cost, transportation/time cost, and quality-of-life burden.

John Wennberg posed the question of "Which rate is right?" almost two decades ago (Wennberg 1986). The ASCO guideline suggests that for elderly NHL patients on

ABC, "the right rate" of G-CSF use should be 100%. Since actual rates of G-CSF use among this demographic fall far below 100%, patients and their physicians must be making G-CSF choices that ASCO guideline makers consider unwise. Such choices might be made in two scenarios.

In the first scenario, patients along with their physicians are mistaken in their expectations of G-CSF benefits and costs. It could be that patients along with physicians have pessimistic beliefs about G-CSF benefits and underestimate G-CSF's effect in reducing NH risk. For example, ASCO guideline makers relying on Randomized Controlled Trial (RCT) evidence believe G-CSF significantly reduces neutropenia incidence, while in practice physicians and patients may not share this belief in G-CSF's benefit of reducing neutropenia. This disparity might be due to potential reasons such as slow dissemination of clinical knowledge. It could also be that patients along with their physicians are overestimating the likelihood of discomfort or the risks of side-effects. For example, when compared with guideline-makers, patients may perceive a higher risk of side-effects such as bone pain.

In the second scenario, patients along with their physicians are correct in their expectations of G-CSF treatment consequences. However, the valuations they place on treatment benefits and costs differ from the valuations of the guideline makers. For example, patients, physicians and guideline makers may equally expect the clinical benefits of G-CSF in reducing NH risk, while patients and physicians may value neutropenia risk reduction much less than guideline makers do. It could also be possible that patients weigh the costs associated with daily injection or travel much higher than guideline makers do.

If patient and physician expectations of G-CSF benefits and costs were correct, observed G-CSF utilization rates, which only reflect patient and physician valuations

placed on these consequences, are considered "right" utilization rates. Alternatively, patients along with their physicians may have incorrect expectations of either G-CSF risk reduction or the risks of side-effects in that they differ from the true risk reduction of G-CSF or the actual risks of side-effects. Incorrect expectations of consequences may lead to suboptimal treatment rates with G-CSF. If we were able to demonstrate that G-CSF has a greater benefit in terms of reducing neutropenia risk than is currently expected by patients and physicians, this information would help inform clinicians' and policy-makers' decisions about whether current utilization of G-CSF needs to be increased.

This analysis of decision-making by physicians and patients is further complicated because evidence suggests that G-CSF benefits of reducing neutropenia incidences may vary or be heterogeneous across elderly NHL patients on ABC. A summary of clinical trials investigating G-CSF as primary prophylaxis in patients with NHL and on ABC chemotherapy is listed in Table I-2. This table indicates that absolute neutropenia rate differences between controlled and G-CSF treated patients vary between 8% and 48%, suggesting treatment-effect heterogeneity among NHL patients.

Given the evidence of G-CSF treatment effect heterogeneity, it is possible that current G-CSF utilization rates reflect the correct sorting of patients on chemotherapy to receive G-CSF. It means that patients with greatest perceived net benefit of G-CSF, defined as perceived G-CSF benefits minus perceived G-CSF costs, may receive G-CSF while those patients with little or no perceived net benefit of G-CSF do not receive treatment. Of course, this sorting process is based on expectations of G-CSF benefits (neutropenia risk reduction) and costs across patients, and these expectations may not be correct. If expectations of G-CSF benefits are wrong, for example, patients along with their physicians have pessimistic beliefs of G-CSF treatment effects, and then higher G-CSF rates may be warranted. Likewise, if expectations of G-CSF costs are wrong, for example, patients along with their physicians have overestimated G-CSF side-effect risks, and then higher G-CSF rates may be warranted as well.

Three hypothetical graphic examples in terms of expected utility that incorporate heterogeneity in G-CSF's benefit in reducing NH risk are provided in order to show 1) a correct G-CSF treatment rate with correct expectations of benefits relative to costs, and 2) an incorrect treatment rate driven from incorrect expectations of either G-CSF benefits (neutropenia risk reduction) or costs such as side-effect risks. In the first scenario (as seen in Figure I-1), patient expectations of G-CSF treatment benefit in terms of neutropenia risk reduction are correct, current G-CSF treatment rates (e.g. 11.9%) only reflect patient valuations for the outcomes and are the correct rates. For ease of illustration, we assume in the figure that patient valuations of outcomes are constant across patients so that the differences in expected utility of treatment benefit of neutropenia risk reduction reflect only the differences in expected treatment effectiveness. The vertical (Y) axis measures the expected utility of G-CSF treatment benefits and costs, and the horizontal (X) axis measures the percentage of patients receiving G-CSF. The solid curve in the figure represents the expected utility of treatment benefits. Patients are distributed across the X axis by sources of treatment-effect heterogeneity or with the decrease in true treatment effectiveness from left to the right of the X axis. Patients in concert with physicians make choices depending on the expected utility of treatment benefit relative to cost. R represents the percent of patients who would choose G-CSF as the expected utility of treatment benefit is greater than or equal to the expected utility of G-CSF cost. At higher G-CSF treatment rates, the benefits for the additional patients would be less than treatment costs. Pushing treatment rates to a higher level would result in society loss and the current treatment rate is the right rate.

In the second scenario (seen in Figure I-2), the G-CSF treatment rate is an incorrect rate resulting from incorrect (pessimistic) expectations of G-CSF benefit in terms of neutropenia risk reduction. In addition to the solid curve representing the true expected utility of treatment benefits, the dashed curve in the figure represents pessimistic expected utility of treatment benefits. Under the pessimistic belief of the

benefits, patients and physicians stopped opting for treatment at a rate of R percent with the expectation that there would be little or no gain for patients with a higher treatment rate. Current treatment rate would be sub-optimal as the benefits from NH risk reduction would be greater than expected costs for patients between R and R_1 percent. In this scenario, reducing barriers in clinical knowledge diffusion and implementing other interventions to educate physicians and patients to encourage greater G-CSF use might help to push treatment rates nearer to optimal levels.

In the third scenario (as seen in Figure I-3), the G-CSF treatment rate is an incorrect rate resulting from incorrect (inflated) expectations of G-CSF costs in terms of side-effect risks or likelihood of daily injection discomfort. There are two expected utility of treatment cost curves. The dotted curve represents patients' and physicians' overestimated expected utility of treatment cost, while the dashed curve represents the expected utility of treatment cost reflecting true cost. If the current perceived treatment cost is driven by oncologists' overestimation of side effect risks or patient's overestimation of injection discomfort, then the current treatment rate, represented by R in the figure is not the right rate. The optimal treatment rate would be R_1, which may be warranted with a correct understanding of the potential costs of treatment.

In healthcare research, patients whose treatment choices are affected by changing treatment rates have been defined as "patients on the extensive margin" (Brooks 2000; Harris and Remler 1998; McClellan, McNeil, and Newhouse 1994; Park et al. 2008). In the case of G-CSF, answering Wennberg's question as to "which rate is right" requires estimates of G-CSF effect for the set of patients whose G-CSF choices would change if G-CSF treatment rates were increased. In the absence of such estimates, policy decisions concerning guideline implementation will not be reconcilable. Therefore, the major objective of this research is:

To estimate G-CSF effectiveness for patients on the extensive margin, whose treatment decisions are most likely to be affected by policy changes intended to alter the G-CSF treatment rate.

Research Approach

How can the "Which rate is right" question be evaluated for G-CSF? Randomized controlled trials (RCTs) where treatments are randomly assigned have been considered as the gold standard to estimate treatment efficacy in clinical outcomes research (Newhouse and McClellan 1998). Existing clinical trials suggest positive G-CSF benefits in reducing neutropenia risks among NHL patients on ABC chemotherapy (Bertini et al. 1996; Doorduijn et al. 2003; Osby, Hagberg, and Bjorkholm 1999; Osby et al. 2003; Pettengell et al. 1992; Zinzani et al. 1999). As already stated and shown in Table I-2, the RCT estimates suggest treatment effect heterogeneity, as absolute neutropenia rate differences between controlled and G-CSF treated patients vary between 8% and 48%. Due to this treatment effect heterogeneity across patients, it may be inappropriate to assume that elderly NHL patients on the extensive margin will benefit from prophylactic G-CSF. In addition, it may also be difficult to know which RCT estimate is appropriate to be generalized to the patients on the extensive margin. Conducting more trials may be unwise. For example, ethical problems may arise given the fact that G-CSF has been approved for this condition. Most trials are expensive and time-consuming to run. Current RCT estimates do not provide population coverage and cannot help to address real-world questions, such as "Which rate is right" (Wennberg 1986).

Observational studies which investigate estimates of treatment effect using large administrative databases provide population coverage (Roper et al. 1988). Compared to RCTs, observational studies have several advantages. For instance, plenty of variation in treatment choices could be explored, treatment effectiveness in real practice could be estimated, and these studies usually provide long-term follow up and large patient

numbers. However, as administrative databases are often not collected for research purposes, confounding factors which determine patient treatment choice and health outcome may be unobservable to the analysts (Newhouse and McClellan 1998). These unobserved confounders may potentially cause inferential problems (Newhouse and McClellan 1998).

In observational studies, various estimators, defined as rules or strategies to estimate the unknown population parameter by using the patient sample data (Greene 2003), are available to make inferences of treatment effects in certain populations to answer different policy questions. Imbens and Angrist show that instrumental variable (IV) estimator can identify the treatment effect parameter called Local Average Treatment Effect (LATE) that reflects treatment effect for a set of patients called marginal patients whose treatment choices are affected by the levels of an "instrumental variable" or "instrument" (Basu et al. 2007; Imbens GW 1994). An instrument is defined as a naturally varying phenomenon, such as natural force or policy, which has two key properties: 1) it must be related to treatment choice and 2) it must have no direct effect on the outcome variable and be unrelated to unmeasured confounders (Brooks et al. 2003; McClellan, McNeil, and Newhouse 1994; Newhouse and McClellan 1998; Rassen et al. 2009). Previous IV research theorized that IV estimates can be generalized to the patients on the extensive margin, defined as those who would receive treatment first if the treatment rates were increased or those who would first lose treatment if the treatment rates were lowered (Brooks 2000). Both marginal patients and patients on the extensive margin are thought to come from the subset of patients for whom the best treatment choices are least certain (Brooks 2000; Brooks et al. 2003; Harris and Remler 1998; McClellan, McNeil, and Newhouse 1994; Park et al. 2008). However, different instruments may identify different LATEs as they may exploit treatment variation over distinct subsets of patients (Basu et al. 2007). Marginal patients whose treatment choices vary with only a single instrumental variable may not be representative for all patients on

the extensive margin. The ability to generalize IV estimates to those beyond marginal patients defined by certain instruments is limited (Brooks et al. 2003).

Another alternative important treatment effect concept of policy relevance, which might be useful to answer "Which rate is right" question, is the Average Treatment effect on the Treated patients (ATT) (Heckman and Vytlacil 2000; James J Heckman 2006). Estimates of this concept can be useful for addressing the policy question of "whether a given treatment is beneficial among patients who received treatment" (Basu et al. 2007). Risk-adjustment (RA) estimators, such as multivariate regression risk adjustment, defined as a modeling method of treatment on outcome by controlling patient characteristics (DeLong et al. 1997; Huang et al. 2005; Shahian et al. 2001), yield estimates of ATT (Heckman and Vytlacil 2000; James J Heckman 2006).With regard to G-CSF treatment, RA estimates of G-CSF's effect may be biased low from the true values of ATT because patients may be selected into treatment based on unobservable risk factors. For example, patients with lower average neutropenia count (ANC) level are at a higher neutropenia risk and may perceive a greater treatment benefit. These patients may be favorably selected to receive treatment.

Compared to RA estimator, IV estimator provides a potential solution to handle this bias caused by unmeasured confounding problem. Under the two properties of instruments, variation in instrumental values across patients can serve as ex-post randomization of treatment (Basu et al. 2007). Given these conditions, it can be shown that IV estimator generates a consistent treatment-effect estimate, which converges in probability to the true value of treatment effect for "marginal patients" (Brooks et al. 2003; Newhouse and McClellan 1998; Rassen et al. 2009). Moreover, regardless of IV method's capability to handle the unmeasured confounding bias, IV estimator represents a different treatment effect concept than RA estimator does. If perceived G-CSF cost is assumed to be relatively constant across patients, under Hunink's theoretical construct, patients with uncertain choices are those whose perceived treatment benefit is small

enough to be close to perceived treatment cost. Therefore, the actual treatment effect parameter for patients on the extensive margin would more likely be smaller than ATT estimated by RA methods in this scenario. Compared to RA estimators, IV estimators are more applicable to provide estimates of treatment effect for patients on the extensive margin and help to address the question of “Which rate is right”.

Table I-1 Clinical Balance Sheet for Prophylactic G-CSF Treatment and Watchful Waiting among NHL Patients Treated with ABC

CONSEQUENCES	**ALTERNATIVES**	
	Watchful Waiting	**G-CSF (filgrastim)**
Potential Treatment Benefits		
Neutropenia risk reduction	None	Absolute neutropenia risk difference between controlled and G-CSF treated patients ranges from 8% to 48% (Bertini et al. 1996; Doorduijn et al. 2003; Osby, Hagberg, and Bjorkholm 1999; Osby et al. 2003; Pettengell et al. 1992; Zinzani et al. 1999)
NH cost savings per patient	Neutropenia hospitalization cost (hospital) ranges from $716.75 to $4829.20 (Chrischilles et al. 2005)	Cost-savings (hospital) ranges from $716.75 to $4829.20 (Chrischilles et al. 2005)
Oncologist income	None	Reimbursement revenue increases oncologists' income (estimated at approximately $800 for 11 days' supply of G-CSF (Adamson RT 2005))
Oncologist reputation	Less G-CSF use relative to area rates may affect reputation negatively (Brown 1996, Pauly &McGuire 1991, Park 2004)	Too much G-CSF use relative to area rates may affect reputation negatively (Brown 1996, Pauly &McGuire 1991, Park 2004)
Potential treatment costs		
Possible side effects	None	Numerous side effects from bone pain to red itchy skin, fever, chills, and fluid retention, or nausea, vomiting and diarrhea in 24% patients, patients treated with prophylactic G-CSF were 4 times more likely to have bone or musculoskeletal pain than controls in trials (Kuderer et al. 2007)
Comfortableness	None	Very uncomfortable about the daily injection for up to 14 days (Amgen 2007)

Table I-1 Continued

Out-of-pocket costs	Medicare Part A deductible for neutropenia hospitalization ($768 in 1999) (HCFA Press Office 1998)	$534 for 11 days' supply of G-CSF (Adamson RT 2005)
Transportation and time costs	Transportation and time costs associated with neutropenia hospitalization	Patients have to travel daily to the treatment center and take time off from work (Haithcox et al. 2003a)
Quality of life	None	Quality-of-life burden associated with time commitment and travel due to the daily injection (Haithcox et al. 2003b)

Table I-2 Summary of clinical trials investigating G-CSF as primary prophylaxis in patients with NHL and on ABC chemotherapy

Reference	**NHL type**	**ABC regimens**	**Patient Age**	**Principal inclusion/exclusion criteria**	**G-CSF effect**
Pettengell et al.(Pettengell et al. 1992)	High grade NHL	VAPEC-B: adriamycin, cyclophosphamide, vincristine, bleomycin, etopeside, prednisone, clotrimazole, ketoconazole	16-71	Inclusion: all patients had to have normal renal and hepatic function, normal peripheral blood count. Exclusion: patients with central nervous system (CNS) involvement and with other uncontrolled serious medical conditions were excluded. Patients should not take medications that are likely to affect white blood cell counts.	Absolute neutropenia rate difference between controlled and G-CSF treated patients was 48% (85% vs. 37%)
Bertini et al. (Bertini et al. 1996)	Advanced stage, Intermediate to high grade NHL	P-VEBEC (Epirubicin, cyclophosphomide, etoposide, vinblastine, bleomcin, prednisone)	65+	Inclusion: all had stage III and IV and stage II with B symptoms. Performance status should be less than 3 on the ECOG scale. Exclusion: patients with AIDS or HIV positive were excluded. Patients with severe concomitant medical problems or primary CNS lymphoma were excluded.	Absolute neutropenia rate difference between controlled and G-CSF treated patients was 25% (46% vs. 21%)

Table I-2 Continued

Zinzani et al. (Zinzani et al. 1997)	High grade NHL	VNCOP-B (cyclophosphamide, mitoxantrone, vincristine, etoposide, bleomycin and prednisone)	60+	Inclusions: patients had stage II to IV NHL. Performance status ranged from 0 to 2 on ECOG scale. All should have normal hepatic, cardiac and renal functions. Exclusion: patients with HIV positive were excluded.	Absolute neutropenia rate difference between controlled and G-CSF treated patients was 32% (55% vs. 23%)
Bjorkholm et al. (Osby, Hagberg, and Bjorkholm 1999)	High grade NHL	CHOP (cyclphosphamide, doxorubicin, vincristine and prednisone) or CNOP (cyclophosphamide, mitoxantrone, vincristine, prednisone)	60+	Inclusion: All had stage II-IV high grade NHL. Exclusion: patients with CNS lymphoma and HIV positive were excluded.	Absolute neutropenia rate difference between controlled and G-CSF treated patients was 29% (91% vs. 62%)
Osby et al. (Osby et al. 2003)	Aggressive NHL	CHOP or CNOP	60+	Inclusions: all had stage II to IV NHL, performance status was <=3. Exclusions: patients who had HIV infection, history of low-grade lymphoma, overt CNS disease, and congestive heart failure, history of neoplasm or abnormal liver function were excluded.	CHOP patients randomized to receive G-CSF had 34% fewer neutropenia (55% vs. 89%), 16% fewer febrile neutropenia (34% vs. 50%); CNOP patients randomized to receive G-CSF had 22% fewer neutropenia (64% vs. 86%), 18% fewer febrile neutropenia (32% vs. 50%)

Table I-2 Continued

Doorduijn et al. (Doorduijn et al. 2003)	Aggressive NHL	CHOP	65+	Inclusion: all had stage II-IV disease and a cardiac left ventricular ejection fraction 45%. Exclusion: patients had lymphoblastic NHL, HIV positive, other malignancy, abnormal liver or fidney function, previous indolent lymphoma or CNS involvement were excluded.	Absolute febrile neutropenia rate difference between controlled and G-CSF treated patients was 8% (45% vs. 37%)

Figure I-1 Graphic Example in Terms of Expected Utility Showing a Correct Rate with Correct Expectations

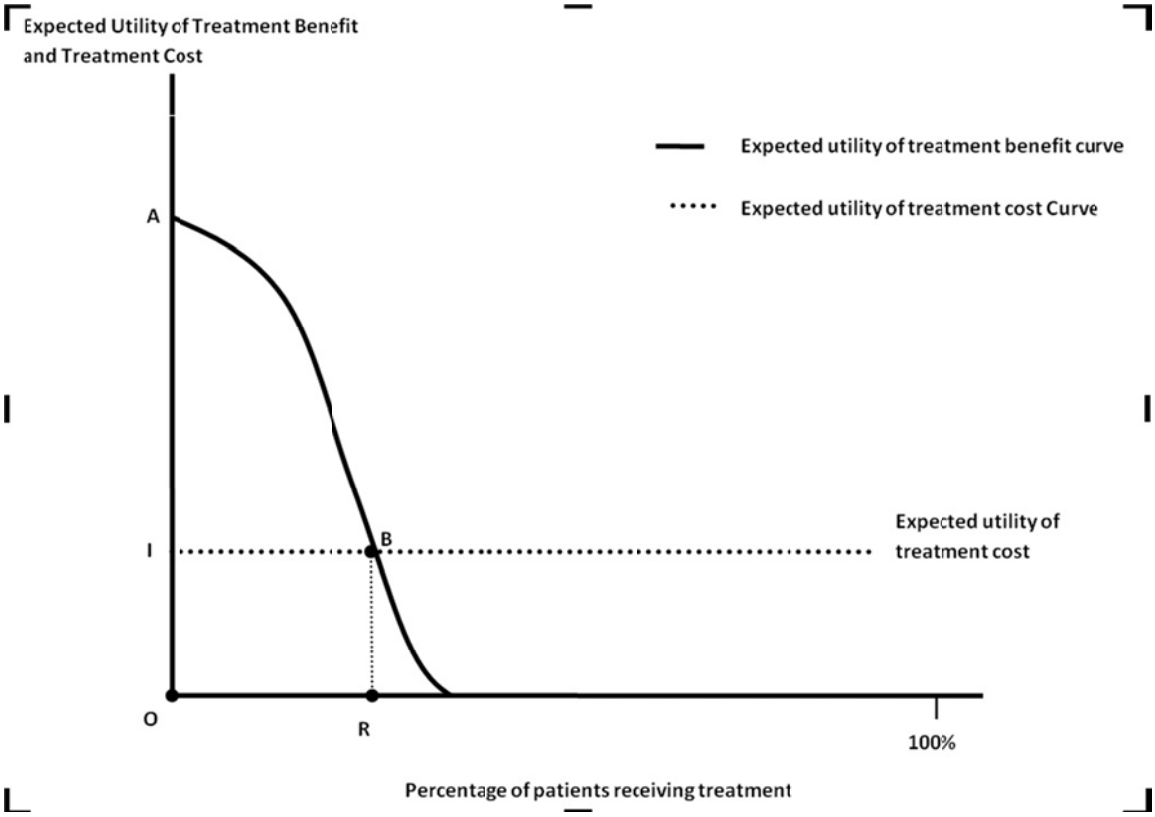


Figure I-2 Graphic Example in Terms of Expected Utility Showing an Incorrect Rate with Incorrect Expectations of Treatment Benefit

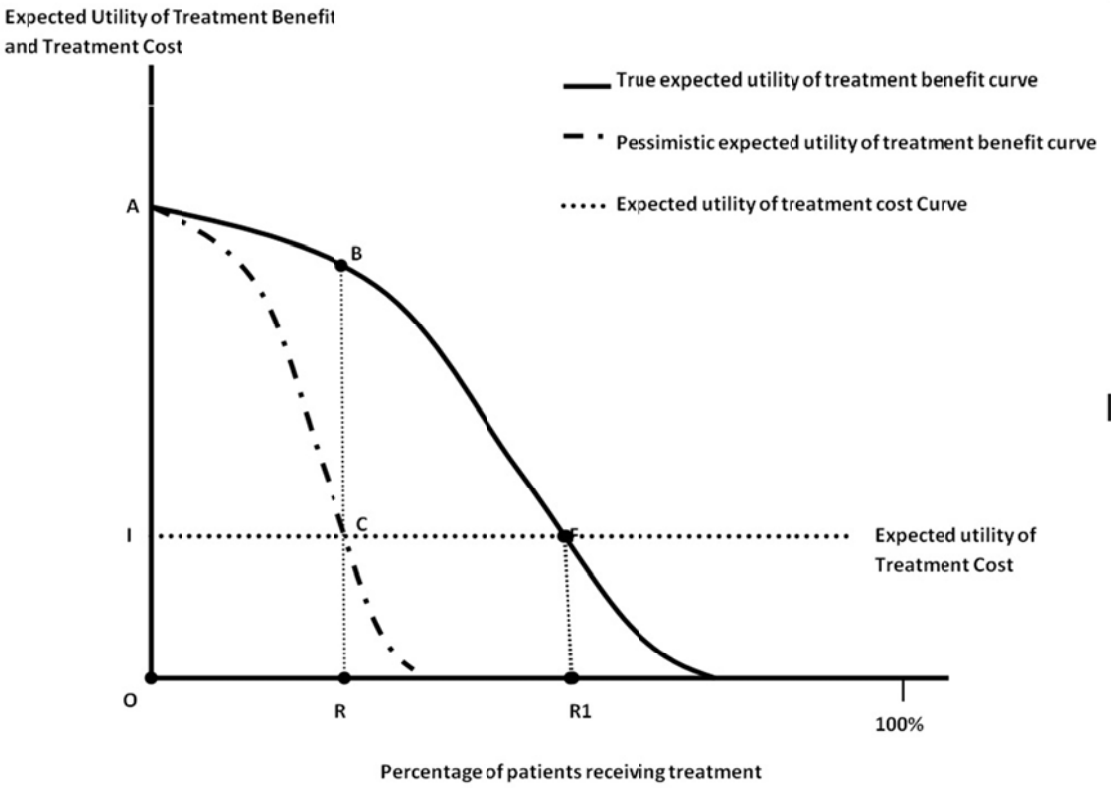
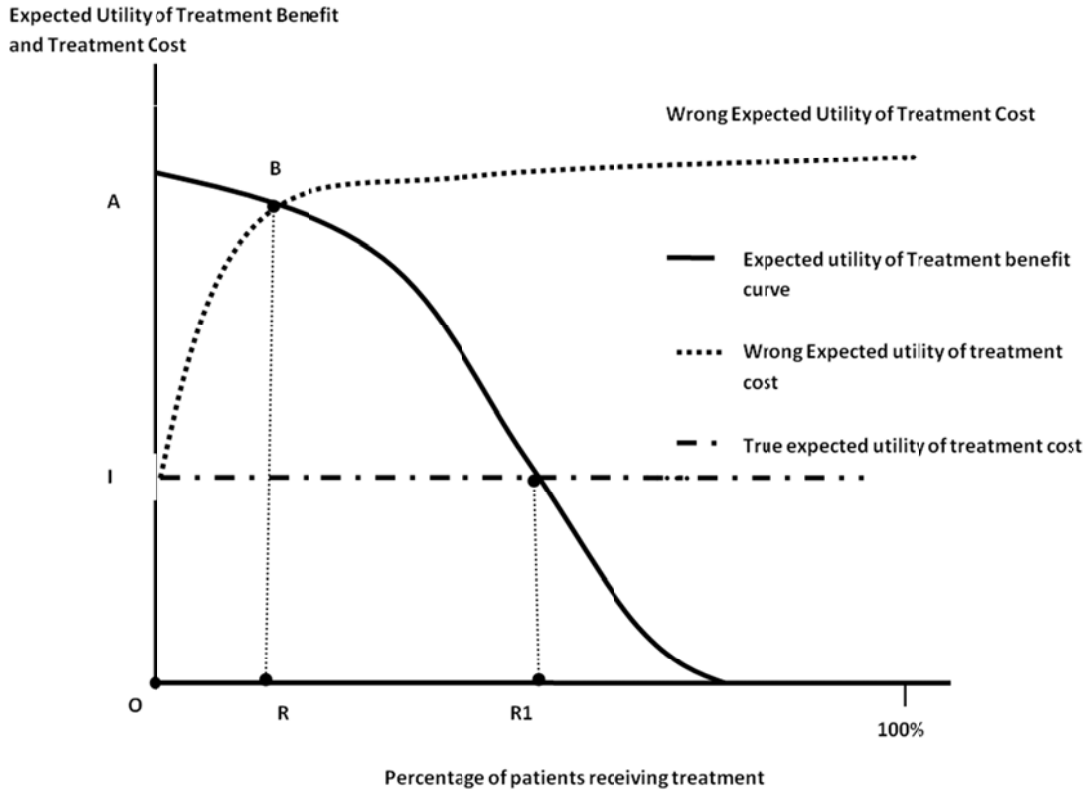


Figure I-3 Graphic Example in Terms of Expected Utility Showing an Incorrect Rate with Incorrect Expectations of Treatment Cost



CHAPTER II THEORETICAL FRAMEWORK

Conceptual Health Production Equation (HPE)

The Health production function has been used as a theoretical construct to illustrate the relationship between health status and a set of inputs, such as medical care utilization, environmental factors and socioeconomic variables (Auster, Leveson, and Sarachek 1969; Contoyannis and Jones 2004; Conway and Kutinova 2006; Jacobs et al. 2004; Koç 2004; Martin, Rice, and Smith 2008; Thornton 2002). Some studies specified treatments as inputs and outcomes as dependent variables in health production functions (Brooks and Fang 2009; Healey et al. 2000; Zethraeus 1998). Based on previous insights, a general conceptual health production equation (HPE) is developed. In this HPE, it is assumed that outcome representing any consequences of treatment is a function of treatment choice, patient clinical factors and socio-demographic factors. The equation is delineated as follows:

$$P(H_{ki})=\beta_{0i} + \beta_{1i}T_i+ \beta_{2i}D_i+ \beta_{3i}Cl_i \quad (2.1)$$

Where $P(H_{ki})$ is the probability of being at health status "k" for patient "i";

T_i is treatment, if patient "i" receives a treatment then T=1, if patient "i" receives alternative treatment then T=0;

D_i represents patient socio-demographic characteristics including age, gender, socioeconomic factors;

Cl_i represents patient clinical characteristics including severity, diagnostic factors, fragility, vulnerability, genetic factors and overall health;

β_{0i} is the probability of being any given health status "k" with the alternative treatment for patients with reference values of factors D_i and Cl_i;

β_{1i} is the change in $P(H_{ki})$ associated with treatment for patient "i";

β_{2i} is the direct change in $P(H_{ki})$ associated with D_i for patient "i";

β_{3i} is the direct change in $P(H_{ki})$ associated with Cl_i for patient "i".

The general HPE model can be applied to studying the relationship between G-CSF and neutropenia-hospitalization risk. In the G-CSF case, $P(H_{ki})$ can be defined as the probability of having neutropenia hospitalization for patient "i". T_i can be specified as a binary variable indicating whether patient "i" receives prophylactic G-CSF. The change in health status associated with a treatment relative to the alternative can be defined as treatment effectiveness (Brooks and Fang 2009). The parameter β_{1i} represents the treatment effectiveness to be estimated. ATT is the average β_{1i} across patients that received G-CSF. LATE is the average β_{1i} across marginal patients, whose treatment choices vary with instruments.

Theoretical Conceptual Model (TCM)

The parameters and concepts in the health production equation (HPE) are useful as they provide a basis for deriving patient expected value of G-CSF treatment relative to the alternative. Based on Hunink's theoretical construct that treatment choices are those with highest expected values (Hunink 2001), a G-CSF treatment choice model can be developed. The treatment choice model is important as it provides a basis for source of confounding, source of potential instrumental variables, justification to support the acceptance of instrumental variables to be useful and interpretation of treatment-effect estimates from various estimators (Angrist 2001; Brooks and Fang 2009; Heckman 2008; Heckman 1985; James J Heckman 2006). Therefore, in the following sections, the ultimate goal is to develop a treatment choice function which incorporates parameters and concepts such as patient socio-demographic and clinical factors.

In a treatment decision making process, because physicians have superior information and knowledge, they can both function as the persons who diagnoses the illness and make treatment plans for patients (Fuchs VR 1978). The physician has been called the "captain of the team" by Fuchs and physicians are able to exert much power on what information they want to transmit to patients (Fuchs VR 1978). Therefore, a variety

of theoretical models have been developed that focus on how physicians influence the health services used by patients (Carlsen and Grytten 1998; Cromwell and Mitchell 1986; Delattre and Dormont 2003; Jostein Grytten, Fredrik Carlsen and Irene Skau 2001; Thomas Rice 1984). As to cancer treatments, many patients accept their oncologist treatment recommendations, while many others patients reject oncologist recommendations mainly because of personal values and experiences (Brock and Wartman 1990; Huijer and van Leeuwen 2000; McKenna 1994). Oncologists state they still respect patient choices even in cases when they did not agree with patient refusals (Huijer and van Leeuwen 2000). Therefore, in this research, we posit that elderly NHL patients on ABC have the autonomy to make G-CSF choices and that their oncologists influence patients' decisions through treatment recommendations. As such our theory is structured in two parts, the first section below describes a model of oncologist G-CSF recommendation and it is then followed by a model of patient G-CSF treatment choice.

A Model of Oncologist G-CSF Recommendation

The model of oncologist G-CSF recommendation is developed based on the theory of utility maximization (Feldman 1981; Torrance, Thomas, and Sackett 1972). Utility is a general way of describing preferences, satisfaction or happiness associated with consequences important to the decision-maker (for example, health outcomes for a given health state) (Drummond 2005; Varian). It is theorized that oncologists make treatment recommendations in a manner to maximize their utility. Treatment recommendations are assumed to affect utility through effects on oncologist goal attainment. In previous theoretical models of physician behavior, physicians are assumed to make treatment recommendations to maximize their utility by balancing the desire to earn more income with the desire to achieve other goals, such as improvement in patient health, more leisure time, as well as esteemed reputations that can be associated with practicing medicine (Brooks 2006; Brown 1996; McGuire and Pauly 1991; Woodward

RS 1984; Zweifel, Peter and Friedrich Breyer 1997). Based on these insights, this study develops an oncologist treatment recommendation model, which theorizes that oncologists' utility (U) is a function of their expectations of patient health (H), their practice income (π), and their professional reputation (P). As G-CSF is usually prescribed with chemotherapy and it can be self-injected by the patient or by a nurse at the doctor's office, a doctor's time spent with this drug is negligible. Therefore, the doctor's leisure time is not taken into account in the oncologist utility function. An oncologist utility function can be denoted as function 2.2:

$$U = U(H, \pi, P; \alpha) \quad (2.2)$$

Where α is a vector of parameters describing the oncologist's preferences that summarize the relative weight or hierarchy of the oncologist's goals. The marginal utility of each goal (H, π, P), is defined as the increase in utility as a result of an extra unit increase of each goal, equals the first derivative of utility with respect to the change of each goal, which can be written as U_H, U_π and U_P. It is assumed that functional relationship U(·) and preference parameter (α) are constrained such that the marginal utilities associated with each oncologist's goal are positive. In other words, holding other goals constant, oncologist utility always increases by increasing achievement of each goal. These assumptions can be denoted as $U_H > 0$, $U_\pi > 0$, and $U_P > 0$ for the goals of expected health, income and reputation, respectively. Moreover, it is further assumed that functional relationship U(·) and the preference parameter (α) are constrained such that the marginal utilities diminish, or the level of increased utility gained from each additional unit of goal attainments decreases with higher initial levels of each goal. The assumption of diminishing marginal utility can be written as the second derivatives of utility to each goal being negative: $U_{HH} < 0$, $U_{\pi\pi} < 0$ and $U_{PP} < 0$. This assumption brings up the notion that no single goal fully dominates an oncologist's preferences. In the spirit of the Becker and Lancaster approaches of consumer choice, oncologist treatment recommendation or

choice is not directly specified in the utility function (Becker 1976; Lancaster 1966). Recommendations affect utility through their effects on the goals in the utility function. The goal functions which incorporate treatment recommendation are developed in the following paragraphs.

The first goal or argument in the utility function (2.2) is oncologist expectation of patient health. It is theorized that oncologist expectation of patient health is a function of expected initial health status and expected G-CSF treatment effectiveness. Expected initial health is theorized to be a function of patient socio-demographic factors (D) and clinical factors (Cl) which are specified in the health production equation (HPE) (2.1). Expected G-CSF treatment effectiveness is theorized to be a function of patient socio-demographic factors (D) and clinical factors (Cl), local oncologist beliefs of G-CSF effectiveness (B), oncologist professional background and treatment experience (J), and information sources available to the oncologist (I).

Previous research has shown large geographical variation in G-CSF treatment rates (Chrischilles et al. 2003). It is possible that in different regions, physicians have different interpolations or extrapolations of G-CSF effectiveness from available RCT evidence to patients unlike those in trials (Brooks and Chrischilles 2007). The geographical variation in G-CSF use may indicate differences in oncologist beliefs about G-CSF treatment effectiveness (Phelps 1997). In the clinical evidence diffusion process, oncologists' information sources (I) may impact their knowledge of RCT evidence and thereby affect their beliefs of treatment effectiveness. Oncologists with different backgrounds and experiences (J) may also have different understandings of RCT evidence and valuation of patient outcomes. Therefore, oncologist expected patient health is derived as the following equation:

$$H = H_0(Cl,D) + \delta(Cl,D,J,I,B)\cdot R \quad (2.3)$$

Where: H is oncologist expectation of patient health;

H_0 is the oncologist expectation of patient health without G-CSF;

δ is the oncologist expectation of patient health improvement from G-CSF;

R is an indicator of whether the oncologist recommends G-CSF;

B is local average beliefs of G-CSF treatment effectiveness;

D represents patient socio-demographic characteristics including age, gender, socioeconomic factors;

Cl represents patient clinical characteristics including severity, diagnostic factors, fragility, genetic factors and overall health;

J is oncologist professional background and treatment experience;

I is information sources available to the oncologist.

The second argument in the utility function (2.2) is oncologist expected income during the first cycle of chemotherapy. It is theorized that the expected income is a function of oncologist expected income by treating patients with first cycle chemotherapy and expected additional income by prescribing G-CSF. It has been reported that the major portion of oncologist income comes from prescribing chemotherapy (Benson 2001; Berenson 2007). Income from chemotherapy is assumed to be the product of income from treating one patient with chemotherapy and the number of patients who received chemotherapy from the oncologist. Oncologist income of first cycle chemotherapy is defined as the spread between reimbursement rates for chemotherapy and costs associated with drug purchase price and administration procedures (Jacobson et al. 2006). If the drug purchase price and cost of administration procedures are the same across oncologists, oncologist income from chemotherapy will vary with reimbursement rates (Jacobson et al. 2006). As to Medicare reimbursement, the rates for chemotherapy vary with the policies of local Medicare claim-paying agents or fiscal carriers. These agents can decide whether to make payments separately for items and services or to bundle items and services together and make a single payment (Bailes 1995). Given local carrier freedom to choose bundling or not, chemotherapy reimbursements can differ across fiscal

carriers. Medicare fiscal carriers are Medicare local claim-paying agents processing Part B claims (Cowan 1996). The variation in Medicare fiscal carrier policies on chemotherapy reimbursement may result in higher chemotherapy-associated reimbursement rates for some physicians more than others. The other component in income from chemotherapy is number of patients to whom the oncologist prescribes chemotherapy, which is theorized to be a function of local oncologist supply. If the local supply of oncologists is higher, it is assumed that the number of patients to whom an oncologist can prescribe chemotherapy is smaller.

Additional income by prescribing G-CSF is theorized in the oncologist expected income function. An oncologist would gain income ranging from $330 to $566 by providing an 11-day course of G-CSF (Adamson RT 2005). Oncologist expected income from G-CSF is theorized to be a function of both income from G-CSF before the physician makes the next G-CSF recommendation and income by prescribing G-CSF to the additional patient. Given the assumptions and information on oncologist income, expected income based on the oncologist's G-CSF recommendation for the oncologist's next chemotherapy patient is represented by the following equation:

$$\pi = \mu \bullet (N + R) + \gamma (F) \bullet K(S) \qquad (2.4)$$

Where: π is oncologist expected practice income;

μ is the additional expected income received by the oncologist by prescribing G- CSF;

N is the number of physician's patients who had G-CSF before the physician makes the next G-CSF recommendation;

R is an indicator of whether the oncologist recommends G-CSF to the next patient;

γ is expected income received by oncologist from treating a patient with chemotherapy if a patient is not treated with G-CSF;

F represents Medicare local carriers' reimbursement policies;

K is the number of patients to whom the oncologist prescribes chemotherapy;

S is oncologist supply defined as number of oncologists seen by each patient in a local area.

The third argument in the oncologist utility function is expected oncologist reputation. A recommendation of G-CSF to patients is expected to increase patient health (if δ is positive) and increase physician income (if μ is positive), unless there is some downside or cost that limits oncologist desire to pursue more income or improvement in patient health, the oncologist would prescribe G-CSF to an infinite extent. The third argument includes the speculation that treatment recommendation compliance with other oncologists in a practice area will assist in upholding one's professional standing and increase reputation. If an oncologist induces patient demand for G-CSF or recommends G-CSF against oncologists' best interpretation of G-CSF effectiveness in the practice area, the oncologist is assumed to lose reputation and suffer disutility by recommending that treatment (McGuire and Pauly 1991; Park 2004).

It is theorized that oncologist expected reputation (P) is a function of oncologist's own G-CSF treatment share (ρ), defined as the number of patients treated with G-CSF among all the oncologist's patients on chemotherapy, and local average beliefs of G-CSF treatment effectiveness (Brooks 2006; Park 2004). It is assumed that local average treatment rate is an indicator of region-specific oncologist belief of G-CSF effectiveness. If the oncologist's own treatment rate deviates from the local area treatment rate, the oncologist becomes an under-prescriber or over-prescriber and would lose reputation. It is assumed $P_\rho > 0$ and $P_{\rho\rho} < 0$ until P reaches maximum at the local area treatment rate. After P reaches maximum, it is assumed that $P_\rho < 0$ and $P_{\rho\rho} > 0$. Given these assumptions, an oncologist expected reputation is derived as the following equation:

$P = P(\rho(R), B)$ (2.5)

Where: P is oncologist expected reputation;

ρ is the proportion of patients treated by the oncologist, and it equals $(N + R) / K$;

R is an indicator of whether the oncologist recommends G-CSF;

B is local average beliefs of G-CSF treatment effectiveness.

By substituting the equations of 2.3-2.5 into oncologist utility function of 2.2, a fully specified utility function of recommending G-CSF by oncologist can be written. Following standard discrete choice theory (Ben-Akiva, M., Lerman, S.R. 1985), it is assumed that an oncologist will choose to recommend G-CSF if the oncologist's utility of recommending G-CSF is greater than utility of not recommending G-CSF. The expected net utility (expected utility associated with recommending G-CSF relative to the alternative) can be derived by subtracting oncologist utility when recommending G-CSF from oncologist utility when not recommending G-CSF as function (2.6):

$$NU = U(H_0(Cl,D) + \delta(Cl,D,J,I,B),\ \mu \bullet (N+1) + \gamma(F) \bullet K(S), P((N+1)/K, B); \alpha) - U(H_0(Cl,D), \mu \bullet (N) + \gamma(F) \bullet K(S), P(N/K, B); \alpha)$$

$$= NU(D, Cl, J, I, B, F, S, N, \mu, \gamma, \alpha) \quad (2.6)$$

If NU is greater than zero, the oncologist will recommend G-CSF. If NU is less than zero, the oncologist will choose not to recommend G-CSF. When oncologists make recommendations, they must balance between alternative goals. An oncologist may gain more utility by recommending treatment through the increase in expected income and improvement in patient health, while recommending treatment may also yield disutility to the oncologist if the oncologist's prescribing behavior deviates from the local norm of using G-CSF. The influence of goals in the oncologist's utility function vary with preference parameters (α) and initial level of each goal before a recommendation is made. For example, the recommendation decision to use G-CSF with expected little treatment benefit in a patient which yields substantial income to an oncologist may vary with the initial level of oncologist income.

Given function (2.6), the probability function that i^{th} oncologist chooses to recommend G-CSF can be developed as function 2.7:

$$P(R_i = 1) = P(NU_i > 0) = P(NU_i(D, Cl, J, I, B, F, S, N, \mu, \gamma, \alpha) > 0) \quad (2.7)$$

From probability function 2.7, the oncologist's treatment recommendation function can be derived as function 2.8:

$$R = f(D, Cl, J, I, B, F, S, N, \mu, \gamma, \alpha) \quad (2.8)$$

R is theorized to be affected by patient clinical characteristics (Cl), patient socio-demographic characteristics (D), oncologist professional background (J), information sources available to the oncologist (I), local average belief of treatment effectiveness (B), Medicare local reimbursement policies (F), number of oncologists seen by each patient (S), number of patients who already got G-CSF (N), additional revenue for oncologist by prescribing G-CSF (μ), the reimbursement of first cycle chemotherapy (γ) and preference parameters (α) which relate the change in each oncologist goal to the change in oncologist utility.

Carrier-related reimbursement for first cycle chemotherapy (γ) is theorized to affect oncologist treatment recommendation through its effect on oncologist expected income function. All else being equal, oncologists practicing in areas where Medicare fiscal carriers provide lower average chemotherapy reimbursement will have lower initial incomes. Under the assumption of diminishing marginal utility, with higher initial level of income, the level of increased utility gained from each additional dollar decreases. Compared to oncologists practicing in areas with higher chemotherapy reimbursement, marginal utility of income would be higher for oncologists in areas with lower chemotherapy reimbursement and these oncologists will have more desire to increase their income by means of prescribing G-CSF.

Oncologist supply in a local area (S) is theorized to affect oncologist treatment recommendation through its effect on oncologist income function. Oncologists in areas with a higher oncologist supply have fewer patients, all else being equal, and thus have lower initial income. As a result, marginal utility of income for oncologists in these areas

will be higher. Therefore, oncologists in areas with higher oncologist supply will be more likely to recommend G-CSF.

The average belief of treatment effectiveness of oncologists in areas where a certain treatment pattern holds (B) is theorized to affect an oncologist's treatment recommendation through its effect on oncologist's expected treatment benefit gain from G-CSF and through the relationship between treatment and expected reputation. It is theorized that in areas where oncologists generally have high beliefs of G-CSF treatment effectiveness, the treatment rate will be higher. For individual oncologists in these areas, they will have a higher regard for G-CSF and be more likely to recommend treatment to gain utility. In addition, it is less likely that respect for oncologists in these areas will be reduced when they recommend G-CSF to a large percentage of their patients.

A Model of Patient G-CSF Treatment Choice

Historically, the use of G-CSF requires considerable time and financial commitment from patients. Medicare patients have to pay more than five hundred dollars out-of-pocket and travel daily up to eleven days to receive treatment. This is distinct from cases where intravenous therapy can be given to patients without their consent. There are situations when patients cede all of the decision-making responsibility and these situations often arise in medical emergencies. For example, an unconscious patient is in dire danger or the patient is unable to consent (JDMD Inc. 2009). Except for these cases, treatments in most situations surely do require patient consent, even though patients usually vary in the degree of decision-making autonomy they want to exercise (Degner and Sloan 1992). G-CSF use is the case where patient consent is required and patient decision-making responsibility is needed because patients under treatment are usually conscious and have to commit to daily injections, travel and co-payments. Many elderly cancer patients prefer that their physicians provide information about their clinical conditions and recommend treatment options for plan management. The patients then

choose to accept or reject the recommendations (Degner and Sloan 1992; Huijer and van Leeuwen 2000; Lansdown, Martin, and Fallowfield 2008). In this study, we theorize oncologist treatment recommendation influences patient belief of treatment effectiveness and a patient makes the final G-CSF treatment decision. The choice model can be developed from patient utility maximization theory. We assume that a patient utility is a function of expected health (E) and consumption of other goods or services (G):

$V = V(E, G; \theta)$ (2.9)

Where: θ is a vector of preference parameters which relate the changes in each patient goal (E, G) to the change in his/her utility. It is assumed that higher health expectations and more consumption of other goods or services increase patient utility ($V_E > 0$, $V_G > 0$), and that the increase in utility from additional attainment of these goals diminishes ($V_{EE} < 0$, $V_{GG} < 0$). Equations of patient's expected health (E) and consumption of other goods or services (G) are developed in the following paragraphs.

The first argument or goal in the patient utility function (2.9) is patient expected health. It is theorized that patient expectation of health is a function of expected initial health and expected G-CSF treatment effectiveness relative to the alternative treatment option. As specified in the health production function (2.1), socio-demographic factors (D) and clinical factors (Cl) are theorized to affect patient expected initial health. Patient expected G-CSF treatment effectiveness is assumed to be influenced by socio-demographic and clinical factors, oncologist treatment recommendation and information obtained by patients from the internet or other media before seeing oncologists (Lansdown, Martin, and Fallowfield 2008). Given these assumptions, a patient expected health is derived as the following equation:

$E = E_0(D,Cl) + \eta(D, Cl, L, R) \cdot T$ (2.10)

Where: $R = f(D, Cl, J, I, B, F, S, N, \mu, \gamma, \alpha)$ as seen in equation (2.8)

E is patient expectation of patient health;

E_0 is the patient expectation of health without G-CSF;

η is the patient expectation of health change from G-CSF;

T is an indicator of whether patient chooses G-CSF;

B is local average beliefs of G-CSF treatment effectiveness;

R is an indicator of whether the oncologist recommends G-CSF;

L is information about G-CSF available to patient before seeing the oncologist;

D represents patient socio-demographic characteristics including age, gender, socioeconomic factors;

Cl represents patient clinical characteristics including severity, diagnostic factors, fragility, genetic factors and overall health;

J is oncologist professional background and treatment experience;

I is information sources available to the oncologist;

F is Medicare local reimbursement policies;

S is oncologist supply defined as number of oncologists seen by each patient in a local area.

N is number of patients who already got G-CSF;

μ is additional revenue for oncologist by prescribing G-CSF;

γ is the reimbursement of first cycle chemotherapy;

α is preference parameters which relate the change in each oncologist goal to the change in oncologist utility.

The second argument in patient utility function is patient consumption of other goods or services. Patient expenses related to treatment and consumption of other goods and services are constrained by the level of resources available to the patient, such as income, wealth or social capital. Patient expenses associated with G-CSF treatment include co-payment for G-CSF and access-related costs to receive G-CSF. As presented in the clinical balance sheet (Table I-1), Medicare patients need to pay $534 for 11 days' supply of G-CSF (Adamson RT 2005). Patients have to travel daily up to 14 days to the treatment center to receive G-CSF and may also have to take time off from work

(Haithcox et al. 2003a). Patient consumption of other goods or services is a function of prices and quantities of other goods or services available. An equation containing patient expected consumption of other goods or services can be derived as follows:

$Q = (p_T + p_A) \cdot T + p_G \cdot G$ (2.11)

Where: Q is the level of resources available to the patient, such as income, wealth, or social capital;

p_T is the co-payment by patient for receiving G-CSF;

p_A is the patient access-related costs to receive G-CSF;

T is an indicator of whether the patient chooses G-CSF;

p_G is a composite representing price of other goods or services available for patient consumption;

G represents a composite of other goods or services available to the patient.

By substituting the expected health equation (2.10) into the patient's utility function (2.9), we are able to solve expected utility in terms of patient treatment choice and a composite of other goods (G). A patient utility function associated with treatment choice can be revised as function (2.12):

$V(T) = V(E_0(D,Cl) + \eta(D, Cl, L, R(D, Cl, J, I, B, F, S, N, \mu, \gamma, \alpha)) \cdot T, G; \theta)$ (2.12)

The expected net utility from being treated with G-CSF can be derived by subtracting patient's utility level without using G-CSF from patient's utility level given G-CSF. The net expected utility level of G-CSF use can be written as function 2.13:

$NV = V(E_0(D,Cl) + \eta(D, Cl, L, R(D, Cl, J, I, B, F, S, N, \mu, \gamma, \alpha)), (Q-p_T-p_A)/p_x; \theta) - V(E_0(D,Cl), Q/p_X; \theta)$ (2.13)

Given patient's net utility of receiving G-CSF relative to the alternative, the probability function that i^{th} patient chooses to be treated with G-CSF can be developed as function (2.14):

$P(T_i = 1) = P(NV_i > 0)$

$= P(NV_i(D,Cl,J,I,L,B,F,S,N, \mu, \gamma, \alpha, p_T,p_A,p_x,\theta)>0)$ (2.14)

A patient will choose G-CSF if expected net utility associated with G-CSF treatment relative to the alternative is positive. From probability function (2.14), a patient's G-CSF treatment decision function can be derived as function (2.15):

$$T = f(D,Cl,J,I,L,B,F,S,N, \mu, \gamma, \alpha, p_T,p_A,p_x,\theta) \quad (2.15)$$

Patient treatment choice of G-CSF (T) is a function of patient factors and factors from oncologist recommendation. Patient factors include patient clinical (Cl) and socio-demographic (D) characteristics, information of G-CSF available to the patient before seeing the oncologist (L), co-payment of prophylactic G-CSF by the patient (p_T), access-related cost of getting G-CSF (p_A), a composite representing prices of other goods or services available for consumption (p_x) and preference parameters which relate the changes in each patient's goal to the change in patient's utility (μ). Factors from oncologist recommendation include oncologist's professional background and cancer treatment experience (J), information sources available to the oncologist (I), local average belief of treatment effectiveness by oncologists (B), Medicare local reimbursement policies (F), number of physician's patients who had G-CSF before the physician makes the next G-CSF recommendation (N), per capita number of oncologists in an area (S), additional revenue received by the oncologist from G-CSF (μ), reimbursement for first cycle chemotherapy (γ), and preference parameters which relate the changes in each oncologist's goal to the change in oncologist's utility (α).

As shown in patient treatment choice function (2.15), elements in the patient's budget constraints are factors impacting the patient's choice of using G-CSF. Given the limited level of resources available to some patients, they would be able to consume fewer other goods or services if they choose G-CSF. For patients who live far away from an oncologist, travel cost may be high and constitute a problem for access to treatments. Thus, patients who have long travel distances from their residences place to an oncologist's practice site will be less likely to choose the treatment.

A Linear Treatment-Outcome Model with Interaction Terms

The health production function model with interaction terms developed by Brooks and Fang not only illustrates the treatment-cure relationship but also incorporates the notion of treatment-effect heterogeneity (Brooks and Fang 2009). Heterogeneity in treatment effectiveness is introduced in the linear treatment-outcome model by interacting treatment with additional factors. The model provided by Brooks and Fang is:

$$P(H_{ki}) = \beta_0 + (\beta_{10} + \beta_{11} \cdot X_{1i} + \beta_{12} \cdot X_{2i}) \cdot T_i + \beta_2 \cdot X_{2i} + \beta_3 \cdot X_{3i} + \beta_5 \cdot X_{5i} \quad (2.16)$$

Where $P(H_{ki})$ is the probability of being at health status "k" for patient "i";

T_i is treatment, if patient "i" receives a treatment then T=1, if patient "i" receives alternative treatment then T=0;

X_{1i} is the value for patient "i" of a factor that affects treatment effectiveness but does not directly affect the health status of the patient regardless of treatment;

X_{2i} is the value for patient "i" of a factor that directly affects treatment effectiveness and directly affects the health status of the patient regardless of treatment;

X_{3i} is the value for patient "i" of a factor that had no effect on treatment effectiveness, but directly affects the health status of the patient and the treatment value relative to the alternative;

X_{5i} is the value for patient "i" of a factor that directly affects patient health status, but has no effect on either treatment effectiveness nor the value of the treatment relative to the alternative;

β_0 is the probability of being at any given health status with the alternative treatment for patients with reference values of $X_{2i,}$ X_{3i} and $X_{5i;}$

$(\beta_{10} + \beta_{11} \cdot X_{1i} + \beta_{12} \cdot X_{2i})$ is the change in $P(H_{kii})$ associated with treatment for patient "i" conditional on X_{1i} and $X_{2i;}$

β_2 is the direct change in $P(H_{ki})$ associated with X_{2i} for patient "i";

β_3 is the direct change in $P(H_{ki})$ associated with X_{3i} for patient "i";

β_5 is the direct change in $P(H_{ki})$ associated with X_{5i} for patient "i".

As seen in the model, the interaction term in the general model ($(\beta_{10} + \beta_{11} \cdot X_{1i} + \beta_{12} \cdot X_{2i}) \cdot T_i$) incorporates the concept of treatment-effect heterogeneity and illustrates that actual treatment effectiveness varies with factors within X_1 and X_2. To justify whether treatment effects of G-CSF for NHL elderly patients on ABC are heterogeneous, a Pubmed search of the available clinical evidence has been conducted. All together, six clinical trials investigating primary G-CSF prophylaxis effects among elderly NHL patients on anthracycline-based chemotherapy were identified. The six clinical trials have been summarized in Table I-2 in terms of differences in NHL types, specific ABC regimens, patient inclusion and exclusion criteria, prophylactic G-CSF effects and patient age.

Results from these clinical trials may suggest that G-CSF effectiveness among elderly NHL patients on ABC can vary. Patient characteristics could be the source of variation in treatment-effect. For instance, patients enrolled in trials differ according to age, cancer stage, aggressiveness of NHL, performance status and chronic diseases (Bertini et al. 1996; Doorduijn et al. 2003; Osby, Hagberg, and Bjorkholm 1999; Osby et al. 2003; Pettengell et al. 1992; Zinzani et al. 1999). Previous research suggests that genetic differences among patients might be another cause of variation in treatment effectiveness (Goldstein et al. 2007). Based on the available evidence, it may be reasonable to hypothesize that actual prophylactic G-CSF treatment-effects are heterogeneous across NHL elderly patients on ABC by various underlying patient factors and these factors are within X_1 and X_2. However, further research is needed to confirm the source of treatment-effect heterogeneity and whether physicians properly respond to the heterogeneous treatment effect.

A separate literature search was conducted to explore the direct link between risk factors and neutropenia regardless of G-CSF treatment. The factors identified include patient socio-demographic and clinical characteristics. According to previous studies, patient socio-demographic characteristics such as age, gender, race and ethnic groups are

associated with neutropenia risk (Chrischilles and Brooks 2002; D'Angelo 2009; Gary H. Lyman, David J. Delgado 2003; Gmez et al. 1998; Lyman et al. 2003; Lyman, Kuderer, and Djulbegovic 2002; Morrison et al. 2001). Age is a significant and independent predictor for the development of febrile neutropenia in patients treated with chemotherapy (Chrischilles et al. 2002; Gary H. Lyman, David J. Delgado 2003; Gmez et al. 1998; Lyman et al. 2003; Morrison et al. 2001). Morrison et al analyzed cases involving patients with intermediate and high grade NHL who received CHOP. The researchers stated that patients older than 65 years old had a higher rate of neutropenia hospitalization than patients younger than 65 (28% vs. 16%; $P<0.05$) (Morrison et al. 2001). In the study by Chrischilles et al., older patients were found to have higher incidence of febrile neutropenia hospitalization compared to younger patients (27.6% vs. 16.0%; $P<0.001$) (Chrischilles et al. 2002). Gomez et al. further looked at differences in treatment-related toxicity between two age subgroups (61-69 years) and (>=70 years). Their results showed that neutropenia occurred in 42% of the older subgroup while only 8% of younger patients experienced neutropenia (Gmez et al. 1998). Gender is another demographic factor associated with neutropenia hospitalization. Females were found to be more likely to be hospitalized with febrile neutropenia than males (Lyman, Kuderer, and Djulbegovic 2002). A recent study also found patient race and ethnic group are exposed to various levels of neutropenia risk (D'Angelo 2009).

In addition, clinical factors have been studied widely for their associations with neutropenia risk. Poor performance status is an important risk factor for severe and febrile neutropenia (Lyman, Lyman, and Agboola 2005). Patients with renal and heart diseases had higher risk of contracting febrile neutropenia (Chen-Hardee et al. 2006; Chrischilles et al. 2002; Lyman et al. 2003; Morrison et al. 2001; Scott 2002). Other comorbidities, such as liver disease, anemia, hypertension, chronic obstructive pulmonary disease, pneumonia, prior fungal infection, and sepsis also constituted risk factors associated with febrile neutropenia hospitalization (Gonzalez-Barca et al. 1999;

Klastersky et al. 2000; Kuderer NM, Cosler L, Crawford J 2002). Patients with different histology types are at various risk levels of developing neutropenia. For example, patients with diffuse large cell lymphoma have a higher risk of neutropenia hospitalization compared to patients with histology types other than follicular or diffuse large cell lymphoma (Chen-Hardee et al. 2006). In addition, other clinical factors including absolute neutrophil count (ANC) during the nutrophil nadir in cycle 1 of chemotherapy, an albumin concentration less than or equal to 3.5 g/dL, an above-normal lactate dhydrogenase concentration, bone marrow involvement, lower body surface area, baselin hemoglobin level less than 12 g/dL, baseline absolute neutrophil count less than $1500/mm^3$, serum LDH >1 x normal, a lymphocyte count less or equal to 700 x 106/l at day 5 after chemo and high temperature at admission were found to be associated with neutropenia (Blay et al. 1996; Cappozzo 2004; Chrischilles and Brooks 2002; Gary H. Lyman, David J. Delgado 2003; Intragumtornchai et al. 2000; Lyman et al. 2003; Morrison et al. 2001; Scott 2002; Scott et al. 2003; Hann et al. 1997; Klaassen et al. 2000; Lyman, Lyman, and Agboola 2005; Viscoli et al. 1994).

As seen in the health production equation (HPE), concepts of patient socio-demographic and clinical characteristics are theorized. The HPE can be connected to this Brooks and Gang model by categorizing each of these concepts into X factors. Some clinical and demographic factors could be X_1. An example of an X_1 factor could be generic characteristics which impact how patients respond to G-CSF but do not directly influence outcomes regardless of treatment. It is likely that genetic polymorphism makes G-CSF more active in some patients than others. Some clinical (Cl_i) or demographic (D_i) characteristics could be X_2. Examples of X_2 include performance status representing patient fragility to chemotherapy and baseline ANC level. Some socio-demographic characteristics could be X_3. An example of X_3 could be patient socioeconomic status. Patients who have higher income levels may have a higher baseline health status and value a cure more. Some other demographic and clinical characteristics may be

categorized as X_5, such as a patient's pre-existing overall health condition. There is another set of concepts or factors, which are theorized in the patient treatment choice model but are not theorized in the HPE. In Brooks and Gang's model, these factors are theorized as X_4. X_4 factors include patient treatment price, access costs, local area oncologist practice belief, and local oncologist market supply, etc. According to instrumental variable's two properties, X_4 factors could be considered as source of instrumental variable.

Empirical Implication

Connect Conceptual Framework to Empirical Model

Given theoretical constructs created in the previous sections, these concepts need to be operationalized and fit into an empirical model. An empirical model is the basis of making inferences on the relationship between treatment (T) and outcome P(H) from estimators (risk-adjustment estimator and instrumental-variable estimator). Table II-1 lists variables for each model concepts specified. Column 1 and 2 in this table describe the operationalization of key concepts in the model.

As seen in this table, it is difficult to differentiate which variables belong to which X factors. Even though some available clinical trials of G-CSF may indicate heterogeneous treatment effect, empirically there is not sufficient evidence to support this heterogeneity. The argument that treatment effect could be homogeneous may be correct. For instance, there are no compelling cases as to whether there are variables belonging to X_1 or X_2 factors. Performance status could be either an X_2 or X_5 factor.

Description of Possible Measured and Unmeasured Factors and Discussion of How Estimators Work

To answer the "Which rate is right" question, we need to estimate treatment effectiveness for patients on the extensive margin. Given the HPE theorized previously,

the purpose of the present study is to estimate β_{1i} (treatment parameter in HPE) using data from actual cases. Making inferences of β_{1i} from different estimators needs to be dependent on whether factors within X can be measured or available to researchers (Brooks and Chrischilles 2007; Brooks and Fang 2009). Relying on SEER-Medicare claims linked database used for this study, we collected information on factors within X_1, X_2, X_3, X_4 and X_5. Some of them can be easily measured, such as G-CSF treatment choice and neutropenia hospitalization, while others are not available or are unmeasurable, such as most laboratory test results. Table II-1 provides a list of variables in the empirical model and indicates whether they are measured or unmeasured using SEER-Medicare claims data.

Given the description of possible measured and unmeasured factors, a discussion on how estimators work in this environment is needed. Since the Risk Adjustment estimator and the Instrumental Variable estimator can both be used to estimate this β_{1i}, our discussion will center on how estimators differ to make parameter inferences in the contexts of 1) whether there is treatment-effect heterogeneity and 2) whether unmeasured factors are truly unmeasured confounders (unmeasured factors associated with both treatment choice and outcome).

In the first scenario, suppose only factors within X_4 and X_5 are unmeasured. For example, the information about G-CSF available to a patient before seeing the oncologist is missing in the dataset. As these unmeasured factors are not truly unmeasured confounders (factors within X_4 are only associated with treatment choice and factors within X_5 are only related with outcome), the failure to measure factors within X_4 and X_5 only increases the impreciseness of parameter estimates and does not affect the interpretation of estimates. It would be easy and straightforward to interpret parameter estimates of ATT and LATE in this scenario.

In the second scenario, factors within X_1 are unmeasured, no factors within X_2 are theorized and all factors within X_3 are measured. The unmeasured factors within X_1 are

not truly unmeasured confounders because these factors are only associated with patient treatment choice via treatment response. Therefore, in this scenario, estimate of G-CSF treatment effect generated from risk-adjustment estimators such as multivariate regression methods would constitute an unbiased estimate of average treatment effects on the treated patients (ATT) (Heckman and Vytlacil 2000; James J Heckman 2006). The estimate answers policy questions such as "whether a given treatment should be shut down or retained" (Basu et al. 2007). However, caution should be used when making inferences of β_{1i}. The estimate of β_{1i} only reflects the distribution of X_1 factors across treated patients within the study sample. It would be risky to generalize this estimate to other patient populations with a different X_1 distribution. If instrument variables could be justified from factors within X_4, instrumental-variable estimator yields a consistent estimate of local average treatment effect (LATE) in the marginal patients whose treatment choices vary with X_4 (Harris and Remler 1998; Imbens GW 1994; McClellan, McNeil, and Newhouse 1994). As factors within X_1 are theorized, it is assumed the treatment effect is heterogeneous across patients. If treatment choices reflect "sorting on the gain" (James J Heckman 2006) meaning that doctors react to the treatment-effect heterogeneity and G-CSF cost is assumed to be constant across patients in the sample, true ATT should be greater than true LATE. ATT represents average treatment effect across all patients whose treatment benefit is high enough that each patient's net utility/value of G-CSF relative to the alternative is positive, while LATE represents average treatment effect in patients whose treatment benefit is small enough that patient net utility/value of G-CSF relative to the alternative is dependent on the factors within X_4.

In the third scenario, factors within X_3 are theorized but unmeasured while X_1 or X_2 factors are not theorized by assuming a homogeneous treatment effect (treatment effect is constant across all patients). As treatment effect is homogeneous across patients, true LATE equals true ATT. The unmeasured factors within X_3 are unmeasured confounders which affect patient treatment choice and relate to outcome variable directly.

RA estimators such as multivariate regression methods would yield a biased estimate of ATT. If instrument variables could be justified from factors within X_4, instrumental-variable estimator yields a consistent estimate of LATE.

In the fourth scenario, factors within X_3 are measured, factors within X_1 are not theorized, factors within X_2 are theorized but unmeasured, and unmeasured factors within X_4 provide a stochastic variation for the net utility associated with G-CSF treatment relative to the alternative. Unmeasured factors within X_2 are considered unmeasured confounders as they both affect patient response to G-CSF treatment and risk of neutropenia hospitalization. The problem of unmeasured confounding exists in this scenario. One of the most important assumptions of risk-adjustment estimators such as multivariate regressions is that error terms in the regression are uncorrelated with the independent variables is violated. As a result, a parameter estimate from a risk-adjustment estimator will be a biased estimate of ATT. For example, if it is believed by providers that patients with poorer performance status are expected to get more benefit from NH risk-reduction than patients with better performance status and poorer performance status patients, if all other factors are equal, are more likely to develop severe neutropenia regardless of G-CSF treatment. Performance status would be an X_2 factor. If performance status is unmeasured, the estimate of G-CSF benefit to reduce NH using risk adjustment estimator would be a biased low estimate of ATT and should be interpreted as a lower-bound estimate of true G-CSF treatment effect to reduce NH among patients that received G-CSF. In contrast, an instrument variable estimator which exploits natural experiment in treatment choice yields a consistent estimate of LATE for the subset of patients treatment choices varied with measured factors within X_4 (Harris and Remler 1998; Imbens GW 1994; McClellan, McNeil, and Newhouse 1994). In this scenario where G-CSF treatment effect is heterogeneous and unmeasured confounders exist, caution should be exercised when interpreting estimates from RA estimators and IV estimators. These two estimators are different in two ways 1) the estimators yield

estimates of distinct treatment effect concepts and 2) estimate of ATT would be biased while estimate of LATE would be consistent (Brooks and Chrischilles 2007; Brooks and Fang 2009).

All of the above scenarios may fit into this research of G-CSF. Each X factor is assumed to be measured or unmeasured in various scenarios. As there is no compelling case to indicate which factors are X_1 or X_2, both scenarios with homogeneous and heterogeneous G-CSF treatment effects are discussed.

Table II-1 List of Variables in the Patient G-CSF Treatment Choice and Outcome Model

Model Concept Specified	Key Concept Measures	Measured (Yes) / Not Measured (No) by SEER-Medicare Claims Databse
Patient's clinical Characteristics (factors possibly within X_1, X_2, X_3 and X_5)	Chemotherapy regimen types	Yes
	Grade at diagnosis	Yes
	Node at diagnosis	Yes
	Stage at diagnosis	Yes
	Comorbidities	Yes
	Histology	Yes
	Year of Diagnosis	Yes
	Radiotherapy	Yes
	Heart disease	Yes
	Anemia	Yes
	Renal disease	Yes
	Performance status	No
	Nutritional status	No
	Baseline white blood cell counts	No
	Absolute neutrophil count	No
	Albumin concentration	No
	Lactate dhydrogenase concentration	No
	Bone marrow involvement	No
	Body surface area	No
	Hemoglobin level	No
	Serum LDH	No
	Lymphocyte count	No
	Genetic Characteristics	No
socio- demographic characteristics (factors possibly within X_1, X_2, X_3 and X_5)	Age	Yes

Table II-1 Continued

	Gender	Yes
	Race	Yes
	Residence SEER Site	Yes
	Area socioeconomic level	Yes
	Total wealth of the patient	No
	oncologist's professional background and cancer treatment experience	No
I: information sources available to the oncologist	Conferences oncologists attend, journals they read, communication with other oncologists	No
L: information about G-CSF available to patient before seeing the oncologist	Advertisement or internet patients exposed to, experiences heard from other patients	No
B: local average beliefs of G-CSF treatment effectiveness	Area treatment rate	Yes
F: Medicare local reimbursement policies	Medicare Part B Fiscal carriers	Yes
γ: income received by oncologist from treating a patient with first cycle chemotherapy if a patient is not treated with G-CSF	Average chemotherapy reimbursement for first cycle chemo	Yes
S: oncologist supply in the local area	Number of oncologists seen by each patient in an area	Yes
μ: the additional income received by the oncologist from G-CSF	G-CSF reimbursement for oncologist	Yes
N: number of patients on chemotherapy who have already been treated with G-CSF by the oncologist in the first cycle of chemotherapy	number of patients on chemotherapy who have already been treated with G-CSF by the oncologist in the first cycle of chemotherapy	No

Table II-1 Continued

K: number of patients to whom the oncologist prescribes chemotherapy	number of patients to whom the oncologist prescribes chemotherapy	No
p_T: the co-payment of prophylactic G-CSF by the patient	Patient's co-payment for a cycle of G-CSF	Yes
p_A: access-related for patient to get prophylactic G-CSF	Patient distance to the nearest oncologist	Yes
p_G: a composite representing prices of other goods or services available for consumption	Prices of other goods or services available for consumption	No

CHAPTER III METHODOLOGY

Research Hypothesis

The objective of this research is to estimate G-CSF effectiveness for patients on the extensive margin, whose treatment decisions are most likely to be affected by proposed policy to change the treatment rate. The central hypothesis is that the 100% treatment rate recommended by ASCO guidelines is the right rate and that additional G-CSF treatment benefits, namely the reduction of FN incidence, would be available if current rates were increased. Our rationale for this study is that its successful completion would provide policy-makers with additional information to answer the "right rate" question in the G-CSF case. Evidence provided in this research will also assist in the design of proper policies in order to modify the treatment rate. We propose the following two specific aims along with their hypotheses:

Specific Aim #1:

Estimate effectiveness of prophylactic G-CSF for elderly NHL patients receiving anthracycline-based chemotherapy on the extensive margin.

Our working hypothesis is that by using the instrumental variable (IV) method we would identify substantial treatment benefits available for patients on the extensive margin, who are defined as the set of patients who would be the first to receive G-CSF if the G-CSF treatment rate is expanded. Several factors are described in the treatment choice framework which could be potential IV candidates: 1) oncologist reimbursement rate for the first cycle of chemotherapy; 2) per capita number of oncologists in an area; 3) patient travel distance to the nearest oncologist; 4) G-CSF treatment in an area which is relatively self-contained with respect to provision of oncology care.

Specific Aim #2:

Discuss how the estimates of G-CSF effectiveness found by Specific Aim #1 help to answer Wennberg's "which rate is right" question in different scenarios.

Our working hypothesis is that the "right rate" needs to be determined in different scenarios and from different perspectives. The discussion is dependent on the comparison of IV estimates of treatment effect with RA estimates and RCT results. It is hypothesized three possible IV estimates may be generated from this research. The estimates could be minimal, moderate and substantial, on a scale from zero benefit to significant benefit close to RCT estimates. "Which rate is right" could be inferred in each of the three scenarios.

At the completion of this project, it is our expectation that our findings will be able to provide policy makers with estimates of prophylactic G-CSF benefits with regard to NH reduction for patients on the extensive margin. This evidence may help us to determine "Which rate is right." Therefore, this study can be expected to have a significant positive impact, allowing policy makers to be better informed about current G-CSF utilization and benefits in formulation recommendations for future medical practice for elderly NHL patients on anthracycline-based chemotherapy.

Research Design

This study was a retrospective cohort study using a large observational database. The cohort of elderly patients diagnosed with Non-Hodgkin's Lymphoma from 1994 to 2002 was followed up retrospectively until 6 months after their diagnosis or death. Individuals in the cohort who differed by their use of prophylactic G-CSF use were compared by the outcome of neutropenia hospitalization after their first chemotherapy cycle. The risk of developing neutropenia if not using prophylactic G-CSF could then be established.

Sources of Data

The Surveillance, Epidemiology, and End Results (SEER)-Medicare database was the major data source for this study. The SEER data was used to identify patients diagnosed with Non-Hodgkin's Lymphoma from 1994 to 2002. Currently, SEER collects

and publishes data from cancer registries representing about 26 percent of the US population. The SEER data is customized in a file known as the Patient Entitlement and Diagnosis Summary File (PEDSF). The PEDSF file contains thirteen SEER registries and important patient demographic and clinical information. Demographic variables used in this study included age, gender, race, county where the patient resided, and area socioeconomics variables. Some important clinical information used in this study was obtained from the PEDSF file as well, such as histology type, extension code used to define stages, radiation therapy reported by SEER, lymph node involvement, grade, diagnosis year and death date. In addition, the PEDSF file contains Medicare enrollment information, which was used to select patients who had continuous Medicare Part A and/or Part B coverage and no HMO coverage for the study period.

Medicare claims, linked to SEER by patient ID, provide additional important information for this study. Claims data include information of health service utilization and cost components such as chemotherapy regimens, G-CSF use, service or drug reimbursement amount, diagnosis codes (International Classification of Diseases [Ninth Revision], Clinical Modification [ICD-9-CM]) and procedure codes (Healthcare Common Procedure Coding System [HCPCS] procedure codes).

The US zip code database (obtained from www.zip-codes.com) was used as a supplementary resource for this study. The database contains zip codes and their corresponding latitude and longitude. Using this information, it is possible to calculate distance between two zip codes. The distance variable is useful to define local oncologist markets and patient travel distance to the nearest oncologist.

Study Population

The study sample consisted of Medicare patients 66 years or older diagnosed with first primary Non-Hodgkin's Lymphoma (NHL) residing in one of the 13 SEER registry areas from 1994 to 2002. Selected patients had at least one non-in situ NHL cancer. This

information could be found from variables of "SEER Historic Stage A" and "ICD-O-3 Behavior Code" in PEDSF file. Patients with "benign" in the behavior code or "in-situ" in the historic stage variable were excluded. Medicare patients 66 years or older were selected because we wanted to have one year of their Medicare claims data before their diagnosis to calculate the comorbidity score. Patients who had a prior cancer or simultaneous malignancy diagnosis were excluded because we would like to focus on patients with first primary NHL diagnosis. To fully determine patient health service utilization during the follow-up period and calculate pre-diagnosis comorbidity score, only patients continuously enrolled in Medicare Part A and/or Part B and not enrolled in an HMO from one year prior to diagnosis until the end of six months after diagnosis or death were included. Patients whose residence zip code was outside the SEER area or without latitude or longitude coordinates were excluded. All study patients had anthracycline-based chemotherapy (ABC) as their first line chemotherapy within the first five months of their diagnosis month. The first five months after the patient diagnosis month is used to define the first course of chemotherapy (Chrischilles et al. 2003). Patients who were hospitalized or had emergency room visits during the first cycle of chemotherapy were excluded because G-CSF or ABC use could not be determined from hospital or ER visit claims. In order to estimate chemotherapy reimbursement by Medicare fiscal intermediaries and carriers (Medicare local paying agencies), patients who only had Medicare Part B claims were used to estimate local area average chemotherapy reimbursement. Patients whose cancer site code was any part of the central nervous system (CNS) were removed because these patients are less likely to get systemic chemotherapy (Chrischilles et al. 2003; Link et al. 2008). Study sample size along with inclusion and exclusion criteria will be shown in the chapter of results.

Dependent Variable

For Specific Aim #1, the final outcome we studied was whether a patient had neutropenia hospitalization after the first chemotherapy cycle and within six months after the diagnosis date. The measurement of this dependent variable was described in the following section and Table III-1.

A dummy variable was created to indicate whether a patient had neutropenia hospitalization (NH) within the earliest of the following: six months after diagnosis date or death date. The event of NH was identified if a patient had an inpatient claim with ICD-9 code of 288.0 (Derek Weycker, Jennifer Malin, Andrew Glass, and Gerry Oster April 2007), excluding skilled nursing home stays during the spanned time period from the end date of first cycle chemotherapy (+1 day) through the end of six months after diagnosis or through his/her death date if death occurs prior to six months post diagnosis. This base-case measure of neutropenia hospitalization was assumed to capture NH events during first course chemotherapy. A previous study used this measure to define neutropenia-related inpatient stay in first course chemotherapy (Chrischilles et al. 2005). The other measure of this outcome variable for sensitivity analysis was neutropenia hospitalization occurring during the spanned time period from the end date of first chemotherapy cycle (+1 day) through the end date of second chemotherapy cycle. A previous study using the SEER-Medicare database found that among all first neutropenia hospitalization, 56% happened within the first 42 days of treatment (Margaret D. Voelker, et al 2004). Using this measure for sensitivity analysis, we were likely to capture a high percentage of first neutropenia hospitalization. This measure also provided an appropriate time frame to investigate the causal relationship between G-CSF and neutropenia hospitalization incidences. However, when this measure was taken, follow-up time would be limited and the association between G-CSF and NH beyond the second chemotherapy cycle could not be identified.

Key Independent Variable

Prophylactic G-CSF Treatment (G-CSF)

The independent variable for G-CSF treatment and outcome relationship model was whether a patient had prophylactic G-CSF. Filgrastim (the most common type of G-CSF in the study period) was identified by HCPCS codes as J1440 and J1441. Prophylactic G-CSF use was designated if a patient had a G-CSF claim within the first five days of the first chemotherapy cycle (Chrischilles et al. 2003). Prophylactic G-CSF choice was specified as a dummy variable in the empirical model. If a patient was treated with prophylactic G-CSF, then G-CSF=1; if a patient did not get treated, then G-CSF=0.

Duration of G-CSF as Sensitivity Analysis

When prophylactic G-CSF use as a dummy variable was considered as the main treatment variable, time components such as duration of the treatment were not taken into account. Days of G-CSF use is an important feature of this treatment and affects the optimal outcome. In clinical trials where patients were administered myelosuppressive chemotherapy, an average of 10 to 11 days of prophylaxis with filgrastim was found to reduce febrile neutropenia incidence and restore absolute neutrophil counts (Glaspy et al. 1993; Green et al. 2003; Holmes et al. 2002). However, in practice, the median number of days of prophylaxis G-CSF use was only seven days (Chrischilles et al. 2003). Some studies reported that shorter courses of early G-CSF use were associated with increased risk of neutropenia hospitalization (Chrischilles et al. 2003; Scott et al. 2003; Weycker et al. 2006). Therefore, in this study, days of early G-CSF use was measured by using SEER-Medicare claims data. One way to measure duration was to calculate the number of G-CSF claim service dates not separated by more than a 3-day gap and starting within the first five days of the first cycle. The 3-day gap was chosen to allow treatment interruptions on weekends and holidays. Another way to measure duration was tested as a

sensitivity analysis. The method was to calculate days of early G-CSF use based on the number of submitted units from both physician visit claims and outpatient claims.

Instrumental Variables

Area Average Chemotherapy Reimbursement Variable (AREAREIM):

Carrier-related Reimbursement for First Cycle Chemotherapy (γ) in Treatment Choice Framework

This variable (AREAREIM) measured average chemotherapy reimbursement for counties grouped by Medicare Part B fiscal carrier coverage. An empirical model was used to estimate this variable. The model was based on the method to construct Medicare fee variables for breast cancer conserving surgery (BCS) and mastectomy (MST) by Hadley (Hadley et al. 2003). It was theorized by Hadley et al. that average payment amounts in a geographical area determined by Medicare fee schedule is exogenous to physician's treatment choice. Geographical areas for which fees were measured were defined by three-digit zip codes. In this research project, we assumed that counties grouped by Medical local paying agents (fiscal carriers) contribute to the variation in physician reimbursement for each patient's first cycle of chemotherapy. We estimated a linear regression model (3.1) for reimbursement amount associated with each of the fiscal carriers, adjusting types of chemotherapy, patient demographic and clinical characteristics.

$$REIM_i = \lambda_0 + \lambda_1 TYPE_i + \lambda_2 GCSF_i + \lambda_3 AGE_i + \lambda_4 MALE_i + \lambda_5 RACE_i + \lambda_6 GRADE_i + \lambda_7 NODE_i + \lambda_8 STAGE_i + \lambda_9 COMORB_i + \lambda_{10} HISTOLOGY_i + \lambda_{11} CARRIER_i + \lambda_{12} YRDX_i + \varepsilon_i \quad (3.1)$$

Where: $CARRIER_i$ is a series of binary variables indicating counties grouped by Medicare carrier coverage ($CARRIER_1$- $CARRIER_n$) and ε_i is the error term.

In this empirical model, the dependent variable is a patient's total reimbursement during the first cycle of chemotherapy (REIM). The variable was measured as the total of Medicare physician visit and Medicare outpatient reimbursement within 21 days of the chemotherapy start date for a patient indexed to a standard geographic area. The most common chemotherapy regimens for NHL patients such as CHOP, CHOP plus Rituximab and CNOP, last for 21 days (Dorr and Von Hoff January 30, 1994). The reimbursement was then adjusted by geographical price index and consumer price index. The total reimbursement variable is a continuous variable greater or equal to zero.

The most important explanatory variable in this model is counties grouped by Medicare Fiscal Carrier or Intermediary coverage (CARRIER). This variable was created to assess carrier-specific variation in chemotherapy reimbursement. They were defined as county groups within SEER based on Medicare carrier coverage. Each county was assigned the most frequently used fiscal carriers found from Medicare Part B claims. For example, 95% of physician visit claims for Johnson county patients are submitted to the fiscal carrier at Iowa Wellmark Inc. and 96% of Outpatient claims for Johnson county patients are submitted to the carrier at Nebraska Blue Cross. The fiscal carrier combination of Iowa Wellmark and Nebraska Blue Cross is considered the carrier environment for patients in Iowa Johnson County. Because the fiscal carriers serving a county may change across years —for example, some carriers may have been terminated in a particular year—the carrier environment was assigned annually to each county.

Ordinary least square regression was performed based on this empirical model. A Chow F test (Chow 1960) was used to justify whether there is statistically significant variation in reimbursement across Medical fiscal carriers. If the variation could be confirmed, the next step was calculating the average chemotherapy reimbursement variable for each of the fiscal carriers (AREAREIM). We used the chemotherapy reimbursement equation estimates to compute this carrier-related chemotherapy reimbursement variable. It was computed by adding up average chemotherapy

reimbursement for the referenced county group, the coefficient for each county group, and intercept estimate and average chemotherapy reimbursement for the referenced group.

Per Capita Number of Oncologists (ONCOSUPPLY):

Oncologist Supply in a Local Area (S) in Treatment Choice Framework

The variable of per capita number of oncologists (ONCOSUPPLY) measures oncologist supply in a market. It was defined as the number of oncologists per NHL patient within a radius around each patient's residence zip code. Various measures for this variable were used. In the base-case measurement, the numerator is the number of oncologists within a radius of 50 miles of the patient's zip code. It is assumed that a competitive oncologist supply market exists within a 50 mile radius around the zip code where a study patient resided. The denominator is the number of unique NHL patients found from the entire PEDSF file within a 50 mile radius of the zip code where the study patient resided. For each patient in our sample, this variable was estimated for their diagnosis year, as oncologist supply may change over time. The 50 mile radius was proposed here to define the oncologist supply market area, but this number alone may not be representative of an oncologist supply market. For example, oncologist market area in Iowa is much larger than in New York City because potential patients living on farms are used to traveling a longer distance to seek care and oncologists may compete with each other in a larger geographical area. In contrast, tight neighborhoods in New York City make the oncologist market area radius smaller than 50 miles. In the sensitivity analysis, the radius used to define oncologist market area varies from 5-mile, 10-mile, 20-mile, 25-mile, 30-mile, 40-mile, 50-mile to 75-mile.

Area G-CSF Treatment Rate (AREATR):

A Proxy of The average belief of treatment effectiveness of oncologists in the area where a certain treatment pattern holds (B) in Treatment Choice Framework

Area G-CSF treatment rate was measured by prophylactic G-CSF treatment rate among NHL cancer patients on anthracycline agents within a certain radius around each patient's zip code across diagnosis years. According to a study which tracked types of surgeries given within a community, it was found that similar treatment rates persisted across years in the same geographical region. This phenomenon was called an "epidemiological signature" (Wennberg, Barnes, and Zubkoff 1982). Therefore, in this project, treatment rate was not calculated by each year but across all diagnosis years. In the base-case measurement, the denominator of the treatment rate was the number of NHL patients on anthracycline agents in a geographical area. The area was defined as a region around each study patient with at least 50 NHL patients on anthracycline chemotherapy. The numerator of the treatment rate was the number of NHL patients receiving ABC who were treated with prophylactic G-CSF within a region around each study patient. In the first set of sensitivity analysis, the threshold of 50 cases varied. Areas with at least 25, 75 and 100 NHL patients on anthracycline were tested to see whether different definitions of relatively self-contained area with respect to provision of oncology care would affect results. In another set of sensitivity analysis, the instrumental variable was created by calculating the proportion of patients on prophylactic G-CSF within a certain geographical radius (30-mile, 50-mile) of a patient's zip code centroid. It was assumed that a certain geographical radius of a patient zip code represents a self-contained area with respect to provision of oncology care.

Distance to the Nearest Oncologist (DIST):

Defined in Treatment Choice Framework

Straight line distance from each patient's residence zip code centroid to the centroid of the nearest oncologist practice zip code from carrier claims was calculated based on the zip code file, physician visit claims and the PEDSF file. The zip code file was linked with the PEDSF file by patient zip code and with physician visit claims by provider zip code. Bias may rise if straight line distance does not accurately reflect travel time. However, a previous study indicated that straight line distance could be a proxy for travel time based on the very high correlation (0.987) between straight line distance and travel time (Phibbs and Luft 1995).

Explanatory Variables and Control Variables

Socio-demographic and clinical variables controlled in the treatment-outcome model and the model estimating carrier-specific chemotherapy reimbursement described previously include year of diagnosis, age at NHL diagnosis, gender, race, grade diagnosis, lymph node involvement, stage, histology, comorbidity score calculated from either inpatient or outpatient claims, chemotherapy regimens identified from Medicare claims by specific procedure codes and area socioeconomic variables. The measurements of these variables were described in the following sections and summarized in Table III-4.

Year of Diagnosis (YRDX)

Year of diagnosis is the year when NHL was first diagnosed by a recognized medical practitioner, whether clinically or microscopically confirmed. The source of this variable is the PEDSF file, a customized file of SEER data.

Anthracycline-based Chemotherapy Types (TYPE)

In order to obtain anthracycline-based chemotherapy claims, all chemotherapy claims by the codes (Appendix A) were found first. We limited the line items and claims where reimbursements were allowed, payment was made and the amount of charge is greater than zero. Chemotherapy regimens were then classified based on HCPC codes (Appendix B). Anthracycline-based chemotherapy types (TYPE) were then grouped on the chemotherapy regimens. Depending on neutropenia risk levels associated with ABC regimens, chemotherapy was categorized into five groups, including CHOP; CNOP; doxorubicin alone or with other agents, except CHOP; mitoxantrone alone or with other agents, except CNOP; other anthracycline-based chemotherapy (Scott 2002; Weycker et al. 2006).

Age Group at NHL Diagnosis (AGE)

The variable of patient age at NHL diagnosis was calculated by diagnosis date (if diagnosis date was unknown it was assigned the first date of the month) and patient birth date from PEDSF file. The age at diagnosis was then divided into five groups, including 66 to 70, 71 to 75, 76 to 80, 81 to 84 and 85 years or older.

Gender (MALE)

We directly obtained the gender variable from the PEDSF file. The SEX variable in the PEDSF file indicates whether the patient is a female or male.

Race (RACE)

We obtained the variable of race from the PEDSF file. Races included categories of White, Black, Asian, Native and other races (used if SEER race groups are other race, unknown race or Hispanic).

Grade at Diagnosis (GRADE)

Grade at diagnosis was identified from the PEDSF file. In the PEDSF file, grade was categorized into Grade 1, Grade 2, Grade 3, Grade 4, T-cell, B-cell, Null Cell, NK cell and unknown grade. Based on the frequency of cases in each group, only two groups were created: B-cell and no B-cell which includes Grade 1-4, T-Cell, Null Cell, NK Cell and unknown grade.

Lymph Node Involvement (NODE)

The variable of lymph node involvement was obtained from the PEDSF file. According to SEER data, node involvement was categorized into several groups, including no B symptom, any B symptom, Pruritus, B symptom and Pruritus, and unknown lymph node involvement. Depending on the frequency of cases in each group, two groups were created: no B symptom, and B symptom and others.

Stage (STAGE)

The variable stage was created based on the extension code in the PEDSF file. In the PEDSF file, stage was divided into five groups: Stage 1, Stage 2, Stage 3, Stage 4 and unknown stage.

Comorbidity Index (COMORB)

Patient's comorbidities prior to diagnosis were measured by the new NCI Uniform Weights index, which was previously assessed by Klabunde (Klabunde et al. 2007). In order to calculate this index, chronic diseases including myocardial infarction, CHF (congestive heart failure), peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary, dementia, pralysis, diabetes, diabetes with sequelae, chronic renal failure, various cirrhodites, moderate-severe liver disease, ulcers, rheum and aids were first found from both inpatient and outpatient claims. Then, each disease found in either claims type was assigned a weight of 1. The method for constructing this

index was simply summing these uniformly-weighted chronic conditions and establishing a single index.

Radiation Therapy (RAD)

Information of radiation therapy was obtained from SEER data, which provides clinical information for the first course of therapy within five months after the initial treatments (National Cancer Institute 1998). The radiation use reported by SEER was divided into nine groups, including no radiation, beam radiation, radioactive implants, radioisotopes, combination of beam with implants or isotopes, other radiation, refused, recommended but unknown and unknown. Based on frequency of cases, this variable was grouped into either no radiation, or radiation therapy which includes beam radiation, radioactive implants, radioisotopes and other radiation.

Histology (HISTOLOGY)

Histology code was obtained from the variable of histology ICD-O-3 in the PEDSF file. In a previous research project, use of the ICD-O-3 histology code was validated by investigating the agreement between ICD-O-2 and ICD-O-3 codes (Link et al. 2008). Definitions for histology codes were found in the second edition of the International Classification of Disease for Oncology (ICD-O) published by World Health Organization in 1990. Based on the definitions and oncologist knowledge, histology codes were grouped into diffuse large cell or diffuse large B cell (DLC), follicular, small lymphocytic lymphoma (SL), T-cell lymphoma, marginal zone B-cell lymphoma (Mar), unspecific and unknown histology based on ICD-O-3 histology labels. The matching could be found in Appendix C. Each histology group was assigned a dummy variable. Based on frequency of cases, the variable was divided into patients diagnosed with DLC, and patients diagnosed with other histology types including follicular, small lymphocytic lymphoma, T-cell, marginal zone B-cell lymphoma, unspecific and unknown histology.

Socioeconomic Variables (SES)

Area median income level, education level and percent of white were variables indicating area socioeconomics levels around a patient. Area income level was obtained based on area income in a census tract. If it could not be determined at census tract level, area income level at a zip code was used. Area income level was divided into quartiles grouped by the distribution of area income level in a specific SEER site. The same algorithm applies to the creation of area education level and percent of white.

Empirical Models

The first empirical model was to test the first assumption of the instrumental variable: whether variation in Medicare reimbursement for first cycle of chemotherapy (AREAREIM), per capita number of oncologists (ONCOSUPPLY), patient's distance to the nearest oncologist (DIST) and G-CSF treatment rate (AREATR) in an area affect patient treatment choice of using G-CSF. This empirical model can be summarized as equation 3.2:

$$GCSF_i = \beta_0 + \beta_1 TYPE_i + \beta_2 AGE_i + \beta_3 MALE_i + \beta_4 RACE_i + \beta_5 GRADE_i + \beta_6 NODE_i + \beta_7 STAGE_i + \beta_8 COMORB_i + \beta_9 HISTOLOGY_i + \beta_{10} YRDX_i + \beta_{11} SES_i + \beta_{12} RAD_i + \beta_{13} AREAREIM_i + \beta_{14} ONCOSUPPLY_i + \beta_{15} AREATR_i + \beta_{16} DIST_i + \rho_i \quad (3.2)$$

Where GCSF is a binary variable indicating whether the patient received prophylactic G-CSF or not and ρ_i is the error term that affects the treatment choice.

Based on this empirical model of G-CSF choice, the first assumption of the instrumental variable could be tested. Both ordinary least square and logistic regression analyses were used to test these hypotheses by different error term distribution assumptions. When logistic regression analysis was performed, Wald Chi-square statistics, estimates and odds ratios were used to examine the likelihood of changing prescription behavior with the change in instrumental variables. When ordinary least

square regression was performed, a Chow F-test was used to assess whether instrument variables describe a significant portion of variation in the G-CSF choice.

The second empirical model was constructed to explore the relationship between prophylactic G-CSF use and neutropenia hospitalization. This empirical model was used to test whether G-CSF treated patients benefit from G-CSF in terms of reducing neutropenia hospitalization. The empirical model can be summarized as equation 3.3:

$$NH_i = \alpha_0 + \alpha_1 TYPE_i + \alpha_2 AGE_i + \alpha_3 MALE_i + \alpha_4 RACE_i + \alpha_5 GRADE_i + \alpha_6 NODE_i + \alpha_7 STAGE_i + \alpha_8 COMORB_i + \alpha_{10} HISTOLOGY_i + \alpha_{11} YRDX_i + \alpha_{12} SES_i + \alpha_{13} RAD_i + \alpha_{14} GCSF_i + \mu_i \quad (3.3)$$

Where: NH was a binary variable indicating whether a patient had an inpatient claim with an ICD-9 code of 288.0 during the spanned time period from the end date of first cycle chemotherapy (+1 day) through the end of 6 months after diagnosis, GCSF was a binary variable indicating whether the patient had early G-CSF in the first chemotherapy cycle and μ_i was the error term explaining other unmeasured variations in neutropenia hospitalization. If μ_i contained unmeasured confounders that affect both G-CSF choice and NH, the assumption of multivariate regression that error terms are statistically independent from the independent variable would be violated, and the estimate of α_{14} would be a biased estimate of G-CSF effect on NH risk among treated patients.

By assuming different error term distributions, several estimators were used to estimate α_{14}, such as linear ordinary least square regression, logistic regression and probit regression. Parameter estimates and p-value were used to examine whether treatment affected the neutropenia risk of patients. The third empirical model was constructed so that the hypothesis for Specific Aim #1, that there was substantial neutropenia hospitalization rate reduction available from expanded G-CSF rates, was tested. Two-

stage least square regression (2SLS) was employed to test this hypothesis. The models were specified as equations 3.4 and 3.5:

$GCSF_i$ =

$$\gamma_0 + \gamma_1 TYPE_i + \gamma_2 AGE_i + \gamma_3 MALE_i + \gamma_4 RACE_i + \gamma_5 GRADE_i + \gamma_6 NODE_i + \gamma_7 STAGE_i + \gamma_8 COMORB_i + \gamma_9 HISTOLOGY_i + \gamma_{10} YRDX_i + \gamma_{11} SES_i + \gamma_{12} RAD_i + \gamma_{13} AREAREIM_i + \gamma_{14} ONCOSUPPLY_i + \gamma_{15} AREATR_i + \gamma_{16} DIST_i + \omega_i + \theta_i \quad (3.4)$$

NHi =

$$\tau_0 + \tau_1 TYPE_i + \tau_2 AGE_i + \tau_3 MALE_i + \tau_4 RACE_i + \tau_5 GRADE_i + \tau_6 NODE_i + \tau_7 STAGE_i + \tau_8 COMORB_i + \tau_{10} HISTOLOGY_i + \tau_{11} YRDX_i + \tau_{12} SESi + \tau_{13} RAD_i + \tau_{14} \hat{GCSF}_i + \omega_i + \nu_i \quad (3.5)$$

In the first stage of 2SLS regression, ordinary least squared regression (OLS) was used to estimate the effects of factors impacting G-CSF treatment choice. The empirical model was specified in equation 3.4, where $GCSF_i$ is the treatment variable indicating whether the patient received prophylactic G-CSF, and $TYPE_i$, AGE_i, $MALE_i$, $RACE_i$, $GRADE_i$, $NODE_i$, STAGEi, $COMORB_i$, $HISTOLOGY_i$, $YRDX_i$, SES_i, and RAD_i are measured confounders to be controlled. ω_i indicated the unmeasured confounders that affected both prophylactic G-CSF and the outcome of neutropenia hospitalization. θ_i indicates the unmeasured factors that only impacted G-CSF choice. $AREAREIM_i$, $ONCOSUPPLY_i$, $AREATR_i$, $DIST_i$ were instrumental variables.

In the second stage of 2SLS regression as seen in equation (3.5), NH was a binary variable indicating whether a patient had an inpatient claim with an ICD-9 code of 288.0 during the spanned time period from the end date of first cycle chemotherapy (+1 day) through the end of 6 months after diagnosis. $\hat{GCSF}_i$ was the predicted value of G-CSF treatment probabilities for i^{th} patient from the first stage regression. ν_i was a set of unmeasured factors that impacted neutropenia hospitalization only and did not impact G-CSF choice. Other variables were previously specified in equation (3.4). Equation (3.5) was estimated by using the predicted G-CSF treatment propensity for each patient from equation (3.4). Because measured confounders were controlled in both stages, the only

variation in the predicted G-CSF treatment choice that was used to estimate treatment effect parameter τ_{14} in the second stage came from instrumental variables. Based on the assumptions of instrumental variables, IV would provide a natural experiment in patient G-CSF choice and therefore, IV estimate of the change in NH rate from one-unit change in G-CSF use rate would be consistent.

Statistical analysis was performed to justify the acceptance of instrumental variable assumptions. For the first assumption that instrument is related to treatment choice, it was tested through equation (3.2) a large F value and < 0.05 P value would demonstrate that instrument describes a significant proportion variation in G-CSF treatment. The second assumption that IV is not related to error term ω_i, is an assumption innate in the IV approach. Even though this assumption cannot be justified with available data, it may be scrutinized to some extent (Brooks 2006; Brooks et al. 2003; McClellan, McNeil, and Newhouse 1994). First, theory suggests that an over-identification test can be performed if there are more than two groups of instrumental variables (e.g. instrumental variables were divided into quartiles). Second, testing the association between instrumental variables and observed confounding factors may help answer the question. If measured confounders are unbalanced across instrument groups, the inferences made from 2SLS estimates should be conditional on the assumption that differences in measured confounders are not symptomatic of differences in unmeasured confounders across instrumental variable groups, and we need to directly control these variables in the 2SLS regression.

As a sensitivity analysis for duration of G-CSF use, descriptive statistics, such as days of early G-CSF, comparison of G-CSF durations using different measurements and chi-square test statistics indicating association between G-CSF duration and neutropenia hospitalization, patient baseline characteristics were generated.

All of the above data analyses would be performed by SAS 9.2 (Copyright 2002-2008 by SAS Institute Inc). The significance level was 0.05.

Data Permission and Confidentiality

This research project has been covered by previous data use agreement (DUA) with National Cancer Institute (NCI), which allows the use of the SEER-Medicare linked database for Non-Hodgkin's Lymphoma cases diagnosed from 1986 and 2002. The Health Effectiveness Research Center (HERCe) at the University of Iowa has given the researcher permission to use their data. Since this study involves human subjects, the investigator has completed the National Institute of Health (NIH) online tutorial, met the University of Iowa requirements for human subjects education and been "certified" in human subject protections. An application of conducting this research has been submitted to institutional review boards (IRB) and the human subjects office and approved under the IRB number: 200906787.

Table III-1 Description of Dependent Variables

Dependent Variables	Definitions		Data Sources
	Base-case Definition	Definition for Sensitivity Analysis	
Neutropenia Hospitalization (NH)	Binary variable indicating whether a patient had inpatient claim with ICD-9 code of 288.0 during the spanned time period from the end date of first cycle chemotherapy (+1 day) through the end of 6 months after diagnosis	Binary variable indicating whether a patient had inpatient claim with ICD-9 code of 288.0 during the spanned time period from the end date of first chemotherapy cycle (+1 day) through the end date of second chemotherapy cycle	Inpatient claims

Table III-2 Description of Duration of G-CSF use

Variables	Definitions		Variable Attributes
	Base-case definition	Sensitivity analysis definition	
Duration of G-CSF	Number of G-CSF claim service dates not separated by more than a 3-day gap and starting within first five days of first cycle	Number of submitted units from Part B claims	Continuous variable/ binary variable (<7 days vs. >=7 days)

Table III-3 Description of Instrumental Variables

Instrumental Variable	Specification		Data Sources
	Base-case definition	Definitions for sensitivity analyses	
Area Average Chemotherapy Reimbursement Variable (AREAREIM)	Sum of average chemotherapy reimbursement for the referenced county group, coefficient for each county group, intercept estimate and average chemotherapy reimbursement for the referenced group estimated from empirical model (3.1)	N/A	PEDSF file/ Physician visit claims/ Outpatient claims
Per Capita Number of Oncologists (ONCOSUPPLY)	Number of unique oncologists within a radius of 50 miles / Number of NHL patients within a radius of 50 miles of a patient zip code (PONC50)	Number of unique oncologists within a radius of 5, 10, 20, 25, 30, 40, 50 to 75 miles / Number of NHL patients within 5, 10, 20, 25, 30, 40, 50 to 75 miles of a patient zip code (Multivariate Logistic Regression Model with Continuous Per Capita Number of Oncologists (PONC5, PONC10, PONC20, PONC25, PONC30, PONC40, PONC75)	PEDSF file/ Physician visit claims/US zip code database
Area G-CSF Treatment Rate (AREATR)	Percentage of patients who received prophylactic G-CSF in each geographical area, defined by an area with at least 50 NHL patients on anthracyclines (GRATE50PT)	A. Percentage of patients who received prophylactic G-CSF in each geographical area, defined by an area with at least 25, 75 and 100 NHL patients on anthracyclines (GRATE25PT, GRATE75PT, GRATE100PT) B. Proportion of patients who got early G-CSF within a certain radius (30 or 50 miles) of a patient's zip code centroid (GRATE30M, GRATE50M)	PEDSF file/ Outpatient claims/ Physician visit claims/ US zip code database
Distance to the Nearest Oncologist (DIST)	Straight line distance from centroid of a patient's residence zip code to the centroid of nearest oncologist zip code	N/A	PEDSF file/ Physician visit claims/ US zip code database

Table III-4 Descriptions of Explanatory and Control Variables

Explanatory and Control Variables	Definitions	Reference Group for categorical variables
Year of Diagnosis (YRDX)	Categorical variable	1994
Chemotherapy Types (TYPE)	Categorical variable	CHOP
Age Group at NHL Diagnosis (AGE)	Categorical variable	Age 66-71 years old
Gender (MALE)	Binary variable	Female
Race (RACE)	Categorical variable	White
Grade at Diagnosis (GRADE)	Binary variable	No B-cell
Lymph Node Involvement (NODE)	Binary variable	B symptom and others
Stage (STAGE)	Categorical variable	Stage 1
Comorbidity Index (COMORB)	Binary variable	No comorbidity
Radiation Therapy (RAD)	Binary variable	No radiotherapy
Histology (HISTOLOGY)	Categorical variable	Unspecified
Socioeconomic Variables (SES): area median income level, area education level and area percent of white level	Binary variable	1st quartile

Note: No B-cell category includes: grade 1-4, T-cell, Null cell, NK cell, unknown grade; B symptom category includes: any B symptom, pruritus, B symptom and pruritus.

CHAPTER IV RESULTS

Overview

Study results are shown in this chapter. The description of the study population, including patient demographic and clinical characteristics, outcomes, treatment choices and distribution of potential instrumental variables, is presented first. This section is followed by a description analysis of patient characteristics by G-CSF treatment choice. In order to assess the first assumption of instrumental variable analysis, the associations between instrumental variables and G-CSF treatment were explored by both univariate analysis and multivariate analysis. Sensitivity analyses were conducted to test whether results are robust to different instrumental variable measurements. Sensitivity analyses in the subsets of the study population were also conducted in order to find whether instruments affect treatment choice differently in different subsets. In order to assess validity of using potential instrumental variables, categorical analysis was performed to test the association between instrumental variables with potential confounding variables. Results of various risk adjustment regressions estimating G-CSF treatment effects in the treated patients were compared. In the last section, estimates of prophylactic G-CSF effectiveness from instrumental variable estimator were generated.

Study Population: Tracking of Inclusion and Exclusion

I found 77350 patients diagnosed with NHL over the period of 1994 to 2002 from the PEDSF file. The number of patients who remained in the sample by each inclusion and exclusion criterion was tracked as shown in Table IV-1.

Descriptive Analysis of the Study Population

The study sample consisted of 3340 elderly NHL patients on anthracycline-based chemotherapy. The mean age was 74.96 years old with 29.67% of patients diagnosed at 66 to 70 years old, 30.21% diagnosed at 71 to 75 years old, 24.22% diagnosed at 76 to

81, 10.27% diagnosed at 76 to 80 years old and 5.63% diagnosed at 85 years or older. Among all study patients, the majority were white (93.11%) and the rest of them contained Black, Asian, Native and Others races (6.89%). Females were slightly greater in number than males (51.08% vs. 48.92%). As seen from Table IV-1, more patients diagnosed from 2000 to 2002 were identified as three more cancer registry sites were added to SEER. The most common histology type at diagnosis was Diffuse Large Cell Lymphoma (56.77%). Follicular (14.28%), unspecific histology (11.71%), other histology (10.90%), unknown histology (3.77%), Small Lymphocytic (2.10%) and T-cell Lymphoma (0.48%) were the most common histology types after DLC. The majority of patients were diagnosed with B-cell lymphoma (64.64%) and unknown grade (26.08%). As to lymphoma node involvement, 33.44% of patients did not have B symptom, approximately 14.19% of patients had B symptom or Pruritus, and 52.37% of patients had unknown node involvement. Patients were diagnosed with stage I (33.10%), stage II (21.12%), stage III (13.75%), stage IV (26.12%) and unknown stage (5.96%). Approximately 29.25% of study patients had one or more comorbidity one year prior to diagnosis while 70.75% of all patients did not have any comorbidity within the 12 month period before diagnosis. Most patients had CHOP (81.32%) or CNOP (13.92%) as their first course chemotherapy, leaving only 4.76% of patients who had other chemotherapies. About 74.97% of patients were reported as having radiotherapy from SEER data (Table IV-2).

The neutropenia hospitalization rate after the first cycle of chemotherapy and before the end of six months after diagnosis was 10.90%. Approximately 3.80% of patients had neutropenia hospitalization after the first cycle of chemotherapy and before the end date of the second chemotherapy cycle. Among 3340 patients, about 9.85% had prophylactic G-CSF during the first five days of first cycle of chemotherapy (Table IV-3).

Table IV-4 provides the distribution of candidate instrumental variables with various measurements. The average estimated area chemotherapy reimbursement was about 1,360 dollars. For the base-case definition of per capita number of oncologists within 50 miles, patients lived in an area with an average of 41 oncologists per 100 NHL patients. In sensitivity analysis, the radius varied from 5 miles to 75 miles. Per capita number of oncologists varied from an average of 34 oncologists per 100 NHL patients to 42 oncologists per 100 NHL. Average area prophylactic G-CSF users among anthracycline users ranged from 6% to 11% by various measurements. The average straight line distance from a patient residence to the nearest oncologist was about 9.33 miles. However, the median travel distance was only 3.48 miles. This suggests that the variable of distance had a positive skew. The distribution table indicates there was certain variation to explore in area chemotherapy reimbursement of first cycle chemotherapy, per capita number of oncologists, G-CSF area treatment rate and patient travel distance to the nearest oncologist.

In order to explore the association between patient characteristics and prophylactic G-CSF use, chi-square tests were performed by comparing patient characteristics between the two patient groups receiving and not receiving early G-CSF treatment. The results were summarized in table IV-5. Among patients who received G-CSF, only 7.3% of them had neutropenia hospitalization within six months of diagnosis. While among patients who did not receive G-CSF, about 11.3% of them had neutropenia hospitalization. Without controlling other confounding factors, use of G-CSF was associated with a lower risk of developing neutropenia ($P=0.0272$). The table also showed that patients receiving early G-CSF had characteristics such as older age, which is related to a higher risk of neutropenia ($P=0.0008$). More prophylactic G-CSF use occurred in the most recent years from 1999 representing the diffusion of early G-CSF ($P<0.0001$). The association between other patient characteristics and receipt of early G-CSF was not statistically significant.

The Associations between Instrumental Variables and Prophylactic G-CSF Treatment

The first property of instrumental variables is that instrument variables used in estimation should be correlated with the endogenous variable, which is treatment choice. In order to assess whether the first assumption is valid for the potential instruments, I compared patients grouped by whether the instrument value assigned for the patient was greater or lower than the median, respectively. Chi-square tests were performed to see whether there was significant variation in G-CSF use with patients grouped by instruments. In order to further validate the assumption, logistic regressions were performed to assess the relationship between instruments and prophylactic G-CSF choice, as well as the association between measured confounders and G-CSF choice. Instruments specified as continuous variables would first be included in the regression. If instruments have no predictive power in explaining treatment choice, the instrument may be weak. However, the weak instruments may not be an issue if instruments describe a statistically significant proportion of the treatment variation by estimates of Chow F statistics. Thus, F test statistics were presented too. In some situations, instruments were not linearly associated with treatment choice. Logistic regressions with both linear and squared terms of instrumental variable were performed.

Table IV-6 describes univariate association between instruments and prophylactic G-CSF choice. Patients were first grouped by whether estimated area chemotherapy reimbursement around the patient residence was lower or greater than the median, respectively. Patients were less likely to receive early G-CSF if they lived in an area with higher average chemotherapy reimbursement (9.2 percent versus 10.5 percent). However, the association was not statically significant according to the chi-square test p value ($p=0.1915$).

Study patients were then grouped by whether they lived in the area with a per capita number of oncologists above or below the median. For the base-case analysis, the

chi-square test showed that patients were more likely to have early G-CSF use in areas with higher per capita number of oncologists (10.5 percent versus 9.2 percent). However, the association was not statistically significant according to the chi-square test p value (p=0.1855). Statistical significance of the association was identified when the radius to define the oncologist market was 5 miles (p=0.0445). However, all of the other sensitivity analyses did not confirm this statistical significance of association.

Patients were also grouped by whether prophylactic G-CSF treatment rate around the patient residence was higher or lower than the median, respectively. The chi-square test indicated that patients living in areas with higher G-CSF treatment rate were more likely to use early G-CSF (P<0.0001). For example, according to the base case analysis, 13.0 percent of patients living in areas with higher prophylactic G-CSF use rate received early G-CSF while only 6.7 percent of patients living in areas with lower prophylactic G-CSF use rate received early G-CSF. Sensitivity analyses with various measurements of treatment rate were conducted and the positive association was confirmed.

Study patients were lastly grouped by distance to the nearest oncologist being higher or lower than median. The chi-square test indicated that patients were less likely to receive early G-CSF if they lived farther away from the oncologist (8.4 percent versus 11.3 percent) (P=0.0043).

In order to further confirm whether area chemotherapy reimbursement, per capita number of oncologists, G-CSF area treatment rate and patient travel distance to the nearest oncologist were associated with G-CSF, multivariate logistic regressions were performed to explore the associations by controlling measured confounders using empirical model 3.2. The results of the base-case analysis are presented in Table IV-7.

Table IV-7 shows results from multivariate logistic regression where all the candidate instrumental variables were specified as continuous variables, including estimated area chemotherapy reimbursement of 1000 dollars, per capita number of oncologists practicing within 50 miles of a patient residence zip code, prophylactic G-

CSF treatment rate within a radius of at least 50 patients on ABC around a patient zip code and patient distance to the nearest oncologist. It was found that patients living in areas with a higher rate of prophylactic G-CSF use among ABC users were more likely to be treated with early G-CSF (OR=491.85, 95% CI=95.018->999.999). This result could be interpreted as a patient who lived in areas with higher prophylactic G-CSF rate being about 491 times more likely to get early G-CSF than patients living in areas with lower G-CSF treatment rate when other measured confounders were controlled. As sensitivity analyses, other measurements of G-CSF treatment rate proposed previously were tested to see whether the direction and size of the effect would change. The variable of G-CSF treatment rate was substituted by prophylactic G-CSF treatment rate within a radius of at least 25, 75, and 100 patients around the study patient zip code. The variable was also substituted by prophylactic G-CSF treatment rate within 30-mile and 50-mile radii around the study patient zip code. In most of these sensitivity analyses, results of the treatment rate effect were robust to these different definitions and remained unchanged (Table IV-8).

However, area chemotherapy reimbursement, per capita number of oncologists and distance to the nearest oncologist did not have a significant effect on the likelihood of receiving prophylactic G-CSF. As sensitivity analyses, the per capita number of oncologists practicing within a 50-mile radius of the study patient residence was replaced by the per capita number of oncologists within a 5-mile, 10-mile, 20-mile, 25-mile, 30-mile, 40-mile, 50-mile and 75-mile radius. The effect of oncologist market supply on G-CSF treatment choice remained statistically insignificant (Table IV-9). From Table IV-7, prophylactic G-CSF choice was shown to be insignificantly correlated with area chemotherapy reimbursement, per capita number of oncologists and patient travel distance to the nearest oncologist. Therefore, these three candidate instrumental variables were not linearly associated with prophylactic G-CSF choice.

The multivariate logistic regression was also performed to identify association between G-CSF treatment choice and other measured confounders. It was found that three control variables—age group at diagnosis, stage and diagnosis year—were statistically significant predictors for early G-CSF use. When compared to patients between 66 and 70 years of age as a reference group, patients diagnosed at 71 to 75 were about 1.6 times more likely to be treated with early G-CSF when holding other variables constant (OR=1.572, 95% CI=1.133-2.183). Patients diagnosed at 76 to 80 years old also had a higher probability of receiving early G-CSF by 54% than patients at 66 to 70 years old (OR=1.541, 95% CI=1.090-2.179). When patients were diagnosed at 81 to 84 years old, they were two times more likely to get G-CSF compared to those at 66 to 70 years old (OR=2.214, 95% CI=1.471-3.333). This finding is consistent with clinical studies and meta-analysis suggesting that older patients were at a higher risk of developing neutropenia, and physicians were taking this risk factor into treatment recommendation. Consistent with univariate analysis results, diagnosis year was a statistically significant factor predicting G-CSF choice when holding other control variables constant. When using the diagnosis year of 1994 as a reference group, patients diagnosed in the year of 1999, 2000, 2001 and 2002 were significantly more likely to be treated with prophylactic G-CSF (OR=2.037, 95% CI=1.074-3.864; OR=2.050, 95% CI=1.140-3.689; OR=3.399, 95% CI=1.878-6.152; OR=2.265, 95% CI=1.228-4.178 respectively). This result may be consistent with the diffusion of G-CSF and increased perception of treatment benefit across years. The third variable associated with G-CSF use was stage. Comparing to patients diagnosed with stage 1, patients diagnosed with stage 3 were about 1.6 times more likely to receive early G-CSF (OR=1.556, 95% CI=1.079-2.243). Other important clinical variables related to neutropenia risk were found to be insignificantly associated with G-CSF treatment choice.

When the three candidate instruments—area chemotherapy reimbursement, per capita number of oncologists and distance to the nearest oncologist—were specified as

continuous variable in the multivariate logistic regression, they did not form a statistically significant relationship with G-CSF choice. The results suggest the relationships are not linear. Table IV-10 shows the results of the regression model when both linear and squared terms of these instruments were included. Base-case definitions of these instruments were applied. As seen from the table, the regression coefficients of both instruments and their squared terms were insignificant.

When replacing the per capita number of oncologists with other definitions as sensitivity analyses, the physician density variable and its squared terms were not statistically significant. Therefore, the non-linear relationship between G-CSF treatment and the three candidate instruments could not be confirmed.

The potential instrumental variables were further tested to show whether they describe a statistically significant proportion of the treatment variation by estimates of Chow F statistics. From Table IV-11, which describes Chow F test statistic testing of whether variables contribute a significant portion of variation in treatment choice, prophylactic G-CSF choice was shown to be significantly correlated with area treatment rate as well (F-statistic=60.46, $p<0.0001$).Therefore, if there is a higher rate of prophylactic G-CSF use in an area, the patient living in that area is more likely to use early G-CSF. The other three potential instrumental variables did not describe much variation in G-CSF treatment choice according to their small F-statistics.

Validating Candidate Instrumental Variables

In order to be useful instruments, instrumental variables must meet two assumptions: 1) they are associated with treatment choice; 2) they have no direct effect on the outcome variable and should not be related to unmeasured confounding variables. The first assumption has been tested in previous sections by describing association between instruments and G-CSF choice. The second assumption cannot be validated.

However, comparison analysis can be conducted by looking at the balance of patient demographic and clinical factors across patients grouped by instrumental variable values.

Table IV-12 provides the univariate comparison of patient demographic and clinical factors by patient groups defined by prophylactic G-CSF treatment rate within a radius of at least 50 patients on ABC around a patient zip code. Patients were divided into groups living in areas with a higher G-CSF treatment rate than the median and lower G-CSF treatment rate. The results indicated that there were no differences in chemotherapy types, age, gender, grade, lymphoma node involvement, stage, or prior-diagnosis comorbidity across patients grouped by the value of area G-CSF treatment rate. Significant differences in diagnosis year and ABC chemotherapy regimens were observed. For example, patients diagnosed in more recent years were more likely to live in areas with higher treatment rates. Patients who used CHOP were more likely to reside in areas with higher treatment rates. There measured confounders related to G-CSF treatment rate would be controlled directly in the IV estimation, so that estimates used only the variation in IV that was independent of these measured confounders. Based on previous analysis, F-statistics also indicated that area G-CSF treatment rate as an instrument described a large portion of variation in G-CSF choice after adjustment for patient clinical and demographic characteristics ($F=60.46$, $p<0.0001$). By assuming that differences in measured confounders were not symptomatic of differences in unmeasured confounders across instrumental variable groups, area prophylactic G-CSF treatment rate was chosen as an instrument.

The study examined the univariate comparison of patient demographic and clinical characteristics by estimated area chemotherapy reimbursement of 50% groups. Chemotherapy types, histology types, year of diagnosis, grade, lymphoma node involvement and race were significantly associated with estimated area chemotherapy reimbursement. Based on previous analysis, F-statistics also indicated that area chemotherapy reimbursement as an instrument had no predictive power of G-CSF choice

after adjustment for patient clinical and demographic characteristics (F=0.33, p=0.5686). Since area chemotherapy reimbursement was found to be a weak instrument, and its strong correlation with measured confounders and outcome variable, it would be inappropriate to use area chemotherapy reimbursement as an instrument.

The univariate comparison of patient demographic and clinical factors by patient groups defined by per capita number of oncologists practicing within a 50 mile radius of a patient's residence was performed as well. Patients were divided into groups living in areas with a higher per capita number of oncologists than the median and a lower per capita number of oncologists than the median. Patients treated with CHOP were more likely to live in areas with lower oncologist density, while patients treated with CNOP were more likely to live in areas with higher oncologist density. Oncologist density increased with succeeding years. Patients diagnosed with B cell lymphoma and without B symptom were more likely to live in areas with a higher per capita number of oncologists. Oncologist density was also correlated with stage at diagnosis. Based on previous analysis, F-statistics also indicated that per capita number of oncologist as an instrument had no predictive power of G-CSF choice after adjustment for patient clinical and demographic characteristics (F=0.01, p=0.9068). Since oncologist density was found to be a weak instrument, and its strong correlation with measured confounders and outcome variable, it would be inappropriate to use it as an instrument.

The univariate comparison of patient demographic and clinical factors by patient groups defined by patient distance to the nearest oncologist was performed last. Patients were divided into groups living closer to the oncologists than the median and farther away from the oncologists than the median. White patients lived farther away from the oncologists than patients with other races. Based on previous analysis, F-statistics indicated that patient distance to the nearest oncologist as an instrument had no predictive power of G-CSF choice after adjustment for patient clinical and demographic characteristics (F=0.74, p=0.3908). Since distance to the nearest oncologist was found to

be a weak instrument, and its strong correlation with measured confounders and outcome variable, it would be inappropriate to use it as an instrument.

The Effectiveness of Prophylactic G-CSF on Reducing Neutropenia Hospitalization

According to Specific Aim #1, the most important research question to address in this section is whether substantial neutropenia hospitalization rate is available by expanding the prophylactic G-CSF rate. An instrumental variable estimation approach using two-stage least square regression was developed. For comparison purposes, the question of whether patients treated with prophylactic G-CSF benefited in terms of reduced neutropenia hospitalization was also explored. Multivariate logistic regression, ordinary least square regression and probit regression were applied.

Base-case Analysis: Risk Adjustment Models of the Effect of Prophylactic G-CSF on Reducing Neutropenia Hospitalization

Table IV-13 presents the results from multivariate logistic regression modeling neutropenia hospitalization within 6 months of diagnosis. After adjustment of patient demographic and clinical characteristics, it indicated that prophylactic G-CSF significantly reduced NH events for the patients who received G-CSF (OR=0.595, 95% CI=0.384-0.922). Patients who had prior-diagnosis comorbidities were more likely to have neutropenia hospitalization within 6 months of diagnosis (OR=1.413, CI=1.117-1.788). Compared to patients diagnosed with DLC histology, patients diagnosed with unknown histology were at a lower risk of neutropenia hospitalization (OR=0.343, CI=0.148-0.795). When stage I was treated as a referenced group, patients with an unknown stage were more likely to have neutropenia hospitalization (OR=1.589, 95% CI=1.0076-2.509). Compared to patients diagnosed with NHL in 1994, patients who had

an NHL diagnosis in 1995 were 1.8 times more likely to have neutropenia hospitalization (OR=1.1812, 95% CI=1.052-3.120).

Table IV-14 shows the results of ordinary least square regression modeling prophylactic G-CSF choice on neutropenia hospitalization within 6 months of diagnosis. The results of ordinary least square regression were generated in order to be compared with the estimate from instrumental variable analysis. After adjustment of patient demographic and clinical characteristics, patients who received prophylactic G-CSF had a 4.3 percent reduction in neutropenia hospitalization rate compared to those who did not receive prophylactic G-CSF. Association between neutropenia hospitalization risk and variables such as histology, diagnosis year, stage and comorbidity remained the same as results from multivariate logistic regression.

Table IV-15 lists the results from the multivariate probit regression model. Prophylactic G-CSF significantly reduced neutropenia hospitalization among patients who received G-CSF (Estimate=-0.252, standard error=0.110, P value=0.0219). Regarding control variables, results were consistent across different risk adjustment regression models.

As a sensitivity analysis, the outcome variable of neutropenia hospitalization within 6 months was replaced by neutropenia hospitalization within the second chemotherapy cycle. Prophylactic G-CSF still showed a negative relationship with neutropenia hospitalization; however, the effect was not statistically significant (OR=0.50 in logistic regression, CI=0.23-1.12; Estimate=-0.019 in ordinary least square regression, P value=0.0973; Estimate=-0.34 in probit regression, P=0.05).

Base-case Analysis: Instrumental Variable Estimation of the Effect of Prophylactic G-CSF on Reducing Neutropenia Hospitalization within 6 Months of Diagnosis

The instrumental variable method was further applied to evaluate whether increases in the G-CSF utilization rate could lead to further reductions in the rate of neutropenia hospitalization. Only local area prophylactic G-CSF treatment rates could be used as an instrumental variable in the two stage least square regression. Table IV-16 presents the results from the second stage of instrumental variable analysis after substitute prophylactic G-CSF use by the predicted value of prophylactic G-CSF use obtained from the first stage model. The results suggested that increasing prophylactic G-CSF rate by 43.48 percent points among marginal patients would have decreased the risk of neutropenia hospitalization within 6 months of diagnosis by 1 percent point. However, instrumental variable estimate was not statistically significant from zero (P=0.8655). It suggests that prophylactic G-CSF did not significantly reduce neutropenia hospitalization among marginal patients whose treatment choices varied by local area prophylactic G-CSF treatment rate.

Instrumental variable analysis was then investigated by specifying local area prophylactic G-CSF treatment rate at different grouping levels. Table IV-17 contains F test of IV effect on prophylactic G-CSF choice, F test of Hausman over-identification test and T test of G-CSF effect on neutropenia hospitalization within 6 months. The instrument was categorized into 2-, 4-, 5-, 10- and 20-groups. For the local prophylactic G-CSF treatment rate specified in 4-, 10- and 20-groups, F test indicated that the instrument was significantly associated with prophylactic G-CSF use (F=4.78-32.46, p=0.0001). The over-identification F test statistics were all statistically insignificant across all instrument groups, suggesting that the instrumental variable was not related to the outcome measure directly or associated with unmeasured confounding factors. The treatment estimates almost remained consistently negative across different IV group

specifications. However, the treatment effect in the marginal patients was not statistically significant across all groups (P value=0.2819-0.9725), and standard errors of IV estimates are large (SE=0.112-0.186).

As a sensitivity analysis, the outcome variable of neutropenia hospitalization within 6 months was replaced by neutropenia hospitalization within the second chemotherapy cycle. Prophylactic G-CSF was still showing a negative relationship with neutropenia hospitalization in the marginal patients, but the effect remained statistically insignificant (P=0.6256).

Sensitivity Analyses: The Effectiveness of Prophylactic G-CSF on Reducing Neutropenia Hospitalization

In the sensitivity analyses of treatment-outcome relationship model, alternative patient inclusion and exclusion criteria were applied. Alternative definitions of treatment and outcome were assessed as well.

All patients with ABC who did not have an inpatient stay or emergency room visit within the first five days post ABC initiation were included. The exclusion criteria that patients should not have any inpatient stays or emergency room visits during first chemotherapy cycle for the inability to calculate the instrument "area reimbursement" was removed.

The date of ABC initiation was defined as the "index date" for each patient. Neutropenia hospitalization incidences were identified based on time periods post the index date. Different time periods were assessed depending on how many chemotherapy cycles need to be followed up. For example, 21 days, 42 days, 63 days and 126 days post index date were assessed in this study. Separate analyses for each time period were performed. For each of these analyses, only those patients who survived to these time periods (e.g. patients who survived to 21 days post index date) were included. If a patient

had a neutropenia hospitalization in the specified time period then outcome variable of NH =1, NH=0 otherwise.

Risk Adjustment Models of the Effect of Prophylactic G-CSF on Reducing Neutropenia Hospitalization

Table IV-18 to Table IV-21 are results of ordinary least square regression modeling prophylactic G-CSF choice on neutropenia hospitalization within different time periods (21 days, 42 days, 63 days and 126 days post ABC initiation). In all sub-group analyses, after adjustment for patient demographic and clinical characteristics, prophylactic G-CSF showed protective effect against having neutropenia hospitalization, regardless of statistical significance. When time period for outcome was specified as period from ABC initiation to 126 days post ABC initiation, prophylactic G-CSF effect on reducing neutropenia hospitalization among patients who received G-CSF was statistically significant. Patients who got prophylactic G-CSF had 5 percent reduction in neutropenia hospitalization rate. Some patient demographic and clinical characteristics affected risk of neutropenia hospitalization as well. These factors include histology, diagnosis year, gender, ABC type, grade at diagnosis and age at diagnosis. The effects of these factors on risk neutropenia hospitalization varied across different model specifications.

Instrumental Variable Estimation of the Effect of Prophylactic G-CSF on Reducing Neutropenia Hospitalization

Instrumental variable method was further applied to evaluate whether increases in the G-CSF utilization rate could lead to further reductions in the rate of neutropenia hospitalization. Only local area prophylactic G-CSF treatment rates were used as instrumental variable in IV models. Table IV-22 presents the results from second stage of instrumental variable analysis after substitute prophylactic G-CSF use by the predicted

value of prophylactic G-CSF use obtained from the first stage model. Results from different model specifications are presented in this table. G-CSF effect on neutropenia hospitalization among marginal patients within the time periods from ABC initiation to 21 days, 42 days, 63 days and 126 days post ABC initiation were assessed. The results suggested that increasing prophylactic G-CSF rate by 4.2 percent points among marginal patients would have decreased the risk of neutropenia hospitalization within first chemotherapy cycle by 1 percent point. This IV estimate reaches statistical significance at 95% confidence level. It suggests that prophylactic G-CSF significantly reduce neutropenia hospitalization within first cycle of chemotherapy among marginal patients whose treatment choices varied by local area prophylactic G-CSF treatment rate. When outcome measures in the IV model was specified as neutropenia hospitalization incidence within 42 days, 63 days and 126 days post ABC initiation, prophylactic G-CSF greatly reduced risk of neutropenia hospitalization, however, results failed to reach statistical significance.

Instrumental variable analysis was then investigated by specifying local area prophylactic G-CSF treatment rate at different grouping levels. Table IV-23 to Table IV-26 show results of this analysis as outcome variables were specified differently. F test of IV effect on prophylactic G-CSF choice, F test of Hausman over-identification test and T test of G-CSF effect on neutropenia hospitalization were conducted. The instrument was categorized into 2-, 4-, 5-, 10- and 20-groups.

In all models with different specifications, local prophylactic G-CSF treatment rate specified in 2-, 4-, 5-, 10- and 20-groups described a significant portion of G-CSF choice variation ($p=0.0001$). In Table IV-23, G-CSF's protective effects of reducing neutropenia hospitalization within first cycle of chemotherapy in the marginal patients were statistically significant across all IV groups. The over-identification F test statistics were all statistically insignificant across all instrument groups suggesting exclusion of IV from the outcome equation is appropriate.

In Table IV-24, G-CSF effects of reducing neutropenia hospitalization within 42 days of ABC initiation among marginal patients were large and remained consistently negative across different IV group specifications. IV estimates were statistically significant when instrument was categorized into 10- and 20-groups. The over-identification F test statistics were all statistically insignificant across all instrument groups suggesting exclusion of IV from the outcome equation is appropriate.

In Table IV-25, G-CSF effect of reducing neutropenia hospitalization within 63 days of ABC initiation among marginal patients were large and remained consistently negative across different IV group specification. IV estimates were statistically significant when instrument was categorized into 2-, 10- and 20-groups. The over-identification F test statistics were all statistically insignificant across all instrument groups suggesting exclusion of IV from the outcome equation is appropriate, except when IV was specified as 4- groups.

In Table IV-26, G-CSF effect of reducing neutropenia hospitalization within 126 days of ABC initiation among marginal patients were large and remained consistently negative across different IV group specification. IV estimates were statistically significant when instrument was categorized into 2-, 10- and 20-groups. However, the over-identification F test statistics were all statistically significant across all instrument groups. A large value of the F test statistics rejects the null hypothesis that exclusion of IV from the outcome equation is appropriate.

Sensitivity Analysis: G-CSF Duration

In the sensitivity analysis, the association between prophylactic G-CSF duration and neutropenia hospitalization, and patient baseline characteristics were investigated. Across the entire study population, 329 of 3340 patients (9.85%) received early G-CSF. As seen in Table IV-27, when the duration of G-CSF was measured by a number of G-CSF claim service dates, the median number of days of early G-CSF use was nine. 75.1%

of 329 patients received G-CSF for at least 7 days. When the duration was measured by number of submitted units from Part B claims, median days of early G-CSF use was seven days. 58.1% of 329 patients received early G-CSF for at least 7 days.

Univariate association between patient characteristics and early G-CSF duration, measured by number of submitted units, was performed as well. Neutropenia hospitalization rates were not statistically significantly different between patients treated by different durations of G-CSF (P=0.6467). Patients who had radiation therapy were more likely to have longer durations of G-CSF treatment (P=0.0116). These results were robust when univariate association between patient characteristics and early G-CSF duration measured by the number of G-CSF claim service dates was performed.

Table IV-1 Non-Hodgkin's Lymphoma (NHL) National SEER-Medicare Study Population: Tracking of Inclusion and Exclusion Criteria

Inclusion/Exclusion Criteria	Hierarchy
Total in NHL cancer PEDSF file	77350
Number with at least one non-in situ NHL cancer (based on ICD-O-3)	77350
Number with a known month of diagnosis	76775 (99.26%)
All numbers below out of the 76775	
First NHL diagnosis from 1994-2002	50501 (65.78%)
First primary NHL[a]	41216 (53.68%)
Age 66 years or older at Diagnosis	30481 (39.70%)
Death date reliable Excluded cases with a SEER date of death only (i.e., no Medicare date of death) or date of death was before NHL diagnosis date	30421 (39.62%)
Continuous Medicare Part and B coverage and no HMO coverage from 12 months prior to diagnosis, the month of diagnosis, and the earlier of 6 months after diagnosis or death	20829 (27.13%)
Exclude those with no latitude and longitude data available	20818 (27.12%)
Exclude those with a zip code of residence outside their SEER area	20344 (26.50%)
Remove cases when the first two digit of NHL site code are 70, 71, 72 Assumptions: 70:meninges; 71:Brain; 72: Spinal cord, cranial nerves and other parts of CNS No microscopic confirmation of disease. Cases other than "positive histology" were excluded.	18356 (23.91%)
Include patients who had first course chemotherapy	9646 (12.56%)
Include patients who had ABC chemotherapy as their first chemo regimens	4468 (12.56%)
Exclude patients who had inpatient stays in the first cycle of chemo (within 21 days of start use of chemo)	3614 (4.71%)

Table IV-1 Continued

Exclude patients who had emergency visit during the first cycle of chemo (within 21 days of start use of chemo)	3366 (4.38%)
Exclude patients who have missing census variables	3340 (4.35%)

[a] Patients with a malignancy prior or simultaneous to NHL were excluded, while those where all prior or simultaneous tumor type(s) were in situ were included. In addition, patients that had a SEER first sequence number that was not "00" or '01' were excluded.

Table IV-2 Description Statistics of Patient Characteristics (N=3340)

Variable	**Mean/Column Percentage**	**Percent of Patients Who Had G-CSF***	**Percent of Neutropenia Hospitalization***
Age (years)	74.96		
Age (%)			
66.00-70.99	29.67	6.86	10.39
71.00-75.99	30.21	10.41	11.60
76.00-80.99	24.22	10.51	11.12
81.00-84.99	10.27	14.29	10.79
85+	5.63	11.70	9.04
Race (%)			
White	93.11	10.10	10.77
Black	2.69	4.44	15.56
Asian	3.17	9.43	12.26
Native and other race	1.02	2.94	5.88
Gender (%)			
Male	48.92	10.16	10.83
Female	51.08	9.55	10.96
Histology (%)			
DLC	56.77	10.92	11.81
Follicular	14.28	7.55	9.01
Other	10.90	8.24	10.99
Small lymphocytic and T-cell lymphoma	2.58	5.81	18.60
Unknown	3.77	12.70	4.76
Unspecific	11.71	8.95	8.95
Diagnosis Year (%)			
1994	9.10	5.26	8.22
1995	8.65	5.19	13.84
1996	10.54	9.09	11.65
1997	9.34	8.01	8.97
1998	9.52	6.29	11.64
1999	9.58	10.31	8.75
2000	17.99	11.15	11.65

Table IV-2 Continued

2001	12.96	16.86	11.78
2002	12.31	11.68	10.71
Grade (%)			
B-cell	64.64	10.47	10.75
No B-cell	35.36	8.72	11.18
Node			
No B symptom	33.44	9.13	9.94
B symptom, Pruritus	14.19	10.55	13.29
Unknown	52.37	10.12	10.12
Stage			
stage1	33.10	9.77	9.86
stage2	21.12	8.51	10.64
stage3	13.75	12.42	11.11
stage4	26.12	10.09	11.35
unknown	5.96	8.04	15.08
Comorbidity			
No	70.75	9.44	9.90
Yes	29.25	10.85	13.31
Chemotherapy Category (%)			
CHOP	81.32	9.68	11.19
CNOP	13.92	11.61	10.54
H with Other Agents	2.54	9.41	5.88
N with Other Agents	2.13	5.63	8.45
Other Anthracyclines	0.09	0.00	0.00
Radiotherapy			
Yes	74.97	9.70	11.30
No	25.03	10.29	9.69

Note: No B-cell category includes: grade 1-4, T-cell, Null cell, NK cell, unknown grade; B symptom category includes: any B symptom, pruritus, B symptom and pruritus.

* Percentages for each row are shown in the table.

Table IV-3 Description Statistics of Dependent and Key Independent Variable (N=3340)

Variable	Definition	Mean/Percentage
Prophylactic G-CSF*	G-CSF use during the first five days of first cycle of Chemotherapy	9.85%
Neutropenia Hospitalization	Neutropenia hospitalization during the spanned time period from the end date of first cycle chemotherapy(+1 day) through the end of 6 months after diagnosis †	10.90%
	Neutropenia hospitalization during the spanned time period from the end date of first cycle chemotherapy(+1 day) through the end date of second chemotherapy cycle ‡	3.80%

* Prophylactic G-CSF as a dummy variable.

† Base-case measure for neutropenia hospitalization.

‡ Measure of neutropenia hospitalization for sensitivity analysis.

Table IV-4 Distribution of Candidate Instrumental Variables (N=3340)

Instrumental Variable Measurements		N	Min	The 1st Quartile	Median	The 3rd Quartile	Max	Mean
Measurement for Base-case analysis	Area Reimbursement Variable in 1000 dollars (AREAREIM)	3340	-3.38	1.11	1.26	1.40	13.72	1.36
Measurement for Base-case analysis	Per Capita Number of Oncologists (PONC50)	3340	0.00	0.28	0.36	0.48	10.86	0.41
Measurements for sensitivity analysis	Per Capita Number of Oncologists (PONC5)	3340	0.00	0.00	0.19	0.48	11.00	0.34
	Per Capita Number of Oncologists (PONC10)	3340	0.00	0.08	0.32	0.51	17.50	0.37
	Per Capita Number of Oncologists (PONC20)	3340	0.00	0.22	0.34	0.51	7.40	0.38
	Per Capita Number of Oncologists (PONC25)	3340	0.00	0.23	0.34	0.50	7.40	0.38
	Per Capita Number of Oncologists (PONC30)	3340	0.00	0.25	0.34	0.51	4.75	0.39
	Per Capita Number of Oncologists (PONC40)	3340	0.00	0.26	0.34	0.49	7.0	0.40
	Per Capita Number of Oncologists (PONC75)	3340	0.00	0.31	0.38	0.48	4.00	0.43
Measurement for base-case analysis	Area G-CSF Treatment Rate (GRATE50PT)	3340	0.00	0.05	0.10	0.14	0.38	0.11

Table IV-4 Continued

Measurements for sensitivity analysis	Area G-CSF Treatment Rate (GRATE25PT)	3340	0.00	0.05	0.09	0.15	0.38	0.10
	Area G-CSF Treatment Rate (GRATE75PT)	3340	0.00	0.06	0.10	0.14	0.38	0.11
	Area G-CSF Treatment Rate (GRATE100PT)	3340	0.00	0.06	0.10	0.13	0.38	0.11
	Area G-CSF Treatment Rate (GRATE30M)	3338	0.00	0.03	0.06	0.09	1.00	0.06
	Area G-CSF Treatment Rate (GRATE50M)	3338	0.00	0.06	0.12	0.14	1.00	0.10
Measurement for base-case analysis	Distance to the Nearest Oncologist (DIST)	3340	0.00	1.05	3.48	9.22	224.65	9.33

Table IV-5 Patient Characteristics by Prophylactic G-CSF Treatment (N=3340)

Characteristics	**Category**	**Total (N)**	**Patients receiving GCSF column%**	**Patients not receiving G-CSF column%**	**p-value (Chi-square)**
Neutropenia Hospitalization (%)	No	2976	92.7	88.7	0.0272*
	Yes	364	7.3	11.3	
Chemotherapy regimens (%)	CHOP	2716	79.9	81.5	0.3371
	CNOP	465	16.4	13.6	
	H and other	85	2.4	2.6	
	N and other ABC	74	1.2	2.3	
Age Groups (%)	66.00-70.99	991	20.7	30.7	0.0008*
	71.00-75.99	1009	31.9	30.0	
	76.00-80.99	809	25.8	24.0	
	81.00-84.99	343	14.9	9.8	
	85+	188	6.7	5.5	
Histology Types (%)	DLC	1896	62.9	56.1	0.0932
	Follicular	477	10.9	14.6	
	Other	364	9.1	11.1	
	Small Lymphocytic/ T cell lymphoma	86	1.5	2.7	
	Unknown	126	4.9	3.7	
	Unspecific	391	10.6	11.8	
Diagnosis Year (%)	1994	304	4.9	9.6	<0.0001*
	1995	289	4.6	9.1	
	1996	352	9.7	10.6	
	1997	312	7.6	9.5	
	1998	318	6.1	9.9	
	1999	320	10.0	9.5	
	2000	601	20.4	17.7	

Table IV-5 Continued

	2001	433	22.2	12.0	
	2002	411	14.6	12.1	
Gender (%)	Male	1634	50.5	48.8	0.5578
	Female	1706	49.5	51.2	
Grade (%)	No B-cell	1181	31.3	35.8	0.1054
	B-cell	2159	68.7	64.2	
Node (%)	B symptom and Pruritus /unknown node	2223	69.0	66.3	0.3231
	No B symptom	1117	31.0	33.7	
Stage (%)	stage1	1105	32.8	33.1	0.2283
	stage2	705	18.2	21.4	
	stage3	459	17.3	13.4	
	stage4	872	26.7	26.0	
	unknown	199	4.9	6.1	
Cormobidity (%)	No	2363	67.8	71.1	0.2127
	Yes	977	32.2	28.9	
Race (%)	White	3110	95.4	92.9	0.1702
	Black	90	1.2	2.9	
	Asian	106	3.0	3.2	
	Native/Other	34	0.3	1.1	
Radiation therapy (%)	No	836	26.1	24.9	0.6245
	Yes	2504	73.9	75.1	

Table IV-6 Univariate Association between Prophylactic G-CSF Use and Instrumental Variable (N=3340)

Instrumental Variable		**Treatment Category**	**Total (N)**	**Above (on) median of instrument value n (col%)**	**Below median of instrument value n(col%)**	**p-value (Chi-square)**
Measure for base-case analysis	Area Reimbursement Variable in 1000 dollars (AREAREIM)	no G-CSF	3011	1551(90.8)	1460(89.5)	0.1915
		G-CSF	329	157(9.2)	172(10.5)	
Measure for base-case analysis	Per Capita Number of Oncologists(PONC50)	no G-CSF	3011	1495(89.5)	1516(90.8)	0.1855
		G-CSF	329	176(10.5)	153(9.2)	
Measure for sensitivity analysis	Per Capita Number of Oncologists (PONC5)	no G-CSF	3011	1490(89.1)	1521(91.2)	0.0445*
		G-CSF	329	182(10.9)	147(8.8)	
	Per Capita Number of Oncologists (PONC10)	no G-CSF	3011	1499(89.5)	1512(90.8)	0.2450
		G-CSF	329	175(10.5)	154(9.2)	
	Per Capita Number of Oncologists (PONC20)	no G-CSF	3011	1515(90.4)	1496(89.9)	0.6347
		G-CSF	329	161(9.6)	168(10.1)	
	Per Capita Number of Oncologists (PONC25)	no G-CSF	3011	1509(89.9)	1502(90.4)	0.6664
		G-CSF	329	169(10.1)	160(9.6)	
	Per Capita Number of Oncologists (PONC30)	no G-CSF	3011	1513(90.5)	1498(89.8)	0.5082
		G-CSF	329	159(9.5)	170(10.2)	
	Per Capita Number of Oncologists (PONC40)	no G-CSF	3011	1515(90.2)	1496(90.1)	0.9551
		G-CSF	329	165(9.8)	164(9.9)	
	Per Capita Number of Oncologists (PONC75)	no G-CSF	3011	1497(89.6)	1514(90.7)	0.3236
		G-CSF	329	173(10.4)	156(9.3)	
Measure for base-case analysis	Area G-CSF Treatment Rate (GRATE50PT)	no G-CSF	3011	1471(87)	1540(93.3)	<0.0001*
		G-CSF	329	219(13)	110(6.7)	
Measure for sensitivity analysis	Area G-CSF Treatment Rate (GRATE25PT)	no G-CSF	3011	1451(86.5)	1560(93.9)	<0.0001*
		G-CSF	329	227(13.5)	102(6.1)	

Table IV-6 Continued

	Area G-CSF Treatment Rate (GRATE75PT)	no G-CSF	3011	1458(87.3)	1553(93)	<0.0001*
		G-CSF	329	212(12.7)	117(7)	
	Area G-CSF Treatment Rate (GRATE100PT)	no G-CSF	3011	1460(87.1)	1551(93.3)	<0.0001*
		G-CSF	329	217(12.9)	112(6.7)	
	Area G-CSF Treatment Rate (GRATE30M)	no G-CSF	3011	1443(87.8)	1509(92.5)	<0.0001*
		G-CSF	329	199(12.2)	122(7.5)	
	Area G-CSF Treatment Rate (GRATE50M)	no G-CSF	3011	1445(86.5)	1564(93.8)	<0.0001*
		G-CSF	329	225(13.5)	104(6.2)	
Measure for base-case analysis	Distance to the Nearest Oncologist (DIST)	no G-CSF	3011	1531(91.6)	1480(88.7)	0.0043*
		G-CSF	329	140(8.4)	189(11.3)	

* $P < 0.05$ and ** $P<0.01$

Note: Instrumental variables are divided into two groups based on median.

Table IV-7 Multivariate Logistic Regression Model of Factors on Prophylactic G-CSF Use with Continuous Base-Case Instruments (N=3340)

Variable	**Parameter Estimates**	**Adjusted Odds Ratio (95% confidence interval)**	**p-value**
Instruments			
Chemo Reimbursement			0.7768
AREAREIM (in 1000 dollars)	-0.031	0.969 (0.780-1.204)	0.7768
Patient Distance to Nearest Oncologist			0.4388
ONCDIST	-0.003	0.997 (0.988-1.005)	0.4388
G-CSF Area Treatment Rate			<0.0001**
GRATE50PT	6.198	491.853 (95.018->999.999)	<0.0001**
Per capita number of oncologists			0.9218
PONC50	-0.026	0.974 (0.577-1.646)	0.9218
Control Variables †			
Age at Diagnosis (reference = 66-70)			0.0034**
71-75	0.452	1.572 (1.133-2.183)	0.0069**
76-80	0.432	1.541 (1.090-2.179)	0.0145*
81-84	0.794	2.214 (1.471-3.333)	0.0001**
85+	0.486	1.626 (0.955-2.770)	0.0733
Stage (reference = stage 1)			0.0539
Stage 2	-0.089	0.915 (0.648-1.291)	0.6129
Stage 3	0.442	1.556 (1.079-2.243)	0.0179*

Table IV-7 Continued

Stage 4	0.172	1.188 (0.863-1.636)	0.2913
Unknown stage	-0.183	0.833 (0.466-1.490)	0.5379
Year of Diagnosis (reference =1994)			<0.0001**
1995	-0.058	0.944 (0.452-1.971)	0.8783
1996	0.538	1.712 (0.907-3.233)	0.0971
1997	0.353	1.423 (0.734-2.760)	0.2960
1998	0.137	1.147 (0.574-2.293)	0.6979
1999	0.712	2.037 (1.074-3.864)	0.0294*
2000	0.718	2.050 (1.140-3.689)	0.0166*
2001	1.223	3.399 (1.878-6.152)	<0.0001**
2002	0.818	2.265 (1.228-4.178)	0.0088*

* P < 0.05 and ** P<0.01

† Other control variables without statistically significant association with treatment choice variable were not shown in the table. These variables include ABC types, gender, race, grade at diagnosis, lymph node involvement, comorbidity, radiation therapy, histology and area SES variables.

Table IV-8 Sensitivity Analysis - Multivariate Logistic Regression Model of Factors on Prophylactic G-CSF Use with Continuous Instruments (G-CSF Treatment Rate is tested) (N=3340)

	Instrumental Variable	**Parameter Estimates**	**Adjusted Odds Ratio (95% confidence interval)**	**p-value**
	G-CSF Area Treatment Rate			
Base-case	GRATE50PT	6.198	491.853 (95.018->999.999)	<0.0001**
Sensitivity analysis	GRATE25PT	5.982	396.128 (86.254->999.999)	<0.0001**
	GRATE75PT	6.690	804.155 (136.903->999.999)	<0.0001**
	GRATE100PT	7.009	>999.999 (168.098->999.999)	<0.0001**
	GRATE30M	5.641	281.672 (34.741->999.999)	<0.0001**
	GRATE50M	4.507	90.610 (17.011-482.632)	<0.0001**

* P < 0.05 and ** P<0.01

Note: Other instruments in the model are specified as base-case measurements.

† Other control variables were not shown in the table. These variables include ABC types, gender, race, grade at diagnosis, lymph node involvement, comorbidity, radiation therapy, histology, age at diagnosis, diagnosis year, stage, and SES variables.

Table IV-9 Sensitivity Analysis - Multivariate Logistic Regression Model of Factors on Prophylactic G-CSF Use with Continuous Instruments (Per Capita Number of Oncologists is tested) (N=3340)

	Instrumental Variable	**Parameter Estimates**	**Adjusted Odds Ratio (95% confidence interval)**	**p-value**
	Per Capita Number of Oncologists			
Base-case	PONC50	-0.026	0.974 (0.577-1.646)	0.9218
Sensitivity analysis	PONC5	0.149	1.160 (0.939-1.434)	0.1697
	PONC10	0.122	1.130 (0.923-1.385)	0.2374
	PONC20	-0.005	0.995 (0.696-1.421)	0.9764
	PONC25	0.102	1.107 (0.781-1.571)	0.5672
	PONC30	-0.023	0.977 (0.622-1.537)	0.9209
	PONC40	-0.085	0.919 (0.555-1.521)	0.7418
	PONC75	-0.115	0.891 (0.492-1.615)	0.7047

* $P < 0.05$ and ** $P<0.01$

Note: Other instruments in the model are specified as base-case measurements.

† Other control variables were not shown in the table. These variables include ABC types, gender, race, grade at diagnosis, lymph node involvement, comorbidity, radiation therapy, histology, age at diagnosis, diagnosis year, stage, and SES variables.

Table IV-10 Multivariate Logistic Regression Model of Factors on Prophylactic G-CSF Use with both Linear and Squared Instruments (N=3340)

Variable	**Parameter Estimates**	**Adjusted Odds Ratio (95% confidence interval)**	**p-value**
G-CSF Area Treatment Rate			
GRATE50PT ‡	7.787	>999.999 (8.095->999.999)	0.0074**
Per Capita Number of Oncologists			
PONC50	0.757	2.132 (0.440-10.322)	0.3468
PONC50* PONC50	-0.5726	0.564 (0.178-1.788)	0.3307
Patient Distance to Nearest Oncologist			
ONCDIST	-0.004	0.996 (0.981-1.011)	0.6057
ONCDIST*ONCDIST	0.00003	1.000 (1.000-1.000)	0.6100
Chemo Reimbursement			
AREAREIM	0.045	1.046 (0.698-1.567)	0.8269
AREAREIM*AREAREIM	-0.017	0.983 (0.902-1.072)	0.7035

Note: only base-case measurements are shown. Control variables in the regression model include ABC types, gender, race, grade at diagnosis, lymph node involvement, comorbidity, radiation therapy, histology and area SES variables, diagnosis year, stage and age.

* $P < 0.05$ and ** $P<0.01$

‡ GRATE50PT as a continuous base-case instrument is specified in this model. The squared term of this variable is not added into the model because GRATE50PT as a linear continuous instrument significantly predicts prophylactic G-CSF choice.

Table IV-11 OLS Regression of Factors on Prophylactic G-CSF Choice: F-Statistics Testing of Whether Potential Instruments (Base-case Measurement) Describe a Significant Portion of Variation in Prophylactic G-CSF Choice (N=3340)

Instruments	**Estimate**	**Standard Error**	**P value**	**F-Statistics**
Area Chemotherapy Reimbursement	-0.006	0.010	0.5686	0.33
Per Capita Number of Oncologists	-0.002	0.017	0.9068	0.01
G-CSF Area Treatment Rate	0.610	0.078	<0.0001**	60.46
Distance to Nearest Oncologists	-0.0003	0.0003	0.3908	0.74

Note: only base-case measurements are shown in this table.

* P < 0.05 and ** P<0.01

† Control variables in the regression model include ABC types, gender, race, grade at diagnosis, lymph node involvement, comorbidity, radiation therapy, histology and area SES variables, diagnosis year, stage and age.

‡ The weak instruments may not be an issue if instruments describe a statistically significant proportion of the treatment variation by estimates of Chow F statistics. Thus, F test statistics were presented too (Ajmani and Wiley InterScience (Online service) 2009).

Table IV-12 Univariate Comparison of Patient Characteristics by G-CSF Treatment Rate (GRATE50) 50% Group (N=3340)

Variable Category	Above (on) median column%	Below median column%	p-value (Chi-square)
G-CSF (%)			<0.0001**
No G-CSF	87	93.3	
G-CSF	13	6.7	
Neutropenia Hospitalization (%)			0.9724
No	89.1	89.2	
Yes	10.9	10.8	
ABC Regimen (%)			0.0488*
CHOP	83.1	79.5	
CNOP	12.4	15.5	
H and other	2.5	2.5	
N and other/ other ABC	2	2.5	
Age (%)			0.4386
66.00-70.99	28.6	30.7	
71.00-75.99	29.9	30.5	
76.00-80.99	24.9	23.5	
81.00-84.99	10.4	10.1	
85+	6.2	5.1	
Histology type (%)			0.1548
DLC	57.8	55.7	
Follicular	12.7	15.9	
Other	11.5	10.2	
Small Lymphocytic/ T cell lymphoma (ST)	2.7	2.5	
Unknown	3.8	3.8	
Unspecified	11.5	11.9	
Diagnosis Year (%)			<0.0001**
1994	7.1	11.2	
1995	8.5	8.8	
1996	9.5	11.6	
1997	8.9	9.8	

Table IV-12 Continued

1998	9.1	10	
1999	9.6	9.6	
2000	19.2	16.7	
2001	14.1	11.8	
2002	14	10.6	
SEER Sex (%)			0.5235
Male	49.5	48.4	
Female	50.5	51.6	
Grade (%)			0.1596
No B-cell	36.5	34.2	
B-cell	63.5	65.8	
Node (%)			0.0807
B symptom and Pruritus	65.1	68	
No B symptom	34.9	32	
Stage (%)			0.8512
stage1	33.6	32.6	
stage2	21.5	20.7	
stage3	13.3	14.2	
stage4	25.7	26.5	
unknown	6	5.9	
Comorbidity (%)			0.0757
No	72.1	69.3	
Yes	27.9	30.7	
Race (%)			0.0523
White	93.7	92.5	
Black	2.4	3	
Asian	2.6	3.8	
Native/Other	1.3	0.7	
Radiation therapy (%)			0.4240
No	24.4	25.6	
Yes	75.6	74.4	

* $P < 0.05$ and ** $P<0.01$

Table IV-12 Continued

† G-CSF treatment rate as the instrument is divided into two groups (50% groups) by its median value.

‡ N: Mitoxantrone; H: Doxorubic; ABC: anthracycline-based chemotherapy

Table IV-13 Multivariate Logistic Regression Model of Prophylactic G-CSF Choice on Neutropenia Hospitalization within 6 Months of Diagnosis (N=3340)

Variable	**Parameter Estimates**	**Adjusted Odds Ratio (95% confidence interval)**	**p-value**
Treatment Choice			0.0202*
G-CSF vs. Watchful Waiting	-0.520	0.595 (0.384-0.922)	0.0202*
Comorbidity (reference=No)			0.0039**
Yes	0.346	1.413 (1.117-1.788)	0.0039**
Stage (reference = stage 1)			0.3955
Stage 2	0.063	1.065 (0.776-1.463)	0.6968
Stage 3	0.130	1.138 (0.790-1.641)	0.4867
Stage 4	0.122	1.130 (0.834-1.529)	0.4306
Unknown stage	0.463	1.589 (1.0076-2.509)	0.0466*
Diagnosis Year (reference=1994)			0.3064
1995	0.5942	1.812 (1.052-3.120)	0.0322*
Histology Type (reference=DLC)			0.0066**
Follicular	-0.329	0.721 (0.504-1.028)	0.0704
Other histology	-0.132	0.876 (0.606-1.268)	0.4832
Small lymphocytic and T-cell lymphoma (ST)	0.540	1.716 (0.963-3.058)	0.0670
Unknown histology	-1.071	0.343 (0.148-0.795)	0.0127*

Table IV-13 Continued

Unspecific Histology	-0.352	0.703 (0.479-1.033)	0.0726

Note: In base-case analysis, the dependent variable is neutropenia hospitalization after the first cycle of chemotherapy and within 6 months of diagnosis. Control variables which did not show statistically significant association with NH were not shown in the table.

† Other control variables were not shown in the table. These variables include ABC types, gender, race, grade at diagnosis, lymph node involvement, radiation therapy, age at diagnosis, and SES variables.

* $P < 0.05$ and ** $P<0.01$

Table IV-14 Multivariate Ordinary Least Square Regression Model of Prophylactic G-CSF Choice on Neutropenia Hospitalization within 6 Months of Diagnosis (N=3340)

Variables		**Parameter Estimate**	**Standard Error**	**P-value**
Intercept		0.073	0.025	0.0038**
Treatment Choice (reference=no G-CSF)	G-CSF	-0.043	0.013	0.0183*
Histology (reference=DLC)	follicular	-0.032	0.016	0.0537
	Other histology	-0.012	0.018	0.4965
	Hisgology-ST	0.065	0.035	0.0598
	Unspecified histology	-0.034	0.018	0.0535
	Unknown histology	-0.077	0.029	0.0077**
Diagnosis Year (reference=1994)	yr1995	0.058	0.026	0.0235*
Stage (reference=stage 1)	stage2	0.007	0.015	0.6377
	stage3	0.012	0.018	0.4848
	stage4	0.012	0.015	0.4025
	Unknown stage	0.051	0.025	0.0399*
Comorbidity (reference=No comorbidity)	Comorbidity (Yes)	0.034	0.012	0.0041**

* $P < 0.05$ and ** $P<0.01$

‡ Small Lymphocytic/ T cell lymphoma

† Control variables which did not show statistically significant association with NH were not shown in the table. These variables include ABC types, gender, race, grade at diagnosis, lymph node involvement, radiation therapy, age at diagnosis, and SES variables.

Table IV-15 Multivariate Probit Regression Model of Prophylactic G-CSF Choice on Neutropenia Hospitalization within 6 Months of Diagnosis (N=3340)

Variable		**Estimate**	**Standard Error**	**Pr > ChiSq**
Intercept		-1.488	0.417	0.0004**
Treatment Choice (reference=no G-CSF)	G-CSF	-0.252	0.110	0.0219*
Histology (reference=DLC)	follicular	-0.166	0.093	0.0734
	Other histology	-0.071	0.099	0.4727
	Hisgology-ST	0.303	0.165	0.0666
	Unspecified histology	-0.179	0.100	0.0734
	Unknown histology	-0.528	0.200	0.0082*
Diagnosis Year (reference=1994)	yr1995	0.328	0.142	0.0205*
Stage (reference=stage 1)	stage2	0.040	0.084	0.6354
	stage3	0.070	0.097	0.4730
	stage4	0.076	0.080	0.3459
	Unknown stage	0.252	0.126	0.0453*
Comorbidity (reference=No comorbidity)	Comorbidity (Yes)	0.182	0.064	0.0042**

* $P < 0.05$ and ** $P<0.01$

† Control variables which did not show statistically significant association with NH were not shown in the table. These variables include ABC types, gender, race, grade at diagnosis, lymph node involvement, radiation therapy, age at diagnosis, and SES variables.

Table IV-16 Instrumental Variable Estimation (2SLS) when Continuous G-CSF Treatment Rate (GRATE50PT) is the Instrumental Variable (N=3440)

Instrument	**IV Effect on G-CSF Choice**	**G-CSF Effect on NH**
G-CSF Area Treatment Rate (specified as continuous variable)	**F-statistics**	**G-CSF Effect (SD)**
	62.73**	-0.023 (-0.134)

† Other control variables were not shown in the table. These variables include ABC types, gender, race, grade at diagnosis, lymph node involvement, comorbidity, radiation therapy, histology, age at diagnosis, diagnosis year, stage, and SES variables.

* $P < 0.05$ and ** $P<0.01$

Table IV-17 The Instrumental Variable Estimation when G-CSF Treatment Rate Groups (GRATE50PT) are Used as Instrumental Variables (N=3340)

IV Variable	**IV group §**	**Missgrp**	**IV Effect on G-CSF**		**Over-Identification Test of IVs**		**G-CSF on NH**	
			F-statistic	p-value	F-statistic	p-value	Treatment effect (standard error)	P-value
G-CSF rate	05%	N	4.78**	0.0001**	1.11	0.3360	-0.120 (0.112)	0.2819
	10%	N	9.20**	0.0001**	0.87	0.5414	-0.043 (0.117)	0.7106
	20%	N	11.31**	0.0001**	1.06	0.3639	-0.010 (0.158)	0.9516
	25%	N	15.19**	0.0001**	1.63	0.1968	0.060 (0.158)	0.7012
	50%	N	32.46**	0.0001**	0.00	1.0000	-0.006 (0.186)	0.9725

* P < 0.05 and ** P<0.01

† Other control variables were not shown in the table. These variables include ABC types, gender, race, grade at diagnosis, lymph node involvement, comorbidity, radiation therapy, histology, age at diagnosis, diagnosis year, stage, and SES variables.

§ IV groups: patients were assigned into one of two (50%), four (25%), five (20%), ten (10%) and twenty (5%) groups based on median, quartiles, quintiles, deciles and 5 percentiles of prophylactic G-CSF treatment rate.

Table IV-18 Multivariate Ordinary Least Square Regression Model of Prophylactic G-CSF Choice on Neutropenia Hospitalization within the time period from ABC Initiation to 21 Days Post ABC Initiation for Patients Who Survived to 21 Days Post ABC Initiation (N=3857)

Variables		**Parameter Estimate**	**Standard Error**	**P-value**
Intercept		0.054	0.019	0.0057**
Treatment Choice (reference=no G-CSF)	G-CSF	-0.020	0.014	0.1552
Histology (reference=DLC)	Unknown histology	-0.046	0.023	0.0399*
Diagnosis Year (reference=1994)	yr1999	0.041	0.019	0.0340*
Gender (reference=female)	male	-0.032	0.008	0.0001**
ABC Type (reference=CHOP)	N with other agents	0.064	0.028	0.0241*

* P < 0.05 and ** P<0.01

† Control variables which did not show statistically significant association with NH were not shown in the table. These variables include stage, race, grade at diagnosis, lymph node involvement, radiation therapy, age at diagnosis, comorbidity and SES variables.

Table IV-19 Multivariate Ordinary Least Square Regression Model of Prophylactic G-CSF Choice on Neutropenia Hospitalization within the time period from ABC Initiation to 42 Days Post ABC Initiation for Patients Who Survived to 42 Days Post ABC Initiation (N=3856)

Variables		**Parameter Estimate**	**Standard Error**	**P-value**
Intercept		0.104	0.023	<0.0001**
Treatment Choice (reference=no G-CSF)	G-CSF	-0.024	0.016	0.1480
Gender (reference=female)	male	-0.034	0.010	0.0005**
Comorbidity (reference=No comorbidity)	Comorbidity (Yes)	0.024	0.011	0.0257*
ABC Type (reference=CHOP)	H with other agents	-0.066	0.032	0.0421*

* P < 0.05 and ** P<0.01

† Control variables which did not show statistically significant association with NH were not shown in the table. These variables include stage, histology, race, grade at diagnosis, lymph node involvement, radiation therapy, age at diagnosis, and SES variables.

Table IV-20 Multivariate Ordinary Least Square Regression Model of Prophylactic G-CSF Choice on Neutropenia Hospitalization within the time period from ABC Initiation to 63 Days Post ABC Initiation for Patients Who Survived to 63 Days Post ABC Initiation (N=3853)

Variables		**Parameter Estimate**	**Standard Error**	**P-value**
Intercept		0.119	0.025	<0.0001**
Treatment Choice (reference=no G-CSF)	G-CSF	-0.034	0.018	0.0534
Histology (reference=DLC)	Unknown histology	-0.069	0.029	0.0171*
Gender (reference=female)	male	-0.031	0.011	0.0039**
Grade (reference=not B cell)	B-cell	-0.023	0.012	0.0462*
Comorbidity (reference=No comorbidity)	Comorbidity (Yes)	0.028	0.012	0.0177*
ABC Type (reference=CHOP)	H with other agents	-0.078	0.035	0.0276*

* P < 0.05 and ** P<0.01

† Control variables which did not show statistically significant association with NH were not shown in the table. These variables include stage, race, lymph node involvement, radiation therapy, age at diagnosis, and SES variables.

Table IV-21 Multivariate Ordinary Least Square Regression Model of Prophylactic G-CSF Choice on Neutropenia Hospitalization within the time period from ABC Initiation to 126 Days Post ABC Initiation for Patients Who Survived to 126 Days Post ABC Initiation (N=3795)

Variables		**Parameter Estimate**	**Standard Error**	**P-value**
Intercept		0.110	0.028	<0.0001**
Treatment Choice (reference=no G-CSF)	G-CSF	-0.050	0.015	0.0132*
Age at Diagnosis (reference=66-70)	Age 76-80	0.042	0.016	0.0098**
Histology (reference=DLC)	Unknown histology	-0.090	0.032	0.0061**
	Small lymphocytic and T-cell lymphoma	0.085	0.039	0.0296*
Diagnosis Year (reference=1994)	1995	0.057	0.029	0.0474*
	1998	0.066	0.028	0.0184*
	2001	0.054	0.027	0.0430*
Gender (reference=female)	male	-0.029	0.012	0.0170*
Comorbidity (reference=No comorbidity)	Comorbidity (Yes)	0.041	0.013	0.0018**
ABC Type (reference=CHOP)	H with other agents	-0.096	0.040	0.0160*

* P < 0.05 and ** P<0.01

† Control variables which did not show statistically significant association with NH were not shown in the table. These variables include stage, histology, race, grade at diagnosis, lymph node involvement, radiation therapy, and SES variables.

Table IV-22 Second-stage of Instrumental Variable Estimation (2SLS) when Continuous G-CSF Treatment Rate (GRATE50PT) is the Instrumental Variable

Model of Prophylactic G-CSF Choice on Neutropenia Hospitalization	**Variable**	**Neutropenia Hospitalization**			
		Parameter Estimate	**Standard Error**	**t Value**	**Pr > |t|**
within the time period from ABC Initiation to 21 days post ABC initiation for patients who survived to 21 days post ABC initiation (N=3857)	**G-CSF Treatment** (reference=no G-CSF)	-0.238	0.098	-2.43	0.0151*
within the time period from ABC Initiation to 42 days post ABC initiation for patients who survived to 42 days post ABC initiation (N=3856)	**G-CSF Treatment** (reference=no G-CSF)	-0.155	0.114	-1.37	0.1719
within the time period from ABC Initiation to 63 days post ABC initiation for patients who survived to 63 days post ABC initiation (N=3853)	**G-CSF Treatment** (reference=no G-CSF)	-0.208	0.124	-1.67	0.0941
within the time period from ABC Initiation to 126 days post ABC initiation for patients who survived to 126 days post ABC initiation (N=3795)	**G-CSF Treatment** (reference=no G-CSF)	-0.181	0.140	-1.29	0.1965

† Other control variables were not shown in the table. These variables include ABC types, gender, race, grade at diagnosis, lymph node involvement, comorbidity, radiation therapy, histology, age at diagnosis, diagnosis year, stage, and SES variables.

* $P < 0.05$ and ** $P<0.01$

Table IV-23 The Instrumental Variable Model of Prophylactic G-CSF Choice on Neutropenia Hospitalization within the time period from ABC Initiation to 21 days post ABC initiation for Patients Who Survived to 21 Days Post ABC Initiation Where G-CSF Treatment Rate Groups (GRATE50PT) are Used as Instrumental Variables (N=3857)

IV Variable	**IV group §**	**Missgrp**	**IV Effect on G-CSF**		**Over-Identification Test of IVs**		**G-CSF on NH**	
			F-statistic	p-value	F-statistic	p-value	Treatment effect (standard error)	P-value
G-CSF rate	05%	N	5.74**	0.0001**	0.80	0.7011	-0.2482 (0.0856)	0.0037**
	10%	N	9.82**	0.0001**	0.98	0.4490	-0.2951 (0.0963)	0.0022**
	20%	N	20.29**	0.0001**	1.49	0.2151	-0.2889 (0.1003)	0.0040**
	25%	N	25.33**	0.0001**	0.77	0.4651	-0.3031 (0.1041)	0.0036**
	50%	N	51.91**	0.0001**	0.00	1.0000	-0.3894 (0.1299)	0.0027**

* $P < 0.05$ and ** $P<0.01$

† Other control variables were not shown in the table. These variables include ABC types, gender, race, grade at diagnosis, lymph node involvement, comorbidity, radiation therapy, histology, age at diagnosis, diagnosis year, stage, and SES variables.

§ IV groups: patients were assigned into one of two (50%), four (25%), five (20%), ten (10%) and twenty (5%) groups based on median, quartiles, quintiles, deciles and 5 percentiles of prophylactic G-CSF treatment rate.

Table IV-24 The Instrumental Variable Model of Prophylactic G-CSF Choice on Neutropenia Hospitalization within the time period from ABC Initiation to 42 days post ABC initiation for Patients Who Survived to 42 Days Post ABC Initiation Where G-CSF Treatment Rate Groups (GRATE50PT) are Used as Instrumental Variables (N=3856)

IV Variable	**IV group §**	**Missgrp**	**IV Effect on G-CSF**		**Over-Identification Test of IVs**		**G-CSF on NH**	
			F-statistic	p-value	F-statistic	p-value	Treatment effect (standard error)	P-value
G-CSF rate	05%	N	5.59	0.0001**	0.85	0.6365	-0.2444 (0.1018)	0.0164*
	10%	N	9.74	0.0001**	1.35	0.2153	-0.2555 (0.1121)	0.0227*
	20%	N	20.28	0.0001**	0.88	0.4487	-0.2221 (0.1158)	0.0551
	25%	N	25.32	0.0001**	0.94	0.3926	-0.1918 (0.1068)	0.1068
	50%	N	51.89	0.0001**	0.00	1.0000	-0.2368 (0.1018)	0.1018

* $P < 0.05$ and ** $P<0.01$

† Other control variables were not shown in the table. These variables include ABC types, gender, race, grade at diagnosis, lymph node involvement, comorbidity, radiation therapy, histology, age at diagnosis, diagnosis year, stage, and SES variables.

§ IV groups: patients were assigned into one of two (50%), four (25%), five (20%), ten (10%) and twenty (5%) groups based on median, quartiles, quintiles, deciles and 5 percentiles of prophylactic G-CSF treatment rate.

Table IV-25 The Instrumental Variable Model of Prophylactic G-CSF Choice on Neutropenia Hospitalization within the time period from ABC Initiation to 63 days post ABC initiation for Patients Who Survived to 63 Days Post ABC Initiation Where G-CSF Treatment Rate Groups (GRATE50PT) are Used as Instrumental Variables (N=3853)

IV Variable	**IV group §**	**Missgrp**	**IV Effect on G-CSF**		**Over-Identification Test of IVs**		**G-CSF on NH**	
			F-statistic	p-value	F-statistic	p-value	Treatment effect (standard error)	P-value
G-CSF rate	05%	N	5.60	0.0001**	1.24	0.2196	-0.2923 (0.1108)	0.0084**
	10%	N	9.70	0.0001**	1.75	0.0820	-0.3015 (0.1223)	0.0138*
	20%	N	20.19	0.0001**	1.97	0.1159	-0.2441 (0.1258)	0.0524
	25%	N	25.21	0.0001**	4.62	0.0099**	-0.2350 (0.1297)	0.0701
	50%	N	51.68	0.0001**	0.00	1.0000	-0.3595 (0.1606)	0.0252*

* $P < 0.05$ and ** $P<0.01$

† Other control variables were not shown in the table. These variables include ABC types, gender, race, grade at diagnosis, lymph node involvement, comorbidity, radiation therapy, histology, age at diagnosis, diagnosis year, stage, and SES variables.

§ IV groups: patients were assigned into one of two (50%), four (25%), five (20%), ten (10%) and twenty (5%) groups based on median, quartiles, quintiles, deciles and 5 percentiles of prophylactic G-CSF treatment rate.

Table IV-26 The Instrumental Variable Model of Prophylactic G-CSF Choice on Neutropenia Hospitalization within the time period from ABC Initiation to 126 days post ABC initiation for Patients Who Survived to 126 Days Post ABC Initiation Where G-CSF Treatment Rate Groups (GRATE50PT) are Used as Instrumental Variables (N=3795)

IV Variable	**IV group §**	**Missgrp**	**IV Effect on G-CSF**		**Over-Identification Test of IVs**		**G-CSF on NH**	
			F-statistic	p-value	F-statistic	p-value	Treatment effect (standard error)	P-value
G-CSF rate	05%	N	5.79	0.0001**	1.65	0.0403*	-0.2511 (0.1198)	0.0362*
	10%	N	9.93	0.0001**	2.09	0.0337*	-0.2902 (0.1335)	0.0298*
	20%	N	20.25	0.0001**	3.16	0.0237*	-0.2270 (0.1390)	0.1024
	25%	N	25.08	0.0001**	6.12	0.0022**	-0.1990 (0.1437)	0.1662
	50%	N	51.23	0.0001**	0.00	1.0000	-0.4110 (0.1797)	0.0222*

* $P < 0.05$ and ** $P<0.01$

† Other control variables were not shown in the table. These variables include ABC types, gender, race, grade at diagnosis, lymph node involvement, comorbidity, radiation therapy, histology, age at diagnosis, diagnosis year, stage, and SES variables.

§ IV groups: patients were assigned into one of two (50%), four (25%), five (20%), ten (10%) and twenty (5%) groups based on median, quartiles, quintiles, deciles and 5 percentiles of prophylactic G-CSF treatment rate.

Table IV-27 Description of Prophylactic G-CSF Duration in the First Cycle of Chemotherapy among NHL patients on anthracyclines (N=329)

	G-CSF Duration (Median Days)	**Percent of Patients Received G-CSF >= Median Days**
Measured by Number of G-CSF Claim Service Dates	9 days	75.1%
Measured by Submitted Units from Part B Claims	7 days	58.1%

CHAPTER V DISCUSSION

Main Findings

G-CSF Treatment Rate and the Effect of Factors on Prophylactic G-CSF Choice

This study identified that prophylactic G-CSF use rate among NHL patients on anthracyclines from 1994 to 2002 was 9.85%. The low use rate is consistent with the 7.5% prophylactic G-CSF use rate found in an earlier study using SEER-Medicare data from 1994 to 1999 (Chrischilles et al. 2003).

The variables of age, stage, year of diagnosis and local area prophylactic G-CSF treatment rate were factors significantly associated with receipt of prophylactic G-CSF. The other factors which were theorized into G-CSF treatment choice model, such as area socioeconomic levels, gender, ABC chemotherapy types, comorbidity, stage, grade, histology type, lymphoma node involvement, race, radiation therapy were found to be insignificantly related to prophylactic G-CSF treatment.

The study found that patients diagnosed with Stage III were more likely to choose prophylactic G-CSF, compared to patients diagnosed with Stage I NHL. The study also found that when patients diagnosed at 66 to 70 were taken as reference, older patients at age 71 to 85, 76 to 80 and 81 to 84 were more likely to receive prophylactic G-CSF. Prior studies suggested that age is a risk factor for neutropenia and older NHL patients are at a higher risk of febrile neutropenia hospitalization. Therefore, physicians took age into consideration and prescribed prophylactic G-CSF to those more fragile older patients.

The study showed that patients diagnosed since 1999 were significantly more likely to be treated with prophylactic G-CSF than those diagnosed in 1994. The increased likelihood of using early G-CSF might be due to the rapid dissemination and implementation of guidelines. The study also found for patients diagnosed from 1995 to 1998, prophylactic G-CSF use was insignificantly different from those diagnosed in

1994. This result might reflect oncologist hesitation in their prescribing behavior of using primary prophylactic G-CSF since 1994 ASCO Guidelines were published. Survey research involving oncologists identified that deceased and more appropriate G-CSF use occurred from 1994 to 1997 (Bennett et al. 1999).

Prophylactic G-CSF Use Pattern

We found prophylactic G-CSF use among NHL patients on ABC increased substantially across years, from 5.26% in 1994 to 16.86% in 2001. Prophylactic G-CSF use also varied significantly across geographical regions. For example, only 3.32% of NHL patients on ABC received prophylactic G-CSF in Seattle and about 20.56% of NHL patients on ABC received prophylactic G-CSF in New Jersey. These findings are consistent with previous retrospective studies investigating G-CSF practice patterns in patients treated with myelosuppressive chemotherapy (Chrischilles et al. 2003; Du et al. 2005). A recent study by Ramsey et al. found prophylactic G-CSF use among breast cancer and non–small cell lung cancer (NSCLC) patients treated with high risk chemotherapy regimens increased substantially from 2002 to 2005 (Ramsey et al. 2010).

The Influences of Instrumental Variable on Prophylactic G-CSF use

Chow F-statistics showed local area prophylactic G-CSF treatment rate as the instrumental variable described a statistically significant portion in the variation of G-CSF use. Patients living in areas with higher prophylactic G-CSF treatment rate would be more likely to receive early G-CSF. This result justifies the association between local area beliefs of G-CSF treatment benefit with treatment choice in the theoretical framework. It was theorized that for oncologists living in areas with higher regard for G-CSF would be more likely to recommend G-CSF in order to gain more utility.

When local prophylactic G-CSF treatment rate was divided into instrument groups, it was found that F-test statistics of over-identification restrictions were all

insignificant. The result suggests that the residuals are not correlated with the instruments and the instruments are truly exogenous. In order to further assess the association between instruments and measured confounders, univariate comparison of patient observed characteristics by two instrument groups was conducted. It was found that patient groups identified by local G-CSF treatment rate were almost similar, except a few clinical and demographic characteristics. However, the association between instrumental variable groups and these few measured confounders might place the assumption that instrument should be exogenous and unrelated to error terms at risk. The interpretation of our results is based on the assumption that differences found in measured confounders are not symptomatic of differences in unmeasured confounders across instrument groups.

The study also tested the validity of using other candidate instruments which were theorized to affect G-CSF treatment choice but unrelated to error terms or outcome variables directly. Firstly, this study tested the assumption that early G-CSF use is associated with oncologists' reimbursement rate for the first cycle of chemotherapy. Even though F test statistics suggested there was significant variation in chemotherapy reimbursement across counties grouped by Medicare Part B coverage, it was found that first cycle chemotherapy reimbursement was not related to prophylactic G-CSF use after adjustment for patient clinical and demographic characteristics. Univariate analysis suggested that patient demographic and clinical characteristics were not well balanced across patient groups defined by area chemotherapy reimbursement rate. Patients living in areas with higher first cycle chemotherapy reimbursement were more likely to be hospitalized for neutropenia hospitalization, indicating the instrument had positive association with the outcome variable. Furthermore, it was found that the distributions of chemotherapy types, histology, diagnosis year, grade, lymphoma node and use of radiation therapy were significantly different across instrumental variable groups. The finding might indicate that patient severity levels were different across patients groups identified by different levels of chemotherapy reimbursement. Therefore, estimated area

chemotherapy reimbursement would not be appropriate to be used as an instrument variable.

Secondly, the study tested the assumption that early G-CSF use is associated with per capita number of oncologists in an area. When adjusting for patient clinical and demographic characteristics, it was found that per capita number of oncologists both as linear and quadratic terms was not significantly associated with prophylactic G-CSF choice. Per capita number of oncologists was then divided into 50% groups by the median of this variable to check the balance between patient demographic and clinical characteristics across instrumental variable groups. Even though per capita number of oncologists was not correlated to neutropenia hospitalization directly, patient characteristics such as ABC types, diagnosis year, grade, lymphoma node involvement, stage and race were significantly different across the instrumental variable groups. The result indicates the potential relationship between area oncologist supply and area patient severity levels. Patients who were sicker and in need of more health care services might choose to live in areas with higher oncologist supply. The association between unmeasured confounders (e.g. severity) and per capita number of oncologists might contribute to the diluted effect of instrument on G-CSF choice. Therefore, the variation in oncologist supply would not be appropriate to be used as an instrument variable.

Thirdly, the study tested the assumption that early G-CSF use is associated with patient travel distance to the nearest oncologist. After adjustment for patient clinical and demographic characteristics, it was found that distance to the nearest oncologists both as linear and squared terms was not significantly associated with prophylactic G-CSF choice. The reason might be that most patients lived within a reasonable and convenient living distance to oncologists. For example, about 25 percent patients lived within one mile to the oncologist. About 50 percent patient lived within 3.5 miles radius of oncologists and 75 percent patients lived within 9.2 miles radius of oncologists. The balance of patient demographic and clinical characteristics across instrumental variable

groups divided by the median of distance variable was assessed. Even though distance itself was not correlated to neutropenia hospitalization directly, some important patient characteristics were significantly different across distance groups. For example, black patients were more likely to live in areas close to oncologists. We also found that patients with previous heart disease were more likely to reside in closer to oncologists and patients with prior-diagnosis anemia had more likelihood to live closer to oncologists. The results indicate the potential relationship between distance as a candidate instrument and unmeasured patient health conditions. Patients who were sicker and with more prior-diagnosis diseases might choose to live closer to oncologists. The relationship between unmeasured confounding factors such as cancer severity and patient travel distance might attenuate the effect of distance on patient G-CSF choice. Therefore, the variation of patient distance to the nearest oncologists would not be appropriate to be an instrument variable.

Neutropenia Hospitalization Risk Reduction by Prophylactic G-CSF among Treated Patients

The results from risk adjustment models applied in this study, including ordinary least square regression, multivariate logistic regression and probit regression, indicated that prophylactic G-CSF significantly reduced NH event within six months of diagnosis date for the patients who received G-CSF after adjustment for patient demographic and clinical risk factors. Different regression models generated estimates with the same direction of G-CSF treatment effect, suggesting protective effectiveness of prophylactic G-CSF use. The results of primary prophylaxis using G-CSF reported here are consistent with those from a retrospective study using administrative claims from U.S. commercial health plans, a retrospective cohort studies relied on medical records, some randomized controlled trials and a meta-analysis study (Lyman et al. 2003; Lyman, Kuderer, and Djulbegovic 2002; Tan et al. 2009). Patients with prior-diagnosis comorbidities had more

likelihood to develop neutropenia hospitalization within 6 months of diagnosis. This finding was similar to other studies suggesting comorbidities were associated with febrile neutropenia or death (Gonzalez-Barca et al. 1999; Klastersky et al. 2000; Kuderer NM, Cosler L, Crawford J 2002). Compared to patients diagnosed with DLC as reference group, patients diagnosed with unknown histology were less likely to have neutropenia hospitalization. The study also found patients diagnosed with unknown stage were more likely to be hospitalized for neutropenia when compared to patients diagnosed with Stage I NHL. Patients diagnosed in 1995 were more likely to have neutropenia hospitalization than those diagnosed in 1994.

In the sensitivity analyses, the exclusion criteria for the inability to calculate the area reimbursement variable were removed. All patients with ABC chemotherapy that did not have an inpatient stay or emergency room visit within the first five days post ABC initiation were included. Only patients who survived to a date (21 days, 42 days, 63 days and 126 days) post ABC initiation were followed up. Ordinary least square indicated that prophylactic G-CSF significantly reduced NH incidence within 126 days after ABC initiation. The associations between prophylactic G-CSF and NH incidences within 21, 42, and 63 days after ABC initiation among patient received G-CSF were not confirmed in the risk adjustment regression models.

The regression models generated estimates of average G-CSF treatment benefit in reducing neutropenia hospitalization among patients who were treated with prophylactic G-CSF. These estimates might be biased estimates of true Average Treatment effect in the Treated (ATT). The observed differences in average neutropenia hospitalization risk between treated and untreated patients are composed of both ATT and unmeasured confounding bias after controlling measured patient characteristics (Angrist 2008). As discussed in the theory chapter, there are many possible confounding factors which may be related to G-CSF choice and neutropenia hospitalization but were not recorded in administrative claims database. Such information is usually collected by physician

judgment and lab tests, for example, patient performance status, average neutrophil count (ANC), and white blood cell count (WBC). In order to assess the direction of unmeasured confounding bias, the impact of unmeasured confounders on G-CSF choice and the effects of these factors on neutropenia hospitalization should be taken into account. Patients usually with poorer performance status, lower ANC and WBC are at a higher risk of neutropenia hospitalization. If patients in concert with their oncologists perceive a higher neutropenia risk, they would be more likely to receive G-CSF as primary prophylaxis to avoid the decrease of ANC and WBC. In such cases, the protective benefit of prophylactic G-CSF may be underestimated using regression models. The estimated benefit of G-CSF from this study may represent a biased low estimate of the true average benefit in the treated patients.

Neutropenia Hospitalization Risk Reduction by Prophylactic G-CSF among Marginal Patients

Local area prophylactic G-CSF treatment rate among patients on anthracyclines provided significant variation in the prophylactic G-CSF treatment choice. In the base-case analysis, we found protective effect of prophylactic G-CSF on neutropenia hospitalization within 6 months of diagnosis among the marginal patients whose choices varied with local area G-CSF treatment rate. In the sensitivity analyses, where the exclusion criteria for the inability to calculate the area reimbursement variable were removed, substantial G-CSF treatment benefits of reducing NH within the first cycle of chemotherapy were available for marginal patients.

Under the assumptions that local area treatment rate contributes to the variation in G-CSF choice and the instrument does not associated with outcome or unmeasured confounders directly, instrumental variable method yields a consistent estimate of Local Average Treatment Effect (LATE). When the instrument is correlated with the error term or unmeasured confounders, instrumental variable estimate is generally inconsistent. In

this study, it was found patient demographic and clinical characteristics were almost balanced across instrumental variable groups, except for ABC chemotherapy regimens and diagnosis years.

Comparison of Treatment-effect Estimates from Risk Adjustment Estimator and Instrumental Variable Estimator

Table V-1 is a summary table of treatment-effect estimates yielded from different estimators. Both OLS estimates and IV estimates can be interpreted as the reduction of neutropenia hospitalization rate for a 1 percent point increase in the G-CSF treatment rate in the respective subsets of the population. As discussed before, treatment benefit estimate generated from adjusted OLS regression model reflects the average G-CSF treatment effect of reducing neutroepnia hospitalization in the treated patients (ATT). The estimate might be biased low when patients at higher risk of neutropenia and worse prognosis were favorable selected into treatment and the true protective effect of G-CSF might be greater than the estimated effect in the treated patients.

The IV estimates were not statistically significant from zero, while the estimates showed a negative relationship between G-CSF and neutropenia hospitalization among marginal patients whose treatment choices varied with the instrument. The standard errors of IV estimates were relatively much larger than standard errors of OLS estimate. The large standard errors can be explained through the possibility that instrumental variable has linear dependence with unmeasured confounders. If instrument is correlated with unmeasured confounder, the variability “left over” in the predicted value of G-CSF treatment from first stage of 2SLS is reduced. When using the predicted treatment value with reduced variability to predict outcome, the IV estimate may have large standard errors and imprecise (Angrist 2008). In contrast, adjusted OLS estimate is more precise as the actual treatment value with much more variability is used to predict outcome.

Table V-2 is a summary table of treatment-effect estimates yielded from ordinary least square regression and instrumental variable estimator in the sensitivity analysis where neutropenia hospitalization was identified within the time period from ABC initiation to 21 days post ABC initiation. We would expect true value of ATT should be greater than true value LATE if G-CSF effect is heterogeneous, G-CSF costs are homogeneous and patients thought to get the most benefit from G-CSF are most likely to receive the treatment. In this table, the estimate of ATT is smaller than estimates of LATE. It is possible because RA estimate could be biased low as patients with the most potential gain from G-CSF were at the highest risk of neutropenia hospitalization.

In the sensitivity analyses, among IV models with different time-period specification, G-CSF effect among marginal patients was found to be the strongest in the 21-day model. If marginal patients represent patients on the extensive margin, increasing primary prophylactic G-CSF treatment rate will reduce neutropenia hospitalization incidences within the first chemotherapy cycle. Results from the RA models of different time-period specifications showed a trend opposite to results from IV models. Prophylactic G-CSF reduced risk of neutropenia hospitalization within 126 days post ABC initiation among treated patients. With the varying exclusion criteria across time periods, it seems that ATT estimates become significant after those patients who were most likely to die early were removed. It could be possible that patients who died quickly (removed in 126-day time-period model) were at a very high risk of neutropenia and most likely to be selected to receive treatment firstly as they are believed to have the most gain from G-CSF. Therefore, estimates of ATT in the shorter time-period model are attenuated because these sickest patients were included.

As seen in Table V-2, significant and substantial G-CSF benefits for patients on the extensive margin are available. Estimated benefit was relatively larger than OLS estimates. The IV estimate is a number closer to the effect of G-CSF in randomized controlled trials. It refers that higher treatment rates would greatly improve patient

outcome in terms of reduced risk of NH. This scenario could be presented in Figure I-2 and Figure I-3 discussed in Chapter I. It could be that patient expectations of G-CSF benefits or costs were wrong. Higher G-CSF rates may be warranted and current rate is incorrect.

Implications

This research has several scientific novelties. Firstly, it has significant positive impacts for policy makers to be better informed about current G-CSF utilization and benefits. We identified the problem of substantial deviation of G-CSF use from the ASCO guideline recommendation. The problem underscores the question of "Which rate is right" posed by John Wennberg almost two decades ago. Similar problems have been widespread throughout the U.S. healthcare system. For example, on average, 50% of patients did not get preventive care as recommended, 30% of patients did not get care for acute medical conditions as needed and 40% did not receive necessary care for chronic medical conditions (Schuster, McGlynn, and Brook 1998). In this study, we used Huninck's theoretical framework, hypothesized scenarios to justify the correct treatment rates and applied the instrumental variable approach to answer "Which rate is right" question. This study using G-CSF as a case is of significant importance as it provides a unique and scientific example to address many of such issues in the healthcare system.

Secondly, a G-CSF choice model has been developed and specified prior to treatment-effect estimation. This choice model provides source of possible instrumental variables. A novel instrumental variable: area chemotherapy reimbursement was theorized and estimated in this study.

Thirdly, this is the first study to discuss how IV estimates could be used to address "Which rate is right" question. Our results suggest that substantial treatment benefit would be available if the treatment rates were increased. We hypothesized two scenarios where treatment effect is substantial for patients on the extensive margin. It

could be either patients along with their physicians underestimate G-CSF effect in reducing NH risk or they overestimate G-CSF costs. In these two scenarios, current rate is incorrect and higher treatment rate may be guaranteed.

However, policymakers should be cautious when interpreting the results of instrumental variable estimation from this research. Whether patients affected by the single instrument of area G-CSF treatment rate are similar to those patients who are most apt to change treatment behavior due to policy change should be considered. The policy implication is also limited because of sample selection criteria applied in this research.

Nevertheless, this research provides additional important information for policy makers to understand whether current G-CSF use was beneficial to patients who got treated. By performing risk adjustment estimation controlling for measured confounders, significant protective effect of prophylactic G-CSF was found. Treatment choice model as well as treatment-outcome relationship models theorized previously are useful to bound these estimates. In current research, we argued these ATT estimates may be biased low due to the unmeasured confounding problem. When interpreting this estimate, there are several inferential caveats should be noted regardless of the bias (Brooks and Fang 2009). Firstly, the RA estimate reflects the distribution of X_1 and X_2 factors among treated patients, which differs from their distribution among patients who did not receive treatment. Therefore, it would be risky to generalize this estimate to the untreated. Secondly, the RA estimate is an average estimate of treatment benefit among the patient population who got treated. It would not provide clear guidance for treating individual patients. Thirdly, if patients in a new sample were a set of patients with different distribution of X_1 and X_2, RA method would generate another different estimate of treatment effect for the new sample.

In addition, it should be noted that it may be inappropriate to generalize estimates beyond this study time period. In 2003, pegfilgrastim featured by a single injection in each chemotherapy cycle came to the market as a substitute for filgrastim. As the

association between travel distance and filgrastim choice has not been found in this study, it might be reasonable to speculate that improved transportation convenience might not be the reason for patients to switch from filgrastim to pegfilgrastim or increased use of G-CSF in terms of pegfilgrastim. Other possible reasons for G-CSF expansion could be increased treatment belief of pegfilgrastim, enhanced comfortableness and promising patient adherence profile. Fuller justification of whether 100% G-CSF treatment rate in current practice after the year of 2003 should be followed requires additional research using more recent data.

Limitations

This study was potentially limited by its sample selection criteria. Patients who had inpatient claims or emergency room visit claims during the first cycle of chemotherapy were excluded from the study sample. Previous research indicated that 55% of elderly patients who were hospitalized for febrile neutropenia had inpatient stay during the first cycle of chemotherapy (Morrison et al. 2001). Our study sample in the base-case analysis might contain relatively healthier patients at lower risk of neutropenia hospitalization. The exclusion criteria potentially limit the generalizability of results to sicker patients. In this study, we further conducted a sensitivity analysis by removing the exclusion criteria for the inability to calculate area reimbursement variable. Results from the sensitivity analysis could be generalized to a broader patient population.

Another limitation of this study is that neutropenia hospitalization as the outcome variable only represented severe condition of neutropenia and did not represent all neutropenia incidences. Previous literatures demonstrate that a certain subset of patients at neutropenia risk only needs outpatient visits or medication management. For example, among patient at low risk, 70% of them only need outpatient visits and oral antimicrobials. Among patients experiencing febrile neutropenia, 80% were hospitalized and 20% were managed in the outpatient setting (Cosler et al. 2005; Lyman et al. 2009).

Therefore, neutropenia risk reduction by G-CSF was not fully assessed in this study. It is unknown whether outpatient visits or medication use due to neutropenia could be reduced by prophylactic G-CSF use.

The third limitation of this study is that modeling of time to neutropenia hospitalization event was not involved. Neutropenia hospitalization event was not observed in many patients maybe because they were not followed up for an enough time period. Meanwhile, some other patients might be followed for a very long period and it made difficult to justify the causal relationship between prophylactic G-CSF and neutropenia hospitalization which happened a long time after the treatment. Survival models such as Cox proportional hazard model might be applied as a solution.

Inferences from IV estimates were based on the assumption that differences in measured confounders across instrument groups are not symptomatic of differences in unmeasured confounders across the same groups. However, if this assumption does not hold, there might be likelihood that unmeasured confounding factors were not distributed evenly across IV groups. For example, if patients with lower average neutropenia account level lived in areas where there was a higher G-CSF treatment rate, our IV estimate of G-CSF benefit would be biased low from LATE and would be interpreted as a lower-bound estimate of the true benefit of using early G-CSF in the marginal patients.

Conclusions

We conclude that local oncologist practice style measured by local area prophylactic G-CSF treatment rate had significant association with prophylactic G-CSF choice. There was variation in prophylactic G-CSF use rate among patients on ABC across local areas. The associations between prophylactic G-CSF treatment and other three potential instruments were not identified in current study sample.

When patient demographic and clinical characteristics were adjusted, estimates from risk-adjustment estimators (OLS regression model, probit regression model and

logistic regression model) showed that prophylactic G-CSF use significantly reduced neutropenia hospitalization risk within six months after diagnosis date among elderly NHL patients on ABC who received prophylactic G-CSF. These RA estimates might be biased low from the true value of ATT due to unmeasured confounding problem. The effect of prophylactic G-CSF on neutropenia hospitalization among marginal patients whose choices varied with local area G-CSF treatment rate was negative. Substantial G-CSF treatment benefits within first cycle of chemotherapy were available for patients on the extensive margin. Higher treatment rates may be guaranteed to improve patient short-term benefits from G-CSF.

Table V-1 Multiple Regression Models and Instrumental Variable Estimates of Effectiveness of Prophylactic G-CSF in Reducing Neutropenia Hospitalization within 6 Months of Diagnosis (N=3340)

Analysis Method	**IV Specified**	**IV Groups**	**IV Effect on G-CSF (F-Stat)**	**Over-Identification Test of IV (F-Stat)**	**G-CSF Effect on NH (standard error)**
Adjusted Logistic Regression	none	na	na	na	OR=0.595* (0.224)
Unadjusted OLS	none	na	na	Na	-0.040* (0.018)
Adjusted OLS	none	na	na	Na	-0.043* (0.013)
Instrumental Variable Estimates	Local area Prophylactic G-CSF treatment rate	Continuous	60.46**	Na	-0.074 (0.266)
		5%	4.78**	1.11	-0.120(0.112)
		10%	9.20**	0.87	-0.043(0.117)
		20%	11.31**	1.06	-0.010 (0.158)
		25%	15.19**	1.63	0.061(0.158)
		50%	32.46**	na	-0.006(0.186)

*, ** statistically significant at .95and .99 confidence level, respectively

§ IV group: patients were assigned into one of two (50%), four (25%), five (20%), ten (10%) and twenty (5%) groups based on median, quartiles, quintiles, deciles and 5 percentiles of prophylactic G-CSF treatment rate.

† Other control variables were not shown in the table. These variables include ABC types, gender, race, grade at diagnosis, lymph node involvement, comorbidity, radiation therapy, histology, age at diagnosis, diagnosis year, stage, and SES variables.

Table V-2 Sensitivity Analysis Results: Multiple Regression Models and Instrumental Variable Estimates of Effectiveness of Prophylactic G-CSF in Reducing Neutropenia Hospitalization within the Time Period from ABC Initiation to 21 Days Post ABC Initiation for Patients Who Survived to 21 Days post ABC Initiation (N=3857)

Analysis Method	IV Specified	IV Groups	IV Effect on G-CSF (F-Stat)	Over-Identification Test of IV (F-Stat)	G-CSF Effect on NH (standard error)
Adjusted OLS	none	na	na	na	-0.020 (0.1552)
Instrumental Variable Estimates	Local area Prophylactic G-CSF treatment rate	Continuous	82.60**	na	-0.238* (0.098)
		5%	5.74**	0.80	-0.248** (0.0856)
		10%	9.82**	0.98	-0.295** (0.096)
		20%	20.29**	1.49	-0.289** (0.100)
		25%	25.33**	0.77	-0.303** (0.104)
		50%	51.91**	na	-0.389** (0.130)

*, ** statistically significant at .95and .99 confidence level, respectively

§ IV group: patients were assigned into one of two (50%), four (25%), five (20%), ten (10%) and twenty (5%) groups based on median, quartiles, quintiles, deciles and 5 percentiles of prophylactic G-CSF treatment rate.

† Other control variables were not shown in the table. These variables include ABC types, gender, race, grade at diagnosis, lymph node involvement, comorbidity, radiation therapy, histology, age at diagnosis, diagnosis year, stage, and SES variables.

APPENDIX A CODES USED TO IDENTIFY CHEMOTHERAPY

Claim Type	Codes Used to Identify Chemotherapy Claims
NCH	HCPCS code: J8999-J9999, Q0083, Q0084, Q0085, J7150, 964XX, 965XX
Outpatient	HDPCS code: J8999-J9999, Q0083, Q0084, Q0085, J7150, 964XX, 965XX, Revenue Center Code: 0331, 0332, 0335
Medpar	DRG code: 410 Diagnosis code: V581, V662, V672 Surgical Procedure Code: 9925

APPENDIX B CLASSIFICATION OF CHEMOTHERAPY

Chemotherapy Agents	HCPCS code
C: Cyclophosphamide	J9070, J9080, J9090, J9091, J9092, J9093, J9094, J9095, J9096, J9097
H: Doxorubic	J9000, J9001, J9010, J9150, J9211
N: Mitoxantrone	J9293
F: Fludarabine	J9185
R: Rituximab	J9310
V: Vincristine	J9370, J9375, J9380
J: Not otherwise classified, antineoplastic	J9999
Q: Chemotherapy administration by infusion technique only or chemotherapy administration by both infusion and other techniques	Q0084, Q0085
E: Other anthracycline	J9151, J9180
I: Chemotherapy which is very close to cyclophosphamide	J9208
U: Unknown	0000, 92782, Q0081, Q0083, Q0086, Q0093, 96400<=HCPCS<=96599, inpatient chemotherapy claims, outpatient chemotherapy claims with HCPCS code missing
O: Others	Other chemotherapy claims

APPENDIX C HISTOLOGY TYPE CLASSIFICATION BASED ON HISTOLOGY ICD-O-3 CODE FROM PEDSF FILE

Histology code from PEDSF file (ICD-O-3)	Histology label	Histology Type
9679	Mediastinal large B-cell lymphoma	DLC
9680	Malignant lymphoma,large B-cell, diffuse, NOS	DLC
9684	Malignant lymphoma, large B-cell, diffuse immunoblastic, NOS	DLC
9690	Follicular lymphoma, NOS	Follicular
9691	Follicular lymphoma, grade 2	Follicular
9695	Follicular lymphoma, grade 1	Follicular
9698	Follicular lymphoma, grade 3	Follicular
9689	Splenic marginal zone B-cell lymphoma	marginal zone B-cell lymphoma
9699	Marginal zone B-cell lymphoma, NOS	marginal zone B-cell lymphoma
9671	Malignant lymphoma, lymphoplasmacytic	Other
9673	Mantle cell lymphoma	Other
9675	Malognant lymphoma, mixed small and large cell, diffuse	Other
9678	Primary effusion lymphoma	Other
9687	Burkitt lymphoma, NOS	Other
9700	Mycosis fungoides	Other
9701	Sezary syndrome	Other
9709	Cutaneous T-cell lymphoma, NOS	Other
9714	Large cell (K_i-1+) lymphoma	Other
9716	Hepatosplenic gamma-delta cell lymphoma	Other
9718	Primary cutaneous CD30+ T-cell lymphoproliferative disorder	Other
9727	Precursor cell lymphoblastic lymphoma, NOS	Other
9728	Precursor B-cell lymphoblastic lymphoma	Other
9729	Precursor T-cell lymphoblastic lymphoma	Other
9827	Adult T-cell leukemia/lymphoma (HTLV-1 positive)	Other

9823	B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma	Remove
9670	Malignant lymphoma, small B lymphocytic, NOS	small lymphocytic lymphoma
9702	Mature T-cell lymphoma, NOS; Lymphoepithelioid lymphoma	T-cell lymphoma
9705	Angioimmunoblastic T-cell lymphoma	T-cell lymphoma
9708	Subcutaneous panniculitis-like T-cell lymphoma	T-cell lymphoma
9717	Intestinal T-cell lymphoma	T-cell lymphoma
9719	NK/T-cell lymphoma, nasal and nasal-type	T-cell lymphoma
9590	Malignant lymphoma, NOS	Unspecific histology
9591	Malignant lymphoma, non-Hodgkin, NOS	Unspecific histology
9596	Composite Hodgkin and non Hodgkin lymphoma	Unspecific histology

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