

The copyright of this thesis vests in the author. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

Published by the University of Cape Town (UCT) in terms of the non-exclusive license granted to UCT by the author.

**Can Medicare Afford to Pay for Oral Chemotherapy Drugs?:
An Evaluation of the Problem and Introduction of a Model to Estimate Cost**

Thomas Gerald Roberts Jr., M.D.

Student Number: RBRTHO001

A minor dissertation submitted in partial fulfillment of the requirements for the award of the degree of Masters of Social Science

Faculty of the Humanities
University of Cape Town
2003

COMPULSORY DECLARATION

This work has not been previously submitted in whole, or in part, for the award of any degree. It is my own work. Each significant contribution to, and quotation in, this dissertation from the work, or works, of other people has been attributed, and has been cited and referenced.

Signature:

Signed by candidate

 Date: 2/13/03

TABLE OF CONTENTS

LIST OF ABBREVIATIONS	4
ABSTRACT.....	5
CHAPTER 1: INTRODUCTION AND SPECIFIC AIMS.....	6
CHAPTER 2: THE ROLE OF CHEMOTHERAPY IN ADDRESSING THE CANCER PROBLEM IN THE UNITED STATES	9
CHAPTER 3: CHEMOTHERPY AND THE UNITED STATES MEDICARE SYSTEM	15
CHAPTER 4: THE ECONOMICS OF CANCER CARE IN THE UNITED STATES	21
CHAPTER 5: PREVIOUS WORK.....	25
CHAPTER 6: A PILOT MODEL TO ESTIMATE THE COST AND EFFECTIVENESS OF A NOVEL ORAL CHEMOTHERAPY DRUG FOR THE TREATMENT OF NON-SMALL CELL LUNG CANCER.....	32
CHAPTER 7: RESULTS AND POLICY IMPLICATIONS	44
REFERENCES	50
Table 1. Approved Oral Anticancer Drugs in the United States which are Covered	57
and Not Covered by Medicare	57
Table 2. Average Monthly Cost Estimates for Selected Oral Cancer Drugs	58
Table 3. Model Output for Base-Case Analysis Assuming FDA-approval of Gefitinib.....	59
Table 4. Model Output for Base-Case Analysis Assuming FDA-denial of Gefitinib	60
Figure 1. Percentage of Approved Cancer Agents in the United States.....	61
Figure 2. Number of United States Oncology Drugs Approved by 5-year Intervals	63
Figure 3. Estimated Number of Cancer Drugs in Development by Phase of.....	63
Figure 4. Sources of Prescription Drug Coverage for non-institutionalized.....	64
Figure 5. Distribution of Medicare Beneficiaries by Total Prescription Drug.....	65
Figure 6. FDA-Approved Treatments of Advanced Non-Small Cell Lung Cancer	66
Figure 7. Health States, Allowable State Transitions, and Structure of Markov Model Under the Assumption of FDA APPROVAL of Gefitinib (Iressa).....	67
Figure 8. Health States, Allowable State Transitions, and Structure of Markov Model Under the Assumption of FDA DENIAL of Gefitinib (Iressa).....	68
Figure 9. Markov Probability Analysis under the Assumption of FDA Approval of Gefitinib.....	69

LIST OF ABBREVIATIONS

5-FU	5-fluorouracil
AIDS	Acquired Immunodeficiency Syndrome
BSA	Body Surface Area
BID	Twice a day (refers to drug dosing schedules)
CBO	Congressional Budget Office
CE	Cost effectiveness
CML	Chronic myelogenous leukemia
CMS	Centers for Medicare and Medicaid Services
CT	Computed topography
DNA	Deoxyribonucleic acid
EGFR	Epidermal growth factor inhibitor
FACT-L	Functional Assessment of Cancer Therapy for Lung Cancer
GDP	Gross Domestic Product
HCFA	Health Care Financing Administration
HMO	Health Maintenance Organizations
HR	Hazard ration
ICER	Incremental cost effectiveness ratio
IV	Intravenous
LV	Leucovorin
NCI	National Cancer Institute
NDA	New Drug Application
NIH	National Institutes of Health
NPAF	National Patient Advocacy Foundation
NSCLC	Non-small cell lung cancer
PS	Performance Status
QALY	Quality-adjusted life years
QD	Once a day (refers to drug dosing schedules)
QOL	Quality of life
TEM	Temozolomide
U.S.	United States
SEER	Surveillance, Epidemiology, and End Results Program
ZAR	South African Rand

ABSTRACT

Cancer, the second-leading cause of death in North America, is a major public health problem in the United States. Typically chemotherapy has been given to cancer patients by vein. Recently, effective oral cancer drugs are gaining prominence. This trend toward oral chemotherapy has important economic implications: the Medicare system of the United States pays for all intravenous (IV) chemotherapy, but it covers only those oral drugs that have an equivalent IV formulation approved by the Food and Drug Administration (FDA). The majority of oral cancer drugs in the cancer pipeline do not have such an IV equivalent. There are two proposals before the United States Congress to expand the Medicare program to cover all oral cancer drugs. Gefitinib (Iressa; AstraZeneca) is one of the most interesting of the cohort of novel, targeted oral cancer drugs. Already approved in Japan, it is currently under review by the U.S. FDA. This drug has relatively modest efficacy and few side effects; but it is likely to be expensive. Because the sponsor is seeking approval for the treatment of lung cancer, with a large annual incidence, the economic implications of an FDA approval for gefitinib have raised considerable concern. According to a pilot study presented herein, an approval for gefitinib would cost slightly over \$US71 million dollars in total for the Medicare population not already covered by a prescription drug plan. Also, gefitinib was found to be cost-effective when compared to supportive care for the third-line treatment of non-small cell lung cancer, as long as the sponsor prices the drug in a range similar to other recently-approved oral cancer drugs.

CHAPTER 1: INTRODUCTION AND SPECIFIC AIMS

The recent emergence of effective oral chemotherapy (e.g. imatinib mesylate for chronic myelogenous leukemia) represents one of the most important trends in clinical oncology. Historically, most (85-90%) administrations of chemotherapy for cancer have been given by vein, i.e. intravenously. The proportion of new cancer drug approvals that are orally available, however, is growing. In the future, oral cancer drugs may comprise half of all new drug approvals (Figure 1).

Four factors are driving this trend. First, approximately 90% of cancer patients prefer oral chemotherapy when given the choice of an equally efficacious intravenous (IV) agent.^{1,2} Second, economic savings to patients and the health care system may be possible when time-consuming chemotherapy infusions are avoided. The few pharmacoeconomic comparisons between oral and IV agents that have been performed to date appear to confirm such resource savings.³ Third, the vast majority of anticancer drugs under development are targeted therapies that require stable drug levels for effective tumor[†] growth inhibition.⁴ These constant drug levels are best achieved by either oral delivery or IV infusion pumps; but pumps are inconvenient, expensive, and associated with infectious and thromboembolic complications.⁵ Lastly, the chronic use of oral agents is consistent with the paradigmatic shift within oncology to treating cancer as a chronic disease.⁵

The widespread use of oral chemotherapy introduces a major challenge to the United States (U.S.) health care system. While the Medicare program currently pays for the administration of all IV chemotherapy for Medicare enrollees, the program only reimburses for

[†] This manuscript follows standard American spelling rules. The author acknowledges that standard English spelling, which applies in South Africa, may vary and apologizes for any inconvenience while reading.

six of the 23 (26%) approved oral cancer drugs (Table 1). The current reimbursement policy requires that the oral agent be either chemically equivalent to, or a prodrug of, an approved IV chemotherapy drug. For example, capecitabine (Xeloda; Roche, Nutley, NJ), which is fully reimbursed by Medicare, is a prodrug of 5-flourouracil (5-FU) that is converted within tumor cells to the active agent. Since these six agents comprise a minority of all oral antineoplastics, older cancer patients are increasingly required to pay for their cancer drugs, which in some instances can amount to over US\$3,000[†] a month.

Because of growing political pressure (and in light of the failure of the most recent Congress to pass a comprehensive Medicare prescription drug plan), attention is now shifting to a possible Medicare drug plan specifically to reimburse oral chemotherapy. The particular resolution under congressional review would provide US\$2.8 billion in direct funding for Medicare reimbursement of all oral chemotherapeutic agents for a yet unspecified number of years.⁶ Congressional action has been stalled, in part, by insufficient information on the economic and clinical impact of such a resolution. Namely, there have been no studies performed to date evaluating patterns of oral chemotherapy use among Medicare recipients. Nor are there published economic models available to predict the cost to the health care system of the introduction of new oral cancer drugs.

The specific aims of this work were **(1) to review the economic issues surrounding oral chemotherapy in the Medicare population;** and **(2) to construct an economic model capable of predicting the societal economic impact of a widely publicized oral cancer drug, gefitinib (Iressa, formerly ZD 1839; AstraZeneca, Wilmington, DE, USA),** which is currently under review for approval by the United States Food and Drug Administration. This work is intended to

[†] All currency values in this manuscript are given in US dollars. As of 8 February 2003, 1 US\$ equaled approximately 8.39 ZAR (South African Rand).

contribute to the public policy debate, and hopefully insure equitable and timely access to life-saving drugs.

University of Cape Town

CHAPTER 2: THE ROLE OF CHEMOTHERAPY IN ADDRESSING THE CANCER PROBLEM IN THE UNITED STATES

The Cancer Problem

Cancer is the second leading cause of death in the United States, currently representing one in four deaths.⁷ In year 2002 alone, there were an estimated 1,284,900 cases of invasive cancer diagnosed in the United States and approximately 555,500 cancer-related deaths.⁸ In addition to these invasive cancer, there are more than a million non-invasive skin cancers and 55,000 non-invasive breast cancers diagnosed each year in the United States. As mortality from heart disease, the number one killer, continues to decline in North America, cancer is estimated to become the leading cause of death by 2005.⁹ According to statistics from the American Cancer Society, approximately 1,500 Americans die each day of cancer. The lifetime probability of developing cancer for men and women is 43.4% and 38.3% for men and women, respectively.¹⁰ Cancer, therefore, is a major public health problem in the United States, affecting a very large number of people.

This burden is shared disproportionately across the population. Racial minorities and the elderly have the highest incidence and mortality rates from cancer. For example, African Americans have the highest incidence rates for cancer among all racial and ethnic groups in the United States; the incidence rate of cancer is 60 percent higher in African Americans than in Hispanics and Asian/Pacific islanders and is more than twice as high as the rate for American Indians.⁸ Mortality rates also differ among racial groups: the mortality rate from cancer in African Americans is 33% higher than in whites.⁸ With the exception of female breast cancer and female lung cancer, the overall incidence and death rates for the most common cancers are higher for African American than for any of the other racial and ethnic groups.

The burden is also disproportionately heavy for older Americans. Americans 65 years and older shoulder more than half of all new cancer diagnoses.⁷ This translated into approximately 640,000 older Americans diagnosed with cancer in 2002.¹¹ Age, in fact, is the most powerful driver of cancer incidence. The chance of developing invasive cancer in any organ, for example, is estimated to be approximately 8.3% for an American male from age 40 to 59; this chance goes up sharply to 33.1% for an American males from age 60-79.¹⁰ This jump in cancer incidence with age is somewhat less impressive for women. Yet, it is still clear that the threat of cancer increases exponentially as people, and the population as a whole, age.

The National Response

The national focus and investment in cancer research in the United States dates back to December, 1971 when President Nixon signed the National Cancer Act and launched the nation's "War on Cancer." The mandate, as stated in the Act, was to "support basic research and the applications of the results of basic research, to reduce the incidence, mortality and morbidity from cancer." There was the implication by the supporters of the National Act Cancer that cancer could be conquered by 1976, the American bicentennial.¹² Even though most scientists and physicians thought this goal was unrealistic, the success of the American Apollo space missions in the late 1960's inspired such national optimism and exuberance.

The National Cancer Act gave the National Cancer Institute (NCI) a high degree of autonomy at the National Institutes of Health (NIH). The Director of the NCI and its National Cancer Advisory Board became Presidential appointments; special budgetary authority allowed the NCI to bypass the Public Health Services and the Office of Management and Budget and go directly to the President on budgetary matters.¹² Multiple billions of dollars poured into the NCI

and affiliated university research laboratories. The national cancer drug development program was forged. Cancer became unique among other areas medicine in the United States in that the government explicitly sought to discover, develop, and test pharmaceuticals. For other diseases, this function was left to the commercial pharmaceutical industry.

Unfortunately, the enthusiasm surrounding the National Cancer Act did not yield quick cures. The year 1976 came and went, and cancer remained undefeated.¹³ The National Cancer Act became a popular target in the press: the implication was that the NCI was mismanaging its funds and failing to produce results.¹² Indeed, it would be almost 20 years after waging the “War on Cancer” before both overall incidence and mortality from cancer began to fall.¹² There were dramatic instances when new cancer drugs transformed the treatment of a specific type of cancer, but these have generally been rare. Progress, instead, has come incrementally. From 1992-1998, for example, cancer incidence and mortality declined approximately 1.1% per year. Today, slightly more than 50% of patients with invasive cancers are cured. Unfortunately, the prognosis for most patients with advanced-stage, inoperable cancer remains grim. For these patients with advanced disease, treatment depends on the ability of chemotherapy drugs to stabilize the malignancy and, hopefully, extend survival and improve quality of life.

Chemotherapy

The National Cancer Act may not have produced cures for most of the common cancers, but progress *was* made. Newly developed chemotherapy agents, and combinations of established drugs, effected cures for thousands of people with lymphomas, leukemias, and germ cell tumors (e.g. testicular cancer and choriocarcinoma). Chemotherapy also established higher cure rates after complete surgical excision of breast, colon, gastric, and ovarian cancers.

From 1975 through 2002, the U.S. Food and Drug Administration (FDA) granted 132 marketing approvals for cancer drugs for the treatment of over 100 different kinds of cancers.¹⁴ The rate of development and approval for cancer drugs accelerated rapidly over this time (Figure 2). For example, the FDA granted only 3 approvals during the period of 1981 through 1985, compared to 55 approvals from 1996 through 2000. It is too early to tell whether the rate of cancer drug approval in the U.S. can sustain this impressive trend.

Chemotherapy works in principle by killing or inhibiting the growth of neoplastic (cancer) cells to a greater extent than normal cells. Most chemotherapy drugs now on the market work by damaging or interfering with the synthesis of deoxyribonucleic acid (DNA), thereby killing all rapidly dividing cells. Some of these rapidly dividing cells, e.g. hair follicles, are normal cells. Chemotherapy drugs have traditionally had a narrow therapeutic index, meaning that there is little room for error in the dosing of the chemotherapy drug.¹⁵ Too little of the drug will have a sub-therapeutic effect on the tumor; too much of the drug can produce intolerable toxicity or even death. This toxicity to normal tissues has been the major limiting factor in the development of new cancer drugs and has influenced the way cancer drugs are given. Because of the narrow therapeutic index of cytotoxic chemotherapy drugs, most have been developed for IV use in order to limit the variability of drug levels in the blood.

The Future of Cancer Chemotherapy and Drug Development

Cancer drugs classically enter into three sequential phases of development before they are approved, each representing a distinct set of goals and challenges. If the results from these clinical trials yield particularly promising results, the sponsor may choose to submit a new drug application to the FDA to seek marketing approval for a specific indication. The last few years

have witnessed a remarkable and unprecedented proliferation of cancer agents in development. At the end of 2001, there were an estimated 1,345 cancer drugs under investigation, with 837 in the preclinical stage and 196, 219, and 67 in clinical Phases I, II, and III, respectively (Figure 3).¹⁶ According to the Pharmaceuticals Research and Manufacturer's Association, the total number of novel cancer agents in the pipeline has increased 87% since 1995.¹⁷ Almost half of biotechnology firms now concentrate primarily on novel treatments and diagnostic tools for cancer. Cancer drugs under development now exceed the total of the next two most represented therapeutic classes, anti-infectives and cardiovascular agents, combined.^{16, 17}

Most of these cancer drugs are targeted against specific molecules on or inside cancer cells. Because these new "targeted agents" rely on more specific cell killing, their therapeutic indices are much higher. They also rely on constant inhibition of their molecular targets, rendering periodic intravenous dosing ineffective. The combination of higher therapeutic indices and the requirement for steady drug level creates an opportunity and need for cancer drugs that can be safely given by mouth.

A recent example of such an orally available cancer drug is imatinib mesylate (Gleevec; Novartis, East Hanover, NJ, USA).¹⁸ Imatinib mesylate targets a protein on the surface of chronic myelogenous leukemia (CML) cells, the bcr-abl kinase, which is not present on normal cells. When given to patients with CML, this oral drug, given once a day, can induce durable remissions in patients who otherwise would have undoubtedly died of their disease, despite the best alternative chemotherapy drugs.¹⁹ The drug has few side effects and has been taken by some patients for several years with minimal toxicity. Because no IV equivalent formulation exists for imatinib mesylate, Medicare, the insurance plan that covers most Americans aged 65 and over, does not reimburse for it. The average wholesale cost of imatinib mesylate, at US\$2,362 per

month,²⁰ is out of the range of affordability for many American seniors (Table 2). Medicare does, however, reimburse for more toxic and less effective drugs to treat CML. Increasingly, seniors in the U.S. are being placed in the position of choosing between less effective and more toxic IV chemotherapy, which is paid for by Medicare, versus less toxic and more effective oral chemotherapy, which is not.

University of Cape Town

CHAPTER 3: CHEMOTHERPY AND THE UNITED STATES MEDICARE SYSTEM

The rationale for focusing on the Medicare Population

There are several reasons to focus on the Medicare system when examining the economic impact of the shift to oral chemotherapy. First, this system covers the medical expenses of American aged 65 and over; as detailed in Chapter 2, these older Americans have dramatically higher odds of requiring oral chemotherapy drugs. Of the 41.5 million Medicare beneficiaries today, approximately 8.3 million (20%) have at least one diagnosis of cancer.¹¹ Second, while most younger working Americans carry prescription drug coverage, standard Medicare enrollees *do not* carry a prescription drug benefit when the drugs are given outside of a hospital. Almost all oral chemotherapy is designed to be administered at outside of the hospital and is therefore not eligible for Medicare coverage. Third, the public debate in the United States regarding a prescription drug plan for Medicare is heating up once again. The President of the United States, in his State of the Union Address on 28 January 2003, recently highlighted the need to improve access to prescription drugs for the Medicare population.²¹ Senator Bill Frist, a physician who recently became the Majority Leader of the U.S. Senate, has also focused attention on a Medicare drug plan.²² In a time of steep budgetary cutbacks in the United States, the passage of a Medicare drug plan depends on the availability of reliable cost estimates.

Medicare Overview

The United States Congress created Medicare in 1965. The program serves Americans who are aged 65 or over and those qualifying for disability at any age. The disabled must be receiving social security benefits for 2 years to be eligible for Medicare. In 2002, there were 41

million beneficiaries to the Medicare Program: these included 35 million elderly and five million disabled persons. The disabled therefore represented approximately 15% of Medicare enrollees.

^{23, 24} Since its inception, Medicare has evolved into a highly regulated system that has a complex system of price controls. In fact, over 110,000 pages of rules and regulations govern almost every dollar spent under Medicare.²³

Medicare has three parts: Medicare A, B, and C. Part A covers services at institutions, such as surgery and hospital stays; Part B covers outpatient services such as physician visits. Part C, a recent addition to Medicare in 1997 that is also called Medicare+Choice, gives seniors the option of securing more comprehensive serviced by joining a private health plan. Approximately 86% of elderly Medicare beneficiaries participate in Parts A and B; the remainder participate in Part C.²³ For the most part, the cost to seniors to enroll into Medicare is nominal. Most Medicare beneficiaries have contributed sufficient payroll taxes, amounting to 40 quarters of employment, by the time they are 65, to entitle them to receive Medicare Part A benefits without additional cost. Most also choose to participate in Part B to receive coverage for physician services. Unlike Part A, Part B requires a monthly premium. At US\$58.70 per month, however, this premium is affordable to most Americans.²⁵

Whereas over 90% of private health plans in the United States offer a prescription drug plan, traditional Medicare Parts A and B do not with a few exceptions. These exception include the following outpatient drugs: immunosuppressive agents for enrollees who have received organ transplants; erythropoiten for patients with renal disease on dialysis who have anemia; clotting factors for the treatment of hemophilia; and oral cancer drugs that have an intravenous equivalent, comprising the minority of marketed oral cancer drugs.²⁶ Medicare Part C was intended to extend drug coverage to those seniors willing to enroll in private Health Maintenance

Organizations (HMOs). While some aspects of standard Medicare are curtailed for those choosing Part C, such as physician choice, these private plans are typically more comprehensive, providing preventive care, doctors visits, hospitalizations, and prescription drug benefits. Approximately 5.6 million Americans have chosen to participate in Medicare Part C, representing a small minority of seniors. Therefore, the majority of Medicare enrollees still do not carry a drug benefit.

Without a public intervention, it is likely that that the number of older American without a dug benefit will grow. Medicare Part C has run into problems. Many private plans are dropping out of the program because the payments to these HMO's by the government have fallen. When the plans drop their participation, former members must return to traditional Medicare. In 2002 alone, the Centers for Medicare and Medicaid Services announced that 58 plans would withdraw or diminish services, affecting 536,000 seniors nationwide.²⁷ Without structural reform, it is unlikely that Medicare will be able to stop this trend. Medicare Trustees have reported that Medicare itself is heading toward bankruptcy by 2030. These projections are fueled by the rate of health care inflation for seniors. According to the Congressional Budget Office (CBO), total drug spending for the Medicare Population is expected to grow from US\$87 billion in 2002 to US\$278 billion in 2012, representing an average annual rate of over 10% and totaling US\$1.8 trillion over the nine-year period.²⁸ By 2030, the total number of beneficiaries will be nearly double at 77 million; and taxes and premiums paid into the program will be less than the expected medical expenses for retiring "baby-boomers."²⁹

Prescription Drugs in the Medicare Population

Prescription drugs are an important component of the American health care system. From a financing perspective, however, drugs have historically comprised a relatively minor component of total health spending. In 1999, for example, prescription drugs accounted for approximately 8 percent of the total national health spending; but this proportion is expected to increase to 14 percent by 2010.³⁰ These increases in drug spending will be driven by the introduction of new drugs,³¹ aggressive marketing campaigns through advertising directed at consumers,³² and higher prices.³³

For seniors, prescription drugs play a more critical role in their health care than the population in general. In fact, the number of prescription drugs filled per American is more than three times as high for those aged 65 and older compared to those under age 65.³⁴ Unfortunately, almost 4 in 10 (38%) Medicare beneficiaries had no drug coverage as of the Fall of 1999 (Figure 4); disturbingly, the access to these benefits are unequal across the Medicare population and declining.²⁸ The groups with the least drug coverage include those living in rural areas, the near-poor, and the oldest-old.²⁸ For example, in the Fall of 1999 50% of Medicare beneficiaries living in rural areas lacked prescription drug coverage compared to 34% of those living in urban area. Similarly, 45% of enrollees 85 years and older lacked prescription drug coverage compared to 35% of those ages 65-74. Because of volume discounting, those beneficiaries without a prescription drug plan pay the highest prices, estimated at 15% higher, for drugs when they purchase them at community pharmacies.^{26, 35}

The major sources of prescription drug coverage for Medicare beneficiaries are eroding. For example, the prevalence of employee-sponsored plans, which provide benefits for 28% of the Medicare population, is declining precipitously. The proportions of employers with at least

200 employees offering prescription drug coverage to those over age 65 fell from 41% in 1999 to 34% in 2001. This trend was accompanied by an increase in the retirees' share of prescription drug costs secondary to reduced benefits.²⁸ Further erosion of employer-based drug benefits is expected.³⁶

The second largest source of prescription drug coverage for seniors, behind employee-sponsored plans, are Medicare HMOs, or Medicare Plan C (Medicare+Choice) plans. These plans assisted 15% of all beneficiaries with prescription drugs in Fall of 1999 (Figure 4). In recent years, however, the proportion of all Medicare+Choice beneficiaries with drug coverage declined from 84% in 1999 to 71% in 2002; and 69% of all Medicare+Choice enrollees are subject to limits on drug benefits.³⁷

Other sources of funding for prescription drugs in the Medicare population, such as Medigap, are also threatened. Medigap is a program that allows Medicare enrollees to individually purchase supplemental insurance that provides limited prescription drug benefits. Because of adverse selection, these premiums tend to be quite high.³⁶ For example, the average out-of-pocket drug cost in 1999 for an individual that purchased a Medigap policy was US\$570. Perhaps because of these high premiums, the number of Medicare enrollees who purchased a Medigap policy has been declining rapidly over the past five years.²⁷ Efforts by individual American state represent one of the few areas of growth of funding for the funding of prescription drugs in the elderly. As of September 2002, 34 states had either established or authorized pharmacy assistance programs for seniors.²⁸ These programs, however, vary widely with respect to what is covered and are too heterogeneous to represent a structural solution. Also, with the budget crisis faced by most American states, the future of these programs is in doubt.

Out-of-pocket Expenditure on Prescription Drugs for the Medicare Population

The average annual per capita drug spending for the Medicare population is growing briskly. According to the Congressional Budget Office, the current annual spending is estimated at US\$2,149 in 2002, a number which is increasing at an annual rate of 13%. According to the Centers for Medicare and Medicaid Services (CMS) [formerly the Health Care Financing Administration (HCFA)], this rate of increase is approximately twice that of total health care expenditures.³⁰ The amount of drug spending is quite variable across the Medicare population; this skewing is shown in Figure 5. Approximately one-third of the population will incur less than US\$501 in total expenditures in 2002, while fourteen percent of the population with exceeds US\$4,000 in annual drug expenses.

The skewness toward high out-of-pocket expenditure on drugs for seniors is one of the most compelling reasons to have insurance, even more so than average expenditure. For example, the average U.S. per capita spending on prescription drugs in 1999 was only US\$358; this compared to US\$413 for alcohol, tobacco, and entertainment. However, among elderly Americans, the top 4 percent of the heaviest users made up 24 percent of total drug spending for the elderly in 1996, while the bottom 40 percent only accounted for only 5 percent of spending.³⁸ While median per capita drug spending for the elderly in 1998 was only US\$895, per capita spending for the 95th percentile was an alarming US\$4,111.³⁹ These data demonstrate that older American who are ill, and who happen to not have a prescription drug plan, may pay enormous amounts of money for their medicines.

CHAPTER 4: THE ECONOMICS OF CANCER CARE IN THE UNITED STATES

The Cost of Cancer Care in the United States Health Care System

The United States expends enormous resources to pay for its health care system. The latest projections estimate that U.S. national health expenditures will reach US\$2.8 trillion by 2011. These projections represent a projected growth rate of 7.3 percent during the period 2001-2011, which is 2.5 percent per year faster than nominal gross domestic product (GDP). If these projections play out, health spending in the United States will comprise 17 percent of GDP in 2011, up from 13.2 percent in 2000.⁴⁰

The proportion of total health care expenditures spent on cancer care is growing. Cancer-related costs rose approximately 10% per year from the late 1980s through the early 1990s and rose approximately 16% from 1995 to 1998. In 1999, the National Institutes of Health (NIH) estimated that total annual costs of cancer exceeded US\$107 billion, with direct medical costs accounting for US\$37 billion of the total.⁴¹ The acceleration of cancer-related costs appears to be gaining pace. For example, a report from the National Cancer Institute revealed that cancer costs rose 62% over the five-year period from 1985 to 1990;⁴² In 2001, the NIH estimated the overall costs for cancer at US\$157 billion, a jump of 47% over the period of just two years.¹¹

Expenditure on the most common cancers are responsible the bulk of these increases: the American Cancer Society estimates, for example, that breast, lung, and prostate cancer alone account for half of these direct medical costs.⁴³

Drivers of the Increases in Cancer Care Costs in the United States

There are several forces driving the impressive cost increases in cancer care. First, cancer treatment has been expanded to a growing proportion of Americans. Imaging technologies, for

example, now detect cancers at earlier stages and allow patients to be treated who otherwise would have died of advanced cancer with little or no treatment at all. Dramatic improvements in supportive care make it feasible for most patients today, even the advanced elderly, to receive treatment for their disease.^{44, 45}

Whereas primary care physicians would routinely tell older patients with cancer that “nothing can be done,” these patients are now referred to oncologists and receive life sustaining and life-improving treatments. Newer generations of chemotherapy agents developed over the last 10 years have incrementally, but significantly improved the experience of the majority of patients under treatments. Recently, novel drugs have been approved that provide excellent treatments for some diseases where no treatment previously existed. In the case of gastrointestinal stromal tumors (GIST), for example, a novel drug literally transformed the treatment of that disease.⁴⁶ Many dying patients who received the agent, even those who were in hospice care, got better; some even were able to return to work. In other solid tumors, treatment advances have been less dramatic. Even in these cases, however, there have emerged a growing numbers of second- and third-line treatments that have proven efficacy for such diseases as lung and breast cancer. Many of these treatments were not available even 5-10 years ago.

Another driver of cost increases that is often ignored is the substitution of newer, better treatments for older ones. These substitutions are often more expensive; but they must be taken in the context of their improved outcomes. When comparing costs of cancer care over the last 10-15 years, it is important to consider that the experience of most cancer patients receiving treatment in the United States is substantially improved from their experience ten years ago. Newer drugs and radiation techniques have made the difference between patients spending miserable weeks in the hospital versus being at home with their families. In some cases, patients

are even working during treatment. The important trend toward a multidisciplinary approach to cancer care has undoubtedly increased cost but has also provided invaluable services to the most vulnerable patients. Newer, less toxic targeted therapies such as monoclonal antibodies and hormonal treatments are now routinely augmenting or substituting for more toxic cytotoxic chemotherapy, generally improving outcomes.⁴⁷

Even in the cancers where survival has increased only modestly, newer technologies and treatments have allowed patients to escape morbidity until much later in their disease course. This phenomenon, referred to by David Cutler and others as the compression of morbidity effect,⁴⁸ is now routinely seen with treatment of many advanced cancers. In the treatment of metastatic lung cancer, for example, survival has increased only modestly over the past 10 years.⁴⁹ Quality of life while on treatment, on the other hand, has increased substantially. Patients remain symptom free for longer and therefore have much less overall morbidity, limited in general to a short time at the end of life.

The Costs of Chemotherapy in the United States

Given the large increases in the cost of cancer care in the United States over the last several years, surprisingly little quantitative work has been published focusing on the disaggregated components of the total cost. The most complete study to date of outpatient chemotherapy expenditure was performed by Halbert, *et al.*⁴¹ This group studied the outpatient cancer costs in years 1995 and 1998 of a large cohort of patients enrolled in an HMO, including Medicare patients who chose to enroll in the HMO via the Medicare+Choice program. The group included patients from 20 American states who were diagnosed with cancer in either 1995 or 1998. The majority of patient in their cohort (67%) were aged 65 or greater.

A large portion of the cohort (88%) underwent treatment with chemotherapy at some point during the year. Total charges increased from US\$1,218 per patient in 1995 to US\$2,003 per patient in 1998, an average annual increase of 18% per patient. This increase was shared equally by increases in professionally administered drugs, usually given intravenously; and in pharmacy claims, including oral chemotherapy and oral supportive medications. A closer look at these proportions reveals some interesting trends. Whereas the number of pharmacy claims increased by 9 percent from 1995 to 1998, the number of professional claims actually decreased by 5% annually. Therefore, charges per claim increased faster for professionally-administered drugs than for pharmacy claims.

This study also allowed estimates of the various types of therapy on cancer-related drug charged. Chemotherapy contributed most (67%) to the total drug charges in 1998. Chemotherapy adjuncts, such as hematopoietic growth factor that allow chemotherapy to be given more safely, represented 18% of the charges. Supportive therapy, such as antibiotics and antidepressants, comprised 15% of the charges. In support of the assertion that oral chemotherapy is playing an increasingly important role in cancer care, the study reported that the proportion of the total cancer drugs dispensed at an out-patient pharmacy was 14% in 1998, a significant increase from 1995.

CHAPTER 5: PREVIOUS WORK

The Economics of Oral Cancer Drugs

Despite the increasing prominence of oral chemotherapy, and the important resource implications introduced by the transition toward these agents, only a very few studies have been published that directly compare IV chemotherapy to oral chemotherapy in the treatment of a cancer.^{3, 50, 51} Moreover, there have been no published studies to date estimating the demand induced by the approval of a new oral cancer drug. The two most widely cited economic studies comparing an oral to an IV drug in oncology are presented below

Oral Temozolomide versus IV Dacarbazine in Advanced Metastatic Melanoma⁵⁰

Melanoma is a serious cancer that usually arises from pigmented cells in the skin. If it is recognized early, before it has the chance to invade vertically, surgical excision can provide an excellent chance for cure. If the cancer metastasizes to a lymph node, however, the chance for surgical cure decreases; and once the cancer metastasizes to a distant organ, the chance for cure is lost. Chemotherapy can palliate symptoms, and may even extend life, but these benefits are modest. Despite the considerable attention captured by biological therapies such as interferon and interleukin II, no drug has been shown to be consistently superior to IV dacarbazine.⁵² Unfortunately, treatment of metastatic melanoma with dacarbazine is associated with a median survival of only 4-6 months. The drug also causes nausea and vomiting, and requires daily visits to a doctor's office or hospital for five days in a row every 3 weeks. Obviously, this therapy is sub-optimal for most patients with advanced melanoma, providing a compelling rationale to explore new treatments.

Temozolomide (TEM) is a newer agent that, unlike dacarbazine, is taken by mouth; it is, however, metabolized to the same active metabolite as dacarbazine. The FDA granted marketing approval to TEM in 1999 for the treatment of anaplastic astrocytoma, a type of brain cancer. The FDA has not, to date, approved it for the treatment of melanoma. In the late 1990s, TEM's sponsor, Shering, initiated a randomized Phase III trial comparing IV dacarbazine to oral TEM in previously-untreated metastatic melanoma.⁵³ TEM was administered orally once a day for 5 days, repeated every 28 days; dacarbazine was administered IV once a day for 5 days, repeated every 21 days. Treatment was continued to either unacceptable toxicity arose or until the cancer progressed. With 305 patients enrolled, the trial had an 80% power to detect a 3-month prolongation in survival between the two arms. The trial's major clinical finding was that the median progression-free survival was 1.9 months for TEM versus 1.5 months for DTIC ($p = 0.012$, Hazard Ratio = 1.37; 95% CI, 1.07 to 1.75). TEM therapy was also associated with higher health-related quality of life (QOL) at 12 weeks on therapy. The percentage of patients whose tumor shrunk was similar between both arms.

Because oral TEM is more expensive than IV dacarbazine, and marginally superior, if at all, Hillner, *et al* performed a post hoc economic analysis to illustrate pertinent trade-offs.⁵⁰ They chose incremental cost-effectiveness (CE) analysis as the primary assessment. They made the following key assumptions: (1) Patient survival and costs of palliative therapy after the development of progressive disease were assumed to be the same independent of the initial therapy and were therefore excluded. (2) Because maximum treatment was 1 year, and less than 10% of patients were treated for 9 months, costs were not discounted. (3) Out-of-pocket costs and lost wages were not considered in the analysis, as they were assumed to be the same for the two groups. (4) Because the authors believed that the hazard ratio for the two arms may have

been biased because of the more frequent and earlier assessments in the IV dacarbazine arm (every 21 days) versus the TEM group (every 28 days) the lowered the HR from 1.37 to 1.18 for their assessment.

In terms of resources and cost valuation, the authors identified and included in their model important resources used for patients in each arm of the trial, the number of units required per cycle, and each unit's baseline price and range. Drug costs were based on average wholesale prices in the United States, and also included a range for the sensitivity analyses. The cost of administering the IV chemotherapy was based on current reimbursements and not actual costs; the authors acknowledged that this approach may have underestimated the cost of administering the IV dacarbazine. Direct and indirect nonmedical costs, which recent guidelines have recommended including in CE analysis,⁵⁴ were excluded from the base-case analysis because these costs were not collected during the trial. In their sensitivity analysis, they did include the cost of US\$50 per half day per office visit for a family member; patients were assumed to not be able to work.

The authors did not adjust survival in their model for QOL, because they argued that the completion rate for the health-related QOL questionnaires, at less than 66%, was too low to yield reliable estimates. At a 12-week assessment, patients on the TEM arm did indeed report significantly higher health-related QOL; therefore, again, the authors may have biased their results against the TEM arm. For their cost-effectiveness analysis, the authors calculated an incremental CE assessment: the additional cost of the TEM treatment for each added year of survival provided compared with the IV dacarbazine treatment.⁵⁰ The base-case model was from the perspective of a centralized payer, because only direct medical costs were included. The

authors did not show the structure of their model. While the use of hazard ratios might imply the use of a Markov model, they did not state this explicitly.

The results of the base-case determined that the TEM treatment cohort had an average per-patient cost of US\$6,902, compared with US\$3,697 for the IV dacarbazine treatment, representing an increase of US\$3,205 per patient. Assuming based on the trial data, that patients in the TEM group lived an average of 32 days longer, the incremental CE ratio was calculated at US\$36,990. This value translated to US\$101 per extra day of life-gained. Confidence intervals around the point estimate ranged from dacarbazine being dominant (when the survival of the dacarbazine group was assumed to be greater) to an incremental CE ratio for TEM of US\$18,670 per life-year gained. The authors performed a threshold analysis using the commonly employed threshold of US\$50,000 per life-year gained: sixty percent (60%) of the simulations met this threshold. The authors therefore concluded that the incremental CE ratio of oral TEM in the treatment of metastatic melanoma was within the comparable range of many accepted medical interventions. Because Medicare pays for IV dacarbazine in the treatment of melanoma but does not pay for oral TEM--it is not FDA approved for treating melanoma--, the authors highlighted the tension confronting physicians they choose between similar agents that differ substantially in convenience and cost.

Oral Capecitabine versus IV 5-fluorouracil (5-FU) in Advanced Colorectal Cancer

Cancer of the colon and rectum (colorectal cancer) is a public health problem throughout the world. Globally, colorectal cancer is the third most commonly diagnosed cancer and the fourth most common cause of cancer deaths.⁵⁵ Because colorectal cancer afflicts a large number

of people, and because its incidence is projected to rise with demographic shifts, the resources expended in its treatment will grow.³

Like with melanoma, palliative treatments for advanced colorectal are sub-optimal. The standard treatment for advanced colorectal cancer has for years been based on the IV chemotherapy drug 5-fluorouracil (5-FU). This drug, which has a short half-life in the blood, is typically given in conjunction with another agent leucovorin (LV), which helps stabilize 5-FU to its target thereby increasing its ability to shrink tumors.⁵⁶ Another approach is to administer 5-FU with an infusion pump so that continuous drug levels are maintained. The response rates (percentage of patients who tumors shrank) associated with this approach have generally been higher, but infusion pumps are inconvenient, expensive, and prone to complications.⁵⁷ Even with the best treatments available, including the recent addition of irinotecan to 5-FU/LV, patients with metastatic disease tend to live less than 2 years, and cures are not possible. Thus, any innovations in treatment options that increase effectiveness or convenience are welcomed, particularly if they are cost-effective.

One relatively recent innovation is the availability of an oral fluoropyrimidine drug that is formulated in pills and which gets converted to 5-FU in the tumor. This drug, capecitabine (Xeloda; Roche, Nutley, NJ, USA) was approved for the treatment of advanced colorectal cancer in 2001 based on a pivotal Phase III trial which showed higher response rates and equivalent survival when capecitabine was compared to IV 5-FU/LV. The 5-FU/LV treatment was given as an IV infusion at a clinic or hospital each day for 5 consecutive days every 4 weeks; capecitabine was given orally twice daily for 2 weeks followed by a week's rest. Treatment with either regimen was continued for 30 weeks or until the development of progressive disease or unacceptable toxicity.⁵⁸

Because the IV 5-FU/LV and oral capecitabine displayed similar clinical efficacy, but had dramatically different administration schedules, the study prospectively collected resource use data at all participating centers on study case report forms. Information was collected on the number of scheduled visits made to a hospital, clinic, or office to receive therapy; the duration of the visits, the chemotherapy administered; number of unplanned consultations with general practitioners or specialist plus telephone consultations; hospital admission days; and treatments for the management of adverse events. The major findings of the study were (1) patient who received oral capecitabine required substantially fewer hospital visits, spent fewer days in the hospital for the management of adverse events, and required fewer expensive medications for the management of side-effects. (2) Because the patients administered the oral capecitabine at home, there were more unexpected phone consultations and more unscheduled clinic visits for the patients randomized to the capecitabine arm. Because these unscheduled clinic visits were deemed less resource-intensive compared to hospitalization, the authors concluded that capecitabine treatment of colorectal cancer results in substantial resource use saving relative to the IV 5-FU/LV.

The study had three major limitations. First, the authors did not attach any cost estimates to the resource units that they identified and collected. For example, they did not quantify the cost of a scheduled clinic visit compared to an unanticipated hospitalization. This failure to attach cost estimates allowed only a qualitative conclusion, which is generally not as helpful for policy planning as a quantitative one. Second, the authors did not create a model based on their data to estimate whether the increased cost of the new oral drug capecitabine was offset by the resource use savings reported in the study. The failure to model the data also obviated the chance to perform sensitivity analyses. Third, the study was conducted alongside a Phase III registration

trial, which is an artificial and highly monitored setting. While this approach improves the reliability of the data, it does limit its generalizability. Patients entering clinical trials tend to be younger and healthier than the general cancer population; it is not clear that older, less well patients would have done as well with self-administered therapy where, by design, they are seen less frequently by a their physician.

Knowledge Gap in the Literature

Both of these studies produce important insights into the economic implication of administering oral cancer chemotherapy as a substitute for an established IV equivalent. In both examples, the authors concluded that the oral cancer drug is either cost-effective or associated with less resource use. However, most oral cancer drugs in the pipeline are not direct substitutes for IV agents;⁵⁹ most are completely novel agents that do not have an IV equivalent and which would not be paid for by standard Medicare. Also, since most of the novel, targeted oral drugs are less toxic than standard cytotoxic chemotherapy, the market for cancer drugs will likely expand, particularly among patients who have advanced disease and who are too sick to benefit from standard IV-based chemotherapy. To date, however, there have been no studies analyzing the economic impact of this expansion in demand. Therefore, the author set out to develop an economic model to estimate the economic impact of a novel, oral targeted therapy for advanced lung cancer which does not have an IV equivalent and which is currently under FDA review.

CHAPTER 6: A PILOT MODEL TO ESTIMATE THE COST AND EFFECTIVENESS OF A NOVEL ORAL CHEMOTHERAPY DRUG FOR THE TREATMENT OF NON-SMALL CELL LUNG CANCER

The Questions

The previous chapters and sections have described in some detail the very visible transition toward oral, targeted chemotherapy agents and away from IV cytotoxic ones. The previous chapters have also highlighted the challenges that accompany this transition, focusing in particular on the economic impact of oral chemotherapy to Medicare enrollees and to the Medicare system. These issues have come into sharp focus as the FDA reviews the controversial new drug application (NDA) of gefitinib (Iressa), an oral agent for the third-line treatment of non-small cell lung cancer (NSCLC). Approximately 85% of all lung cancer patients have this histologic sub-type of lung cancer.

Gefitinib is a novel inhibitor of the epidermal growth factor receptor (EGFR), a growth-promoting protein on the surface of cells. Particularly when compared to other treatments for lung cancer, gefitinib is relatively non-toxic: its major side effects include an acne-like rash on the face and chest and minor diarrhea. Because of its favorable toxicity profile, it can be given to lung cancer patients who would otherwise be too ill to receive standard cytotoxic chemotherapy. In Phase I and II clinical trials, gefitinib displayed modest activity against lung cancer, even when it was given to cancer patients who had received multiple previous chemotherapy drugs. Based on this modest activity, gefitinib's sponsor, AstraZeneca, submitted an NDA to the FDA to market the drug for the treatment of non-small lung cancer who have already received two

previous lines of chemotherapy treatment or who were inappropriate for standard cytotoxic chemotherapy.

Multiple pivotal clinical trials over the past 5-10 years have clearly established a palliative role for chemotherapy in good-functioning patients with advanced NSCLC (see Figure 6). Based on these trials, the United States FDA has approved three first-line chemotherapy “doublet” treatments, each containing a platinum-based drug along with another newer chemotherapy agent. These two-drug combinations include the following: carboplatin plus paclitaxel, cisplatin plus docetaxel, and cisplatin and gemcitabine. None of the combinations has proven superior to any another.⁶⁰ These drugs are typically given in 1 to 3-week intervals over the course of 12 to 18 weeks, followed by a period of rest.

For those patients who maintain a good functional status, typically called performance status (PS), and whose lung cancer progresses, the FDA has approved docetaxel, given alone, as a second-line chemotherapy. This agent is given once by vein every three weeks for 12 to 18 weeks, followed again by rest. When the cancer progresses after docetaxel treatment, there are no FDA-approved third-line treatments for lung cancer. The treating oncologist can then decide whether to pursue a supportive care strategy alone or to prescribe an “off-label” chemotherapy agent, which means that the chemotherapy is approved for another cancer but not for the treatment of third-line lung cancer. These “off-label” treatments have, in general, a 10-20% chance of shrinking the tumor; one of the factors that discourage oncologists from pursuing “off-label” prescribing is that patients typically display declining PS after two lines of chemotherapy and can therefore not tolerate standard chemotherapy.

The FDA has announced plans to make a ruling on gefitinib’s approval for the third-line treatment of non-small cell lung cancer in May of 2003. The drug is already approved in Japan

for the same indication, and is before the European review regulatory boards as well. On 24 September 2002, the FDA asked its Oncologic Drug Advisory Committee to vote on whether gefitinib's modest (10%) chance of shrinking tumors was meaningful in this disease; the committee voted 11 to 3 that it was. Despite this vote, the approval decision has been delayed in part to explore questions of potential pulmonary toxicity.⁶¹ There have been economic concerns as well. Unlike other industrialized countries, the U.S. FDA has no statutory role in evaluating cost-effectiveness when making their approval decisions; they are to base these decisions on safety and efficacy alone. There is, however, an undercurrent of concern that approving gefitinib for the treatment of lung cancer, which had an annual U.S. incidence of almost 170,000 in 2002,⁸ would lead to inappropriate health care cost inflation for a drug with only modest activity. To date, however, **there have been no published estimates of what the likely cost to the Medicare population would be of an approval for this drug. Nor have there been any published analysis of whether this treatment is likely to be cost-effective from a societal perspective when compared best supportive care in the third-line treatment of non-small cell lung cancer.** The author's original pilot study, presented over the next several sections, will address these questions.

Model Type Chosen

A Markov, state-transition model was chosen as the underlying structure for this pilot study. Markov models are gaining increasing prominence in medical decision analysis. They are distinguished by their relative simplicity, explicit assumptions, ease of modeling prognosis data from clinical trials, and relatively faithful representation of many clinical and policy problems.⁶² And, they are easily adapted to use with cost-effectiveness analyses.⁶³ These models have been

applied to economic question in most areas in oncology. Within the field of lung cancer, for example, they have been used to (1) analyze the cost-effectiveness of various staging strategies prior to cancer surgery⁶⁴ and (2) determine if computed topography (CT) scanning is cost-effective as a screening tool to detect early lung cancers.⁶⁵ Considerable uncertainty surrounds both the costs and effectiveness of gefitinib; fortunately, Markov modeling provides the ability to perform rapid sensitivity analyses to test any underlying assumptions. This ability may be very useful in the planning for contingencies.

The Clinical Trial Data Chosen for the Model

There are no completed Phase III trials comparing gefitinib to best supportive care in the third-line treatment of NSCLC. Therefore, it is unknown whether gefitinib extends survival in this setting. There have been, however, two large-scale open-label Phase II trials in patients with advanced NSCLC to evaluate the efficacy and tolerability of gefitinib in patients previously treated with platinum-based chemotherapy (see also Figure 6). One trial (IDEAL 1) was based mainly in Europe and Japan; the other (IDEAL 2) was based in the United States. These trials provided the basis for gefitinib's approval in Japan and provide the basis for pending new drug applications in the United States and Europe. The results have not been published in final form, but they have been presented in abstract form and have been reviewed elsewhere.⁶⁶ Because the author's home institution, the Massachusetts General Hospital, accrued a large number of patients to the IDEAL 2 trial, the author is intimately familiar with its design.

The patients included in IDEAL 1 had a better prognosis because the entry criteria included patients who had failed one or two prior lines of chemotherapy. In order for patients to be eligible for entry into the IDEAL 2 trial, patients had to have failed at least 2 prior

chemotherapy regimens. Therefore, from an U.S. perspective, IDEAL 2 applies more closely to the question at hand: Is gefitinib cost-effective for the third-line treatment of NSCLC? The clinical data from IDEAL 2 were therefore chosen for use in the model.

The IDEAL 2 trial was a randomized, double-blind Phase II trial investigating tumor response, disease-related symptom response, and safety of daily oral gefitinib (250 mg/day versus 500 mg/day) in advanced NSCLC. Of 216 patients treated (median age 61 years-old), 102 received 250 mg/day and 114 received 500 mg/day. Forty one percent (41%) of the patients had failed 2 previous chemotherapy regimens; the remainder had failed more than 2 previous regimens.

The proportion of patient who displayed objective tumor shrinkage on CT scans with treatment was approximately 10%; this proportion did not differ significantly between the two arms of the trial. The “response rate” of 10% is similar to what is seen with standard chemotherapy in heavily pre-treated patients. The proportion of patients reporting an improvement in their symptoms, such decreased amounts of shortness of breath or fatigue, was considerably higher at approximately 40%. The improvement in symptom relief came rapidly in most patients, as 60% of the patient reporting symptom did so by the second week of treatment. The median survival for both arms of the IDEAL 2 trial was approximately 6 months. The median number of months on therapy was 1.8 in IDEAL 2.⁶⁶ Responses lasted up to 8 months. The patients who were randomized to the lower dose had fewer adverse events. As compared to historical trials of standard cytotoxic chemotherapy, these adverse events were generally mild and reversible; and few patients had to withdrawal from the trial because of drug-related adverse events. The sponsor of the IDEAL 2 trial, AstraZeneca, concluded from the data that gefitinib’ favorable tolerability profile, along with its modest anti-tumor, activity could provide a valuable

alternative to best supportive care in those patients who have received prior approved chemotherapy.

Constructing the Model for Third-Line Treatment of NSCLC Assuming Gefitinib's Approval

The first step to building a Markov model is to enumerate all distinct health states.⁶² Classically, the three health states utilized in Markov models are WELL, ILL, and DEAD. As the model cycles through time, patients can transition between these health states as the model structure permits. These three states, however, often do not provide enough clinical nuance for the disease being modeled. In the case of the IDEAL 2 trial, there appeared to be 4 distinct potential health states: TAKING DRUG/RESPONDING, TAKING DRUG/NOT RESPONDING, OFF DRUG/TERMINAL CARE, and DEAD. A schematic of these transition states, the allowable state transitions, and the accompanying Markov model of the IDEAL 2 trial are shown in Figure 7. This structure is the basis for modeling the effects of a possible FDA approval of gefitinib.

In building the model of patient taking gefitinib for third-line treatment of NSCLC, the following 6 assumptions were made. First, patient who were ultimately going to respond to treatment did so within the first month; the clinical data support this assumption as stated above. Second, once a patient is responding, they will continue to take the drug until there is evidence of disease progression; once disease progression is documented by physical exam or imaging test exam, they will enter the terminal care state. Once a patient enters terminal care, they will stay in that state, without receiving chemotherapy, until they die. Third, patients who do not show a response to the drug will continue taking it until their disease shows signs of progression or until they have intolerable side effects from the drug. This seems like a reasonable assumption since

patients who do not respond initially are likely to continue taking the drug in the hope that they will respond in the future, particularly since the side effects are minimal and since no additional treatment would be available after going off the drug.

Forth, there are assumed to be no treatment-related deaths and no treatment-related morbidity. There have been reports of a 0.4% to 1.0% incidence of acute interstitial pneumonia with the use of gefitinib, accompanied by a 50% mortality rate when present;⁶¹ but lung cancer patients can develop acute interstitial pneumonia at similar rates without the use of gefitinib. Therefore, this is an area of some controversy, and the author acknowledges that the model may need to be adapted in the future to control for these reports. Fifth, patients taking gefitinib were assumed to have no survival over those not taking the drug. Until a Phase III randomized trial has been completed comparing gefitinib to supportive care, a survival advantage can not be assumed; and response rates alone have generally been a poor predictor of survival in oncology.⁶⁷ Finally, it was assumed that all patients who lived long enough with advanced lung cancer to take gefitinib did so. This assumption is reasonable for those patients who could afford to pay for the drug. Few patients with advanced cancer would overlook a treatment with the hope of helping them if the side-effect profile was relative mild.

Constructing the Model for Third-Line Treatment of NSCLC Assuming Gefitinib's Denial

Under the assumption that the FDA does NOT approve gefitinib, there would be no FDA-approved treatment for patients who have failed a platinum-based and a docetaxel-based regimen. Therefore, assuming, somewhat simplistically, that there is no off-label chemotherapy prescribing, patients would only have two health states available to them: TERMINAL CARE and DEATH. A schematic of these states and the accompanying Markov model simulating a

FDA denial are shown in Figure 8. While the assumption of no “off label” prescribing may be unrealistic for the general lung cancer population, it is probably more realistic for the Medicare population. It is a small minority (likely less than 25%) of elderly patients with advanced NSCLC who are well enough after receiving 2 regimens of chemotherapy to receive additional cytotoxic chemotherapy.

Calculating the Hazard Ratios for State Transitions

The state transitions for each health state in Figures 8 and 9 were modeled directly from the data in the IDEAL 2 trial. The survival and response times in IDEAL 2 were reported, like most trials, in median times. In order to model rates, these were converted to mean survival and response times. Survival time was modeled as an exponential function as below, which is a reasonable approximation for a severe disease like lung cancer.⁶⁸. The derivation of this approach is presented in the sequence of equations as follows:

$$f(x) = re^{-rx}$$

At median survival, survival = 0.5, so $0.5 = 1 - e^{(-\text{median}/\text{mean})}$

$$\text{Mean} = \text{median}/\ln(0.5)$$

$$\text{Mean} = \text{median}/0.6931$$

$$r = 1/\text{mean}$$

$$\text{Probability of death (t)} = 1 - e^{-rt}$$

In both models, the Markov termination criteria were set at 24 months. This value was chosen, because patients with advanced NSCLC are very unlikely to live beyond this time, In order to illustrate the approach taken above, the state probabilities over time, under the assumption of FDA approval, are presented in Figure 9.

Economic Evaluation and Resource and Cost Valuation

As recommended by a recently-convened consensus panel, the viewpoint of this analysis is from the United States societal perspective; and the primary assessment was an incremental cost-effectiveness analysis.^{63, 69} The economic analysis was made simpler by the nature of the options under consideration. In both the supportive care only model (assuming the FDA denies marketing approval for gefitinib) and the gefitinib model (assuming the FDA approves gefitinib for third-line treatment of lung cancer), patients and accompanying family members are assumed to present to their treating physician for scheduled monthly visits. There was assumed to be no difference in resource utilization between those patients on supportive care compared to those patients on gefitinib, with the important exception of the cost of gefitinib. These are reasonable assumptions, since gefitinib does not require IV infusions; is not given with supportive medications; and has few side effects, which are relatively inexpensive to treat when they occur. It is also assumed that there are no differences in resource utilization between those patients who respond to gefitinib and those patients who do not. The decrease in tumor-related symptoms defined by responders may decrease resource utilization at the margin, but these effects are likely to be subtle and small when compared to the overall cost of caring for lung cancer patients at the end of life. Likewise, while it is conceivable that patients who respond to treatment are more

likely to return to work, older patients with lung cancer, the population being modeled, generally do not seek employment regardless of their response to therapy.

Drug Costs, Cost of Supportive Care, Personal Costs, and Nonmedical Costs

The cost of gefitinib has not yet been established in the marketplace in the United States. A base-case estimate of US\$1,000 per month of therapy was chosen based on several factors. First, this price is in the conservative range of costs for other oral chemotherapy drugs (Table 2). While other oral chemotherapy drugs may have somewhat higher monthly costs, they are indicated to treat much rarer diseases; in those cases, the sponsor justifies higher prices claiming a tiny market size. There is intense political pressure in the current U.S. health care environment for drug companies adopt conservative pricing policies for new drugs, especially those drugs which treat life-threatening diseases like cancer and AIDS. The US\$1,000 per month is also in the range of the cost for “off-label” chemotherapy agents typically given for third-line treatment of NSCLC. Finally, discussions with some representatives from gefitinib’s sponsor confirmed that this value is in the range that is being considered should gefitinib obtain FDA approval. Fortunately, the Markov model allows for a broad range of pricing to be tested. For both the supportive care and the gefitinib models, it was assumed that no new capital or equipment costs would be incurred.

The precise cost of providing supportive care for advanced-staged patients with NSCLC is unknown. Based on a previous analysis, this base-case cost was estimated to be on average US\$1,800 per month.⁷⁰ The monthly cost of patients treated with gefitinib was therefore modeled as the monthly cost of providing supportive care (US\$1,800 in the base case) plus the monthly cost of gefitinib (US\$1,000 in the base case). Because both arms of the model contained the cost

of best supportive care, the estimate of its cost will have a limited impact on the calculated incremental cost-effectiveness analysis. And again, the modeling allows for sensitivity analyses to be performed around these base-case estimates.

Modeling Effectiveness of Therapy

As detailed above, there was no survival advantage assumed for those patients receiving gefitinib compared to those patients receiving supportive care only. There was also assumed to be no quality of life difference between those patients on supportive care compared to those *non-responding* patients taking gefitinib. Importantly, the model did control, however, for quality of life for those patients taking gefitinib who did respond to treatment.

Utility states for the health states were obtained from published studies contained in a systematic overview of cost-utility assessments in oncology.⁷¹ The utility, or QALY state, for patients with advanced NSCLC receiving supportive care or those taking gefitinib without a response were both assumed to be 0.69, based on previously-published study.⁷² Patients were assumed to stay in this health state until they died, which is a somewhat clinically unrealistic assumption. Due to better supportive treatments, however, the decline in utility at the end of life has been compressed to a relatively short time; particularly with hospice support, this assumption of non-declining utility is becoming more reasonable.

The most difficult aspect of constructing the model was choosing an appropriate utility score for those patients who received gefitinib and enjoyed symptom relief. The quality of life and disease-related symptom relief were evaluated in IDEAL 2 with a common instrument in oncology called the Functional Assessment of Cancer Therapy for Lung Cancer (FACT-L, version 4). This instrument has a lung cancer sub-scale that assesses disease-specific symptoms.

The FACT-L has proven to be reliable and comprehensive, yet brief and sensitive, means of assessing QOL domains in patients with lung cancer.^{73,74} In particular, this instrument was validated by a large study conducted by the Eastern Oncology Cooperative Group.⁷⁵ In the IDEAL 2 trial, approximately 40% of the patients who received gefitinib obtained an meaningful improvement in their FACL-L score that lasted at least four weeks; this improvement tended to occur within the first several week of treatment. Unfortunately, there has been no method to reliably convert from FACT-L scores to utility scores. Therefore, based on expert opinion of several thoracic oncologists and oncology nurses, as well as the author's own experience, a utility score of 0.80 was chosen for this group of "responders." The value 0.80 was chosen in particular because it has been published in a previous study to represent the utility state for patients with locally-advanced NSCLC,⁷² which is a stage of lung cancer just below metastatic lung cancer in its severity. Because patients with advanced lung cancer patients on average live only 6-10 months, discounting was not used for either costs or effectiveness.

CHAPTER 7: RESULTS AND POLICY IMPLICATIONS

Base-case Analysis and Limited Sensitivity Analysis

The Markov models were analyzed using commercially available modeling software (Data version 3.5 for Healthcare; TreeAge Software, Inc., Williamstown, MA, USA) were run using the base-case assumptions. The text report of the Markov analysis under the assumption of FDA-approval for gefitinib and FDA-denial of gefitinib are reported in Tables 3 and 4, respectively. These table were inspected in order to debug the model previous to its final run. As shown in these tables, the average cost of treating a patient with advanced lung cancer in the model with gefitinib was US\$3,161; this cost was associated with an average effectiveness of 0.51 QALYs. These values compared to an average cost of US\$1,230 and average effectiveness of 0.45 QALYs to treat a patient with supportive care only in the third-line treatment setting. The incremental cost effectiveness ratio (ICER) to treating with gefitinib therefore equaled:

$$(US\$3,160 - US\$1,230) / (0.51 \text{ QALYs} - 0.45 \text{ QALYs}) = \text{US\$32,183 per QALY.}$$

Extensive threshold and sensitivity analyses were beyond the scope of this pilot project; but limited sensitivity analysis did reveal some interesting trends. The ICER of gefitinib was not particularly sensitive to the price for the drug. For example, even a doubling of the base-case estimate of gefitinib's cost to US\$2,000 only increased the ICER modestly, to US\$35,516. The model was somewhat more sensitive to the utility state chosen for patients responding to gefitinib. A decrease in this estimate from 0.80 to 0.75, for example, increase the ICER \$38,620. The model provided ICERs under \$50,000 per QALY for the majority of the simulations run under a broad range of values around the base-case estimates.

Policy Implications

These pilot results have several limitations. First, the model is based on a highly controlled clinical trial, decreasing the ability to generalize the results. However, in a much-less controlled expanded access protocol of more than 250 patient treated at the Massachusetts General Hospital and Dana-Farber Cancer Institute in Boston, the clinical results were remarkably similar to IDEAL 2. Second, the pilot model made several assumptions that may not adequately describe the clinical nuance. The author is developing a more complicated model for eventual publication in order to capture this clinical nuance. Third, there will be “off-label” use of gefitinib, which Medicare can not easily identify. This model assumed that oncologist would prescribe gefitinib for its FDA-approved indication. Even within the context of these limitations, it is instructive to place the results in a larger societal perspective.

The calculated base-case estimate of US\$32,183 per QALY is slightly less than US\$100 per day of quality-adjusted survival. Although league tables ranking the cost-effectiveness ratios of new therapies are fraught with limitations, the value of US\$32,183 is less than the commonly-used standard of hemodialysis for end-stage renal disease.^{50, 69} Because gefitinib has an ICER between US\$20,000 and US\$100,000 per year, its level would receive a “C” recommendation based on Canadian guidelines.⁷⁶

What are The Likely Costs to the Medicare System to Cover Patients Treated with Gifitinib?

From a Medicare systems standpoint, the critical question is how much would it cost to pay for all Medical enrollees with metastatic NSCLC to receive gefitinib for treatment after failing two previous regimens. Unlike other countries, the United States does not possess a nationwide cancer registry, so the precise number of cancers diagnosed each year is unknown.⁸

The American Society publishes estimates the number of new cancers occurring annually in the United States by using age-specific cancer incidence rates from the NCI's Surveillance, Epidemiology, and End Results (SEER) Program, coupled with population data from the U.S. Census Bureau.⁷ The American Cancer Society then forecasts the number of cancer cases expected to be diagnosed in the United States in each year by using an autoregressive quadratic model.⁸ Using this approach, the total estimated new cases for lung cancer in 2002 was 169,400. The total estimated to have died of the disease was 154,900. For American patients, non-small cell lung cancer (NSCLC) is the dominant histology, responsible for 86% of lung cancers.⁷⁷

From a Medicare perspective it is important to point out that advancing age is associated with an increased incidence of lung cancer. Those patients over 70 comprise 51% of the incident cases, which is a growing segment of the population.⁷⁸ Approximately 40% of patients have advanced, incurable metastatic (stage IV) disease at the time of diagnosis.⁷⁹ By applying these estimates, the annual incidence of Medicare-eligible patients with advanced NSCLC who are not covered by an HMO drug plan can be calculated as follows:

$$\text{Annual incidence} = 169,400 \cdot N \cdot Q \cdot P \cdot R \cdot (1 - S)$$

$$N = \text{Percent of NSCLC cases} = 0.85$$

$$Q = \text{Percent of incident cases aged } \geq 65 = 0.58$$

$$P = \text{Proportion of patients presenting as Stage IV} = 0.40$$

$$S = \text{Proportion of patients over 65 covered by HMOs} = 0.24$$

$$\text{Annual incidence} = 25,686$$

It is also possible to use the published literature to estimate this number of Medicare-eligible patients who would likely take gefitinib. Earle, *et al* examined the impact of referral patterns on the use of chemotherapy for cytotoxic lung cancer.⁸⁰ They studied patients from the 11 tumor registries participating in SEER program. The SEER registries are estimated to capture 97% of incident cases,⁸¹ covering approximately 10% of the American population.⁸ The coverage patterns are thought to be representative.⁸² Ninety-four percent (94%) of the patients captured by SEER registries have been linked to the Medicare administrative database.⁸³ The Medicare database includes billing data for inpatient and outpatient care, physician and laboratory services, and home health and hospice care.

This group examined all Medicare-eligible patients over age 65 who were diagnosed with stage IV (non-small cell lung cancer), the most common type of lung cancer, between 1 January 1991 and 31 December 1996 (6-year period). Importantly, they excluded patients who had enrolled in a health maintenance organization (HMO), or those who had a previous cancer. Twelve thousand fifteen (12,015) patients met the eligibility criteria for the study. Sixty percent (60%) of the cohort were men, and the average age was 73.5 years. In order to get the annual incidence of lung cancer among Medicare-eligible patients using this data, the following calculations are required:

$$\text{Annual incidence} = \frac{12,015}{T} \cdot \frac{1}{U} \cdot \frac{1}{6}$$

$$T = \text{Percent of incident cases covered by SEER} = 0.97$$

$$U = \text{Proportion of the population covered by SEER} = 0.10$$

$$\text{Annual incidence} = 20,644$$

This annual incidence of 20,644 is close to the estimate calculated from the American Cancer Society data. In the Earle study, 78% saw an oncologist at some time during the course of their disease; and twenty-six (26%) received chemotherapy at some point during their illness. This treated proportion increased from 24.9% in 1991 to 30.3% in 1996; this translated to an odds ratio to receive chemotherapy of 1.1 for each year of the study.

Because not all patients receive treatment for their advanced NSCLC, these annual estimates represent the upper limit of Medicare patients not already covered by an HMO plan who would receive “on-label” use of gefitinib. Under the base-case assumptions, Medicare would be required to pay US\$71,122,500 for the first year of a program to cover newly diagnosed older patients with advanced NSCLC to receive gefitinib. While the drug was shown in the previous section to be cost effective by the commonly-used standard of US\$50,000, the aggregate cost of \$US71,122,500 is substantial. This value does not account for potential substitution effect if patients are treated “on-label” with gefitinib rather than “off-label” with IV cytotoxic chemotherapy. Most experts agree, however, that the approval of gefitinib would instead create an expansion effect of treatment for patients in the Medicare population because of its relatively non-toxic side-effect profile.

Political Response

Several attempts to add outpatient drug coverage, including significant efforts by Presidents Clinton and Reagan, to the Medicare benefit package over the last 15 years have failed.²⁶ Within the field of oncology, the political efforts have shifted to lobbying Congress to allow Medicare to cover all oral cancer drugs. One such Congressional proposals, *the Access to Cancer Therapies Act (House of Representatives 1624/Senate 913)*, would ensure such coverage

of all anti-cancer drugs, whether they be oral or injectable, for Medicare enrollees under Part B. The National Patient Advocate Foundation (NPAF) has been one the strongest supporters of this bill.

According to the NPAF estimates, the overall costs of covering all oral anti-cancer drugs would add US\$438 million to the Medicare budget in 2002 out of the US\$78.5 billion that Medicare was expected to spend on cancer that year. The NPAF estimated that that according to the same (unpublished) analysis, the projected cost over five years is approximately US\$2.8 billion, or one half of one percent of Medicare's budget for cancer.¹¹ Given that gefitinib is only one of many oral cancer drugs that Medicare would need to cover, and that it is likely to cost Medicare over US\$70 million if approved and covered, this estimate of \$438 million seems low.

Concluding remarks

To the authors' knowledge, this original work represents the most comprehensive analysis to date of the funding challenges introduced by the transition to oral cancer drugs. The author's economic model of gefitinib for the third-line treatment of lung cancer, although presented only in its pilot stage, illustrates that novel, oral targeted therapies are likely to be expensive, even if they are cost effective additions to the chemotherapy armamentarium. Because cancer is a disease of the elderly, and because the ability of the elderly to pay for prescription drugs is undeniably declining, the U.S. government should play a role in helping seniors to pay for life-sustaining and life-improving drugs. While seniors in the United States can exert tremendous political influence, it is uncertain whether geopolitical forces besetting the current U.S. government will distract it from taking action on this issue of great public health concern.

REFERENCES

1. Liu G, Franssen E, Fitch MI, Warner E. Patient preferences for oral versus intravenous palliative chemotherapy. *J Clin Oncol* 1997; 15:110-5.
2. Borner MM, Schoffski P, de Wit R, et al. Patient preference and pharmacokinetics of oral modulated UFT versus intravenous fluorouracil and leucovorin: a randomised crossover trial in advanced colorectal cancer. *Eur J Cancer* 2002; 38:349-58.
3. Twelves C, Boyer M, Findlay M, et al. Capecitabine (Xeloda) improves medical resource use compared with 5- fluorouracil plus leucovorin in a phase III trial conducted in patients with advanced colorectal carcinoma. *Eur J Cancer* 2001; 37:597-604.
4. Druker BJ. Perspectives on the development of a molecularly targeted agent. *Cancer Cell* 2002; 1:31-6.
5. Borner M, Scheithauer W, Twelves C, Maroun J, Wilke H. Answering patients' needs: oral alternatives to intravenous therapy. *Oncologist* 2001; 6:12-6.
6. Eastman P. At ACCC Meeting, Medicare Payments for Oral Drugs, Outpatient Services at Issue. *Oncology Times*. Vol. 24, 2002:9.
7. American Cancer Society. Cancer facts and figures 2003. [online]. Available from URL: http://www.cancer.org/docroot/STT/stt_0.asp [Accessed 2003 January 31].
8. Jemal A, Thomas A, Murray T, Thun M. Cancer statistics, 2002. *CA Cancer J Clin* 2002; 52:23-47.
9. Schein PS. The case for a new national program for the development of cancer therapeutics. *J Clin Oncol* 2001; 19:3142-53.
10. DEVCAN Software, Version 4.1, Surveillance, Epidemiology, and End Results program, 1973 to 1998, Division of Cancer Control and Population sciences, National Cancer Institute, 2001.
11. National Patient Advocate Foundation. Why Covering Oral Cancer Drugs for Medicare Beneficiaries Makes Good Sense. [online]. Available from URL: <http://www.npaf.org/initiatives.php?p=159> [Accessed 2003 Feb 1].
12. DeVita VT, Jr. A perspective on the war on cancer. *Cancer J* 2002; 8:352-6.
13. Bailar JC, 3rd, Gornik HL. Cancer undefeated. *N Engl J Med* 1997; 336:1569-74.

14. Food and Drug Administration. Oncology Tools. [online]. Available from URL: (<http://www.fda.gov/cder/cancer/>) [Accessed 2002 August 20].
15. Clark JW. Targeted therapy. In: Chabner BA, Longo D, eds. Cancer Chemotherapy & Biotherapy. Philadelphia: Lippincott Williams & Wilkins, 2001:891-810.
16. Parexel's Pharmaceutical R&D Statistical Sourcebook 2001. Boston: Parexel International Corporation, 2002.
17. America PRaMo. New medicines in development for cancer, 2001:1-56.
18. Druker BJ. STI571 (Gleevec) as a paradigm for cancer therapy. Trends Mol Med 2002; 8:S14-8.
19. Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. N Engl J Med 2001; 344:1038-42.
20. 2002 Drug Topics Red Book. Montvale, NJ: Medical Economics Co., Inc, 2002.
21. George W. Bush. The State of the Union. January, 2003. [online]. Available from URL: <http://www.whitehouse.gov/stateoftheunion/> [Accessed 2003 January 31].
22. Frist Reaction to State of the Union. [online]. Available from URL: <http://www.senate.gov/~frist/press-item.cfm?id=189990> [Accessed 2003 February 5].
23. Turner GM. A profile of the health sector in the United States. Pharmacoeconomics 2002; 20 Suppl 3:31-45.
24. Centers for Medicare and Medicaid Services. Medicare enrollment trends, 1966-2001 [online]. Available from URL: <https://cms.hhs.gov/statistics/enrollment/natlrends/default.asp> [Accessed on 2003 Feb 1].
25. Centers for Medicare and Medicaid Services. Medicare premium amounts for 2003. [online]. Available from URL: <http://www.medicare.gov/Basics/Amounts2003.asp> [Accessed 2003 January 31].
26. Iglehart JK. Medicare and prescription drugs. N Engl J Med 2001; 344:1010-5.
27. Okie S. More HMOs Quit Medicare Plan: About 536,000 Elderly Will Lose Coverage Next Year. Washington Post, 2001.

28. The Henry J. Kaiser Family Foundation. The Medicare Policy Project. Medicare and Prescription Drugs, October, 2002 [online]. Available from URL: <http://www.kff.org/sections.cgi?section=medicare> [Accessed 2003 January 20].
29. Board of Trustees of the Federal Hospital Insurance and Federal Supplementary Medical Insurance Trust Funds. 2002 Annual Report [online]. Available from URL: <http://cms.hhs.gov/publications/trusteesreport/default.asp> [Accessed 2003 Feb 2].
30. Heffler S, Levit K, Smith S, et al. Health spending growth up in 1999; faster growth expected in the future. *Health Aff (Millwood)* 2001; 20:193-203.
31. Dubois RW, Chawla AJ, Neslusan CA, Smith MW, Wade S. Explaining drug spending trends: does perception match reality? *Health Aff (Millwood)* 2000; 19:231-9.
32. Wilkes MS, Bell RA, Kravitz RL. Direct-to-consumer prescription drug advertising: trends, impact, and implications. *Health Aff (Millwood)* 2000; 19:110-28.
33. Berndt ER. The U.S. pharmaceutical industry: why major growth in times of cost containment? *Health Aff (Millwood)* 2001; 20:100-14.
34. The Henry J. Kaiser Family Foundation. Prescription Drug Trends [online]. Available from URL: <http://www.kff.org/content/2001/3112/RxChartbook.pdf> [Accessed 2003 January 20].
35. Frank RG. Prescription drug prices: why do some pay more than others do? *Health Aff (Millwood)* 2001; 20:115-28.
36. Rother J. A drug benefit: the necessary prescription for Medicare. *Health Aff (Millwood)* 1999; 18:20-2.
37. Gold M, Achman L. Average out-of-pocket health care costs for Medicare+Choice enrollees increase substantially in 2002. *Issue Brief (Commonw Fund)* 2002; 575:1-8.
38. Reinhardt UE. Perspectives on the pharmaceutical industry. *Health Aff (Millwood)* 2001; 20:136-49.
39. Steinberg EP, Gutierrez B, Momani A, Boscarino JA, Neuman P, Deverka P. Beyond survey data: a claims-based analysis of drug use and spending by the elderly. *Health Aff (Millwood)* 2000; 19:198-211.
40. Heffler S, Smith S, Won G, Clemens MK, Keehan S, Zezza M. Health spending projections for 2001-2011: the latest outlook. Faster health spending growth and a

- slowing economy drive the health spending projection for 2001 up sharply. *Health Aff (Millwood)* 2002; 21:207-18.
41. Halbert RJ, Zaher C, Wade S, Malin J, Lawless GD, Dubois RW. Outpatient cancer drug costs: changes, drivers, and the future. *Cancer* 2002; 94:1142-50.
 42. Brown ML. The national economic burden of cancer: an update. *J Natl Cancer Inst* 1990; 82:1811-4.
 43. American Cancer Society. Cancer facts and figures 2000. [online]. Available from URL: http://www.cancer.org/docroot/STT/stt_0_2000.asp?sitearea=STT&level=1 [Accessed 2002 December 2].
 44. Paesmans M. Benefits of chemotherapy for quality of life in patients with advanced nonsmall-cell lung cancer. *Curr Opin Oncol* 2002; 14:389-93.
 45. Gridelli C, Perrone F, Gallo C, et al. Vinorelbine is well tolerated and active in the treatment of elderly patients with advanced non-small cell lung cancer. A two-stage phase II study. *Eur J Cancer* 1997; 33:392-7.
 46. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002; 347:472-80.
 47. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002; 346:235-42.
 48. Cutler DM, McClellan M. Is technological change in medicine worth it? *Health Aff (Millwood)* 2001; 20:11-29.
 49. Breathnach OS, Freidlin B, Conley B, et al. Twenty-two years of phase III trials for patients with advanced non-small-cell lung cancer: sobering results. *J Clin Oncol* 2001; 19:1734-42.
 50. Hillner BE, Agarwala S, Middleton MR. Post hoc economic analysis of temozolomide versus dacarbazine in the treatment of advanced metastatic melanoma. *J Clin Oncol* 2000; 18:1474-80.
 51. Stinson TJ, Calhoun E, Yang T, Lurain JR, Bennett CL. Cost analysis of second-line therapies for platinum-refractory ovarian cancer: reimbursement dilemmas for Medicare patients. *Cancer Invest* 1999; 17:559-65.

52. Falkson CI, Ibrahim J, Kirkwood JM, Coates AS, Atkins MB, Blum RH. Phase III trial of dacarbazine versus dacarbazine with interferon alpha-2b versus dacarbazine with tamoxifen versus dacarbazine with interferon alpha-2b and tamoxifen in patients with metastatic malignant melanoma: an Eastern Cooperative Oncology Group study. *J Clin Oncol* 1998; 16:1743-51.
53. Middleton MR, Grob JJ, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol* 2000; 18:158-66.
54. Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. The role of cost-effectiveness analysis in health and medicine. Panel on Cost-Effectiveness in Health and Medicine. *Jama* 1996; 276:1172-7.
55. Midgley R, Kerr D. Colorectal cancer. *Lancet* 1999; 353:391-9.
56. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. Advanced Colorectal Cancer Meta-Analysis Project. *J Clin Oncol* 1992; 10:896-903.
57. Schmoll HJ. Development of treatment for advanced colorectal cancer: infusional 5-FU and the role of new agents. *Eur J Cancer* 1996; 32A Suppl 5:S18-22.
58. Twelves C. Capecitabine as first-line treatment in colorectal cancer. Pooled data from two large, phase III trials. *Eur J Cancer* 2002; 38 Suppl 2:15-20.
59. The author reviewed all oral cancer drugs presented in clinical trials at the American Society for Clinical Oncology in 2001 and 2002. (unpublished data).
60. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002; 346:92-8.
61. Inoue A, Saijo Y, Maemondo M, et al. Severe acute interstitial pneumonia and gefitinib. *Lancet* 2003; 361:137-9.
62. Beck JR, Pauker SG. The Markov process in medical prognosis. *Med Decis Making* 1983; 3:419-458.
63. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *Jama* 1996; 276:1253-8.

64. Esnaola NF, Lazarides SN, Mentzer SJ, Kuntz KM. Outcomes and cost-effectiveness of alternative staging strategies for non-small-cell lung cancer. *J Clin Oncol* 2002; 20:263-73.
65. Mahadevia PJ, Fleisher LA, Frick KD, Eng J, Goodman SN, Powe NR. Lung cancer screening with helical computed tomography in older adult smokers: a decision and cost-effectiveness analysis. *Jama* 2003; 289:313-22.
66. Herbst RS, Kies MS. ZD1839 (Iressa) in non-small cell lung cancer. *Oncologist* 2002; 7 Suppl 4:9-15.
67. Pazdur R. Response rates, survival, and chemotherapy trials. *J Natl Cancer Inst* 2000; 92:1552-3.
68. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making* 1993; 13:322-38.
69. Drummond MF, Richardson WS, O'Brien BJ, Levine M, Heyland D. Users' guides to the medical literature. XIII. How to use an article on economic analysis of clinical practice. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *Jama* 1997; 277:1552-7.
70. Leigh NB, Shepherd FA, Kwong R, Burkes RL, Feld R, Goodwin PJ. Economic analysis of the TAX 317 trial: docetaxel versus best supportive care as second-line therapy of advanced non-small-cell lung cancer. *J Clin Oncol* 2002; 20:1344-52.
71. Earle CC, Chapman RH, Baker CS, et al. Systematic overview of cost-utility assessments in oncology. *J Clin Oncol* 2000; 18:3302-17.
72. Raab SS, Hornberger J. The effect of a patient's risk-taking attitude on the cost effectiveness of testing strategies in the evaluation of pulmonary lesions. *Chest* 1997; 111:1583-90.
73. Natale RB, Zaretsky SL. ZD1839 (Iressa): what's in it for the patient? *Oncologist* 2002; 7 Suppl 4:25-30.
74. Cella DF, Bonomi AE, Lloyd SR, Tulskey DS, Kaplan E, Bonomi P. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. *Lung Cancer* 1995; 12:199-220.
75. Cella D, Eton DT, Fairclough DL, et al. What is a clinically meaningful change on the Functional Assessment of Cancer Therapy-Lung (FACT-L) Questionnaire? Results from

- Eastern Cooperative Oncology Group (ECOG) Study 5592. *J Clin Epidemiol* 2002; 55:285-95.
76. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *Can Med Assoc J* 1992; 146:473-81.
 77. Page NC. The epidemiology of small cell lung cancer. *Proc ASCO* 2002; 21:1216a.
 78. Basche M, Kelly K. Treatment of Non-Small-Cell Lung Cancer in Older Persons. *Oncology* 2003; 17:31-39.
 79. Ihde DC. Chemotherapy of lung cancer. *N Engl J Med* 1992; 327:1434-41.
 80. Earle CC, Neumann PJ, Gelber RD, Weinstein MC, Weeks JC. Impact of referral patterns on the use of chemotherapy for lung cancer. *J Clin Oncol* 2002; 20:1786-92.
 81. Zippin C, Lum D, Hankey BF. Completeness of hospital cancer case reporting from the SEER Program of the National Cancer Institute. *Cancer* 1995; 76:2343-50.
 82. Nattinger AB, McAuliffe TL, Schapira MM. Generalizability of the surveillance, epidemiology, and end results registry population: factors relevant to epidemiologic and health care research. *J Clin Epidemiol* 1997; 50:939-45.
 83. Potosky AL, Riley GF, Lubitz JD, Mentnech RM, Kessler LG. Potential for cancer related health services research using a linked Medicare-tumor registry database. *Med Care* 1993; 31:732-48.

Table 1. Approved Oral Anticancer Drugs in the United States which are Covered and Not Covered by Medicare

Covered	Not Covered
Methotrexate	6-Mercaptopurine
Cyclophosphamide	Chlorambucil
Melphalan	6-Thioguanine
Etoposide	Procarbazine
Capecitabine	Tamoxifen
Temozolamide	Estramustine
	Altretamine
	Lavamisol
	ATRA
	Anastrzole
	Toremifen
	Letrozole
	Bicalutamide
	Celecoxib
	Bexarotene
	Exemestane
	Imatinib mesylate

Source: US Food and Drug Administration; Centers for Medicare and Medicaid Services

Table 2. Average Monthly Cost Estimates for Selected Oral Cancer Drugs

Drug		Average Wholesale Monthly Costs
chemical name (trade name)	Indication	US\$
Capecitabine (Xeloda) [†]	Colon Cancer	650
Imatinib mesylate (Gleevec) [*]	Chronic Myelogenous Leukemia	2,362
Temozolomide (Temodar) [‡]	Anaplastic astrocytoma; Melanoma	1,850

Based on the following Assumptions:

† Price of 240 capecitabine tablets (500 mg) = US\$ 2,254.43. Schedule: 1,000 mg/m² BID for 2 weeks on therapy then 1 week off therapy; this is lower than the labeled dose, but most oncologists have adopted this schedule. Average BSA = 1.85.

* Price of 120 imatinib mesylate tablets (100 mg) = US\$2,362. Schedule: 400 mg QD.

‡ Price of 20 temozolomide tablets (250 mg) = US\$ 6,689. Schedule: 150 mg/ m² QD x 5 days of a 28-day cycle. Average BSA = 1.85.

Source: Average wholesale prices taken from 2002 Drug Topics Red Book.²⁰

Table 3. Model Output for Base-Case Analysis Assuming FDA-approval of Gefitinib

DATA(tm) Markov Analysis

Stage	Stage Cost	Stage Eff	Net Cost	Net Eff	P(S1)	P(S2)	P(S3)	P(S4)
0	0	0	0	0	0.4	0.6	0	0
1	675.5367	0.058299	675.5367	0.058299	0.2828	0.4242	0.293	0
2	515.2696	0.055028	1190.806	0.113328	0.19994	0.29991	0.45825	0.0419
3	396.5746	0.050741	1587.381	0.164068	0.14136	0.21204	0.53918	0.10743
4	308.0414	0.046017	1895.422	0.210085	0.09994	0.14991	0.56562	0.18453
5	241.4926	0.041227	2136.915	0.251311	0.07066	0.10599	0.55794	0.26542
6	191.0524	0.036597	2327.967	0.287908	0.04995	0.07493	0.52991	0.3452
7	152.4859	0.032258	2480.453	0.320166	0.03532	0.05298	0.49073	0.42098
8	122.7294	0.028278	2603.182	0.348444	0.02497	0.03745	0.44642	0.49115
9	99.55778	0.024681	2702.74	0.373126	0.01765	0.02648	0.40088	0.55499
10	81.34674	0.021468	2784.087	0.394594	0.01248	0.01872	0.35648	0.61232
11	66.90434	0.018622	2850.991	0.413216	0.00882	0.01324	0.31465	0.66329
12	55.35048	0.016117	2906.342	0.429333	0.00624	0.00936	0.27612	0.70829
13	46.03088	0.013924	2952.373	0.443257	0.00441	0.00662	0.2412	0.74777
14	38.45549	0.012012	2990.828	0.455269	0.00312	0.00468	0.20994	0.78226
15	32.25433	0.01035	3023.083	0.465619	0.0022	0.00331	0.1822	0.81229
16	27.14562	0.008909	3050.228	0.474528	0.00156	0.00234	0.15776	0.83834
17	22.91289	0.007663	3073.141	0.482192	0.0011	0.00165	0.13634	0.8609
18	19.38825	0.006587	3092.529	0.488779	0.00078	0.00117	0.11765	0.8804
19	16.44033	0.005659	3108.97	0.494438	0.00055	0.00083	0.1014	0.89722
20	13.96536	0.00486	3122.935	0.499298	0.00039	0.00058	0.0873	0.91172
21	11.88064	0.004172	3134.816	0.50347	0.00028	0.00041	0.0751	0.92421
22	10.11972	0.00358	3144.935	0.50705	0.00019	0.00029	0.06457	0.93495
23	8.628775	0.003072	3153.564	0.510122	0.00014	0.00021	0.05548	0.94418
24	7.363877	0.002635	3160.928	0.512757	0.0001	0.00015	0.04764	0.95211
25	0	0	3160.928	0.512757	0.00007	0.0001	0.0409	0.95893

Shorthand state names:

S1 = Responding

S2 = Not Responding

S3 = Terminal Care

S4 = Dead

$P(S_n)$ = Probability of being in state n

$r\{S_n\}$ = Contribution to _stage_reward from state n

Table 4. Model Output for Base-Case Analysis Assuming FDA-denial of Gefitinib

DATA(tm) Markov Analysis

Stage	Stage Cost	Stage Eff	Net Cost	Net Eff	P(S1)	P(S2)
0	0.5	0	0.5	0	1	0
1	134.835	0.04944	135.335	0.04944	0.8989	0.1011
2	121.2032	0.044441	256.5382	0.093881	0.80802	0.19198
3	108.9495	0.039948	365.4877	0.133829	0.72633	0.27367
4	97.93474	0.035909	463.4225	0.169738	0.6529	0.3471
5	88.03354	0.032279	551.456	0.202017	0.58689	0.41311
6	79.13335	0.029016	630.5894	0.231033	0.52756	0.47244
7	71.13297	0.026082	701.7223	0.257115	0.47422	0.52578
8	63.94142	0.023445	765.6637	0.28056	0.42628	0.57372
9	57.47695	0.021075	823.1407	0.301635	0.38318	0.61682
10	51.66603	0.018944	874.8067	0.320579	0.34444	0.65556
11	46.44259	0.017029	921.2493	0.337608	0.30962	0.69038
12	41.74725	0.015307	962.9966	0.352915	0.27831	0.72169
13	37.5266	0.01376	1000.523	0.366675	0.25018	0.74982
14	33.73266	0.012369	1034.256	0.379044	0.22488	0.77512
15	30.32229	0.011118	1064.578	0.390162	0.20215	0.79785
16	27.25671	0.009994	1091.835	0.400156	0.18171	0.81829
17	24.50105	0.008984	1116.336	0.40914	0.16334	0.83666
18	22.024	0.008075	1138.36	0.417215	0.14683	0.85317
19	19.79737	0.007259	1158.157	0.424474	0.13198	0.86802
20	17.79586	0.006525	1175.953	0.430999	0.11864	0.88136
21	15.99669	0.005865	1191.95	0.436865	0.10664	0.89336
22	14.37943	0.005272	1206.329	0.442137	0.09586	0.90414
23	12.92567	0.004739	1219.255	0.446877	0.08617	0.91383
24	11.61888	0.00426	1230.874	0.451137	0.07746	0.92254
25	0	0	1230.874	0.451137	0.06963	0.93037

Shorthand state names:

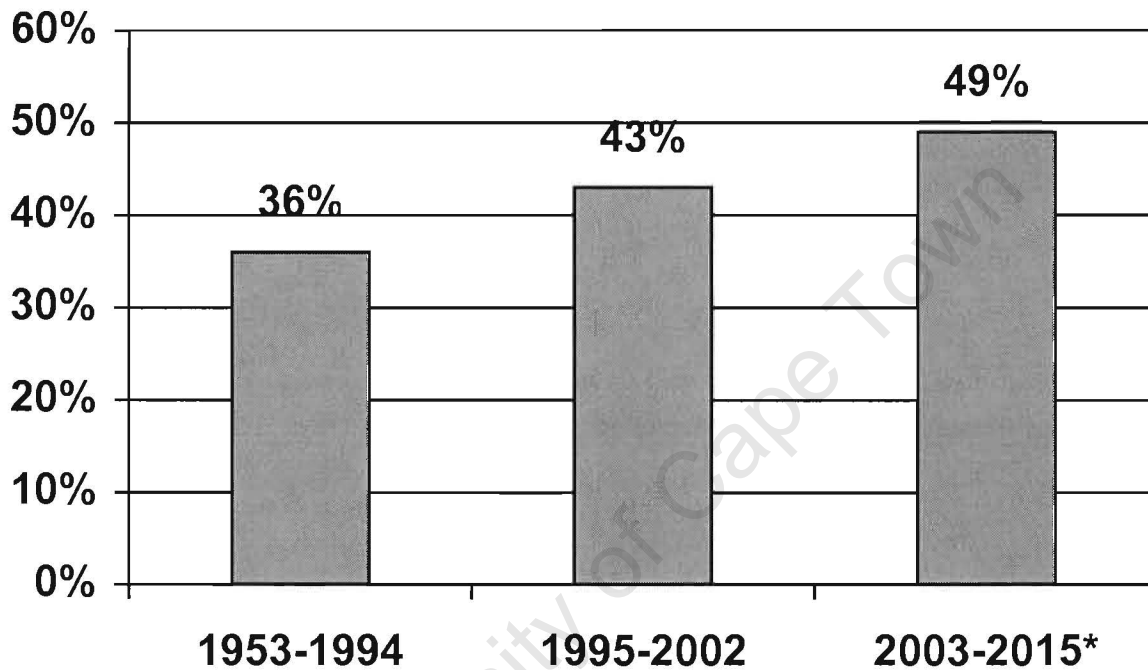
S1 = Terminal Care

S2 = Dead

$P(S_n)$ = Probability of being in state n

$r\{S_n\}$ = Contribution to _stage_reward from state n

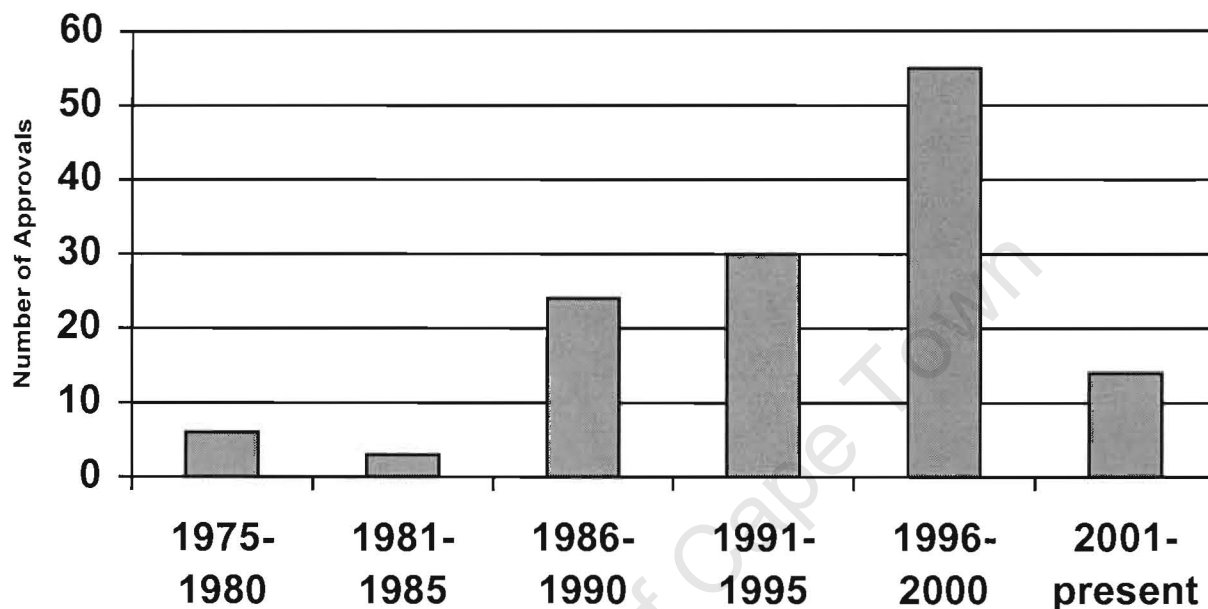
Figure 1. Percentage of Approved Cancer Agents in the United States Administered by Mouth for Each Indicated Period of Years.



Source: Based on publicly available data on the oncology tools section of the FDA web site (<http://www.fda.gov/cder/cancer/>)

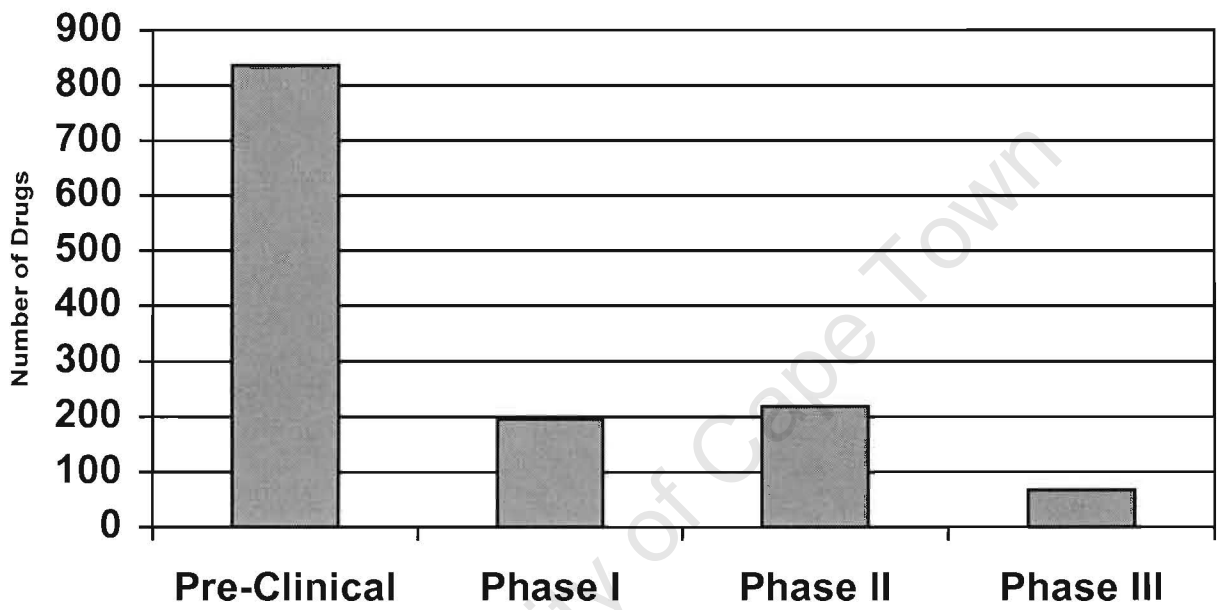
* Authors estimate based on composition of current cancer pipeline and by analyzing the trend line.

Figure 2. Number of Unites States Oncology Drug Claims Approved by 5-year Intervals.



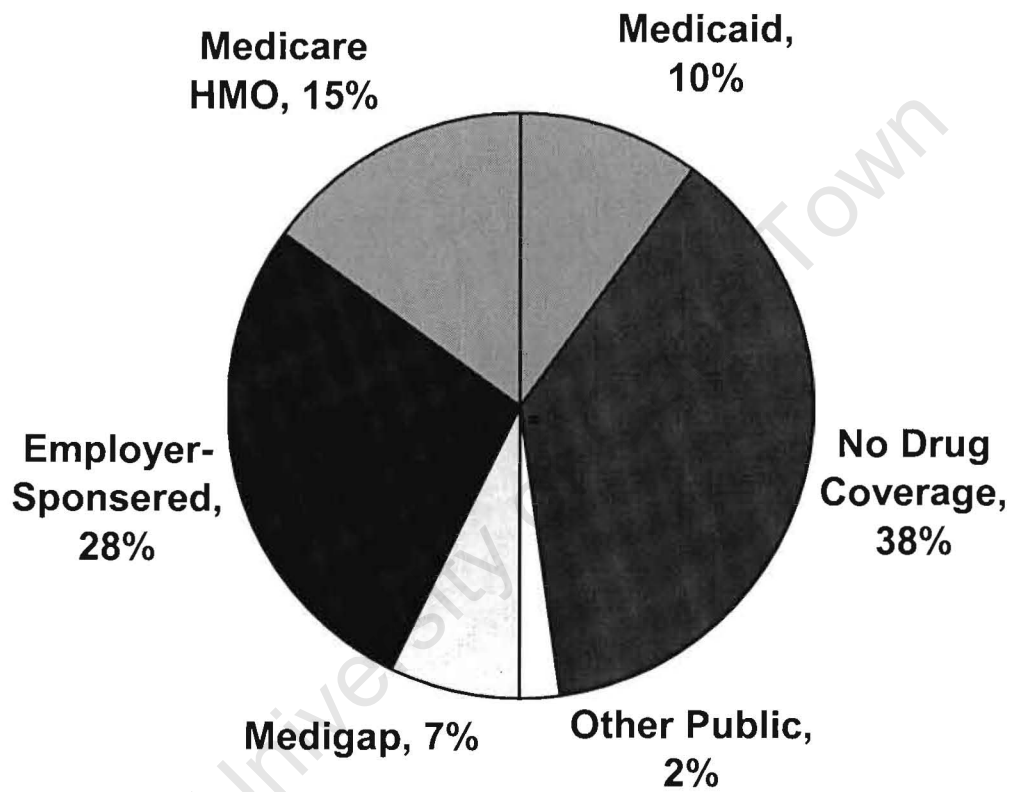
Source: Based on publicly available data on the oncology tools section of the FDA web site (<http://www.fda.gov/cder/cancer/>) as of December, 2002.

Figure 3. Estimated Number of Cancer Drugs in Development by Phase of Development.



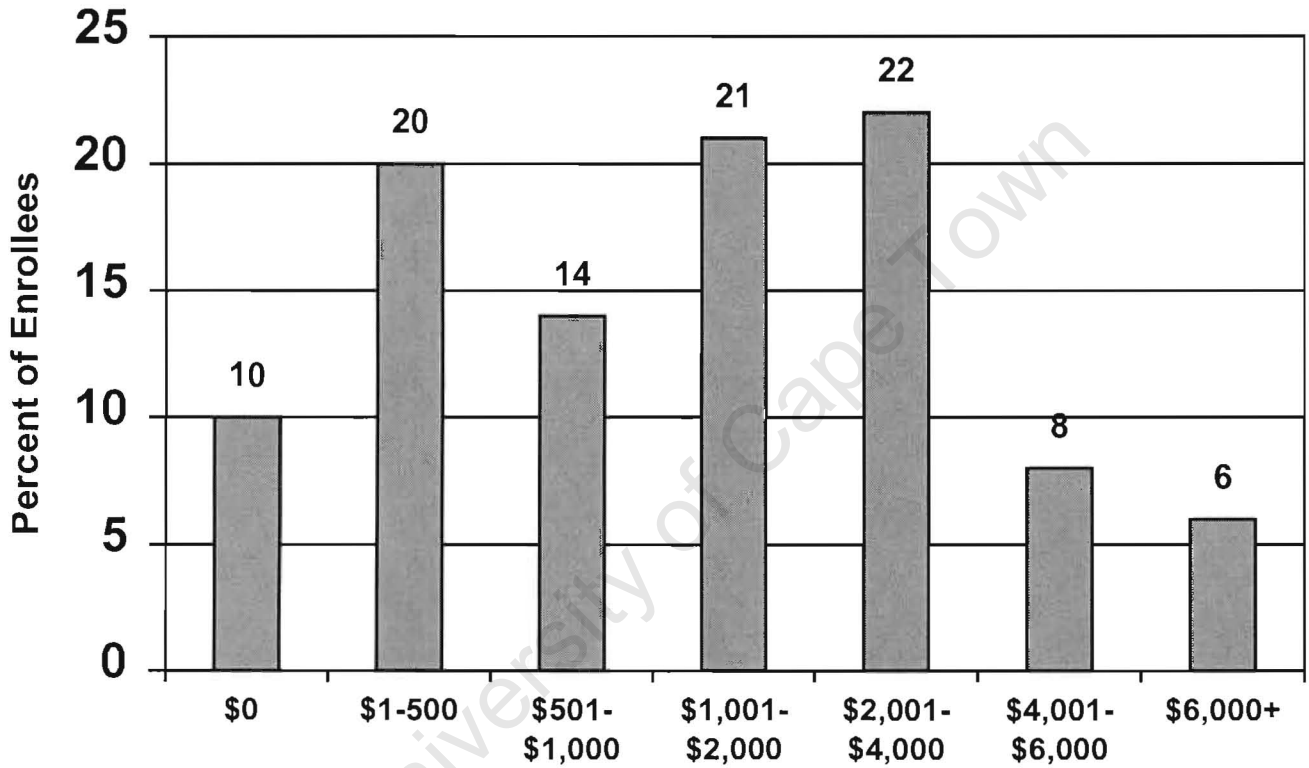
Source: Parexel's Pharmaceutical R&D Statistical Sourcebook 2001.¹⁶

Figure 4. Sources of Prescription Drug Coverage for non-institutionalized Medicare Beneficiaries



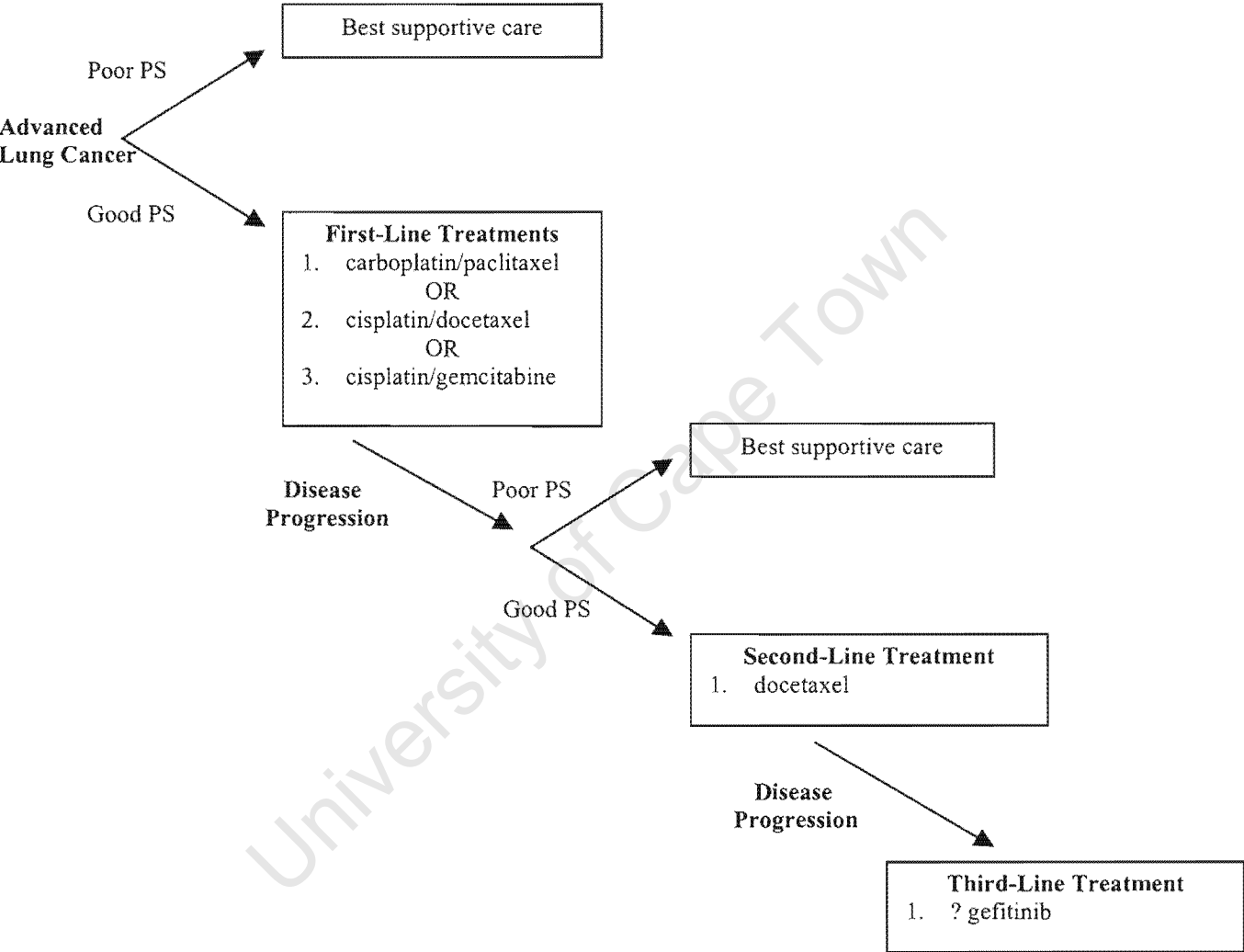
Source: Adapted from Congressional Budget Office Data.²⁸

Figure 5. Distribution of Medicare Beneficiaries by Total Prescription Drug Expenditures, 2002



Source: Adapted from Congressional Budget Office Data.²⁸

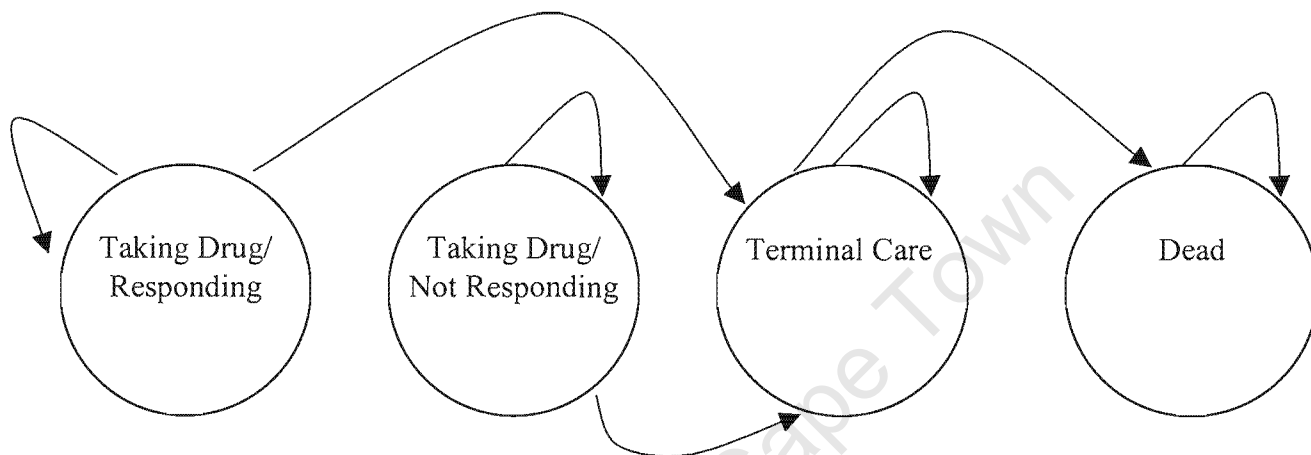
Figure 6. FDA-Approved Treatments of Advanced Non-Small Cell Lung Cancer



Abbreviation: PS, Performance Status.

Figure 7. Health States, Allowable State Transitions, and Structure of Markov Model Under the Assumption of FDA APPROVAL of Gefitinib (Iressa).

Allowable State Transitions Under the Assumption of FDA Approval



Markov Model Based on Above

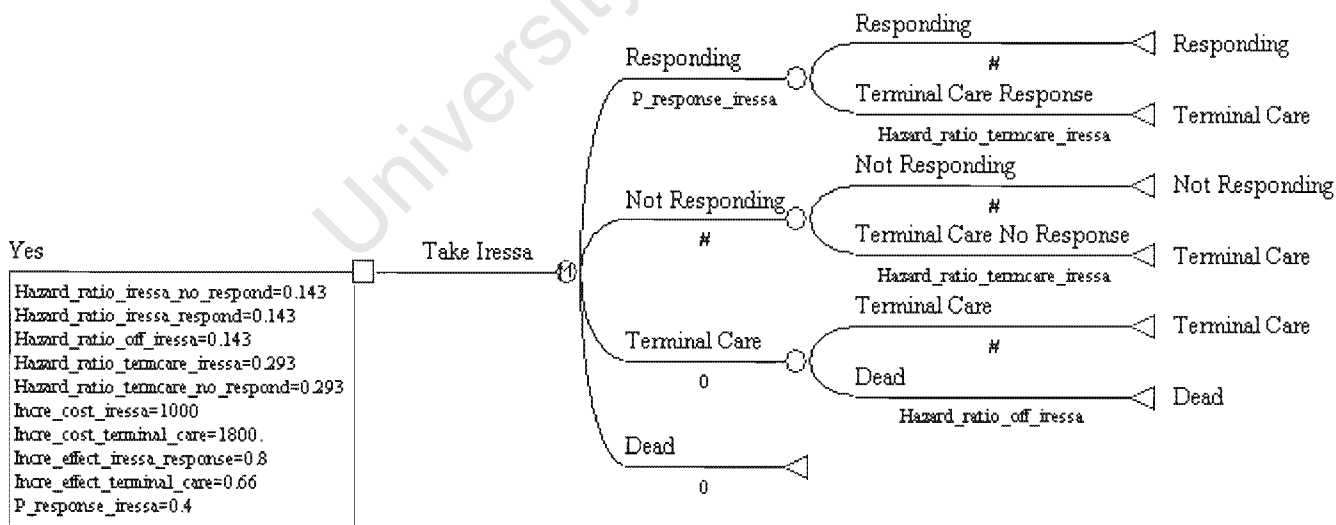
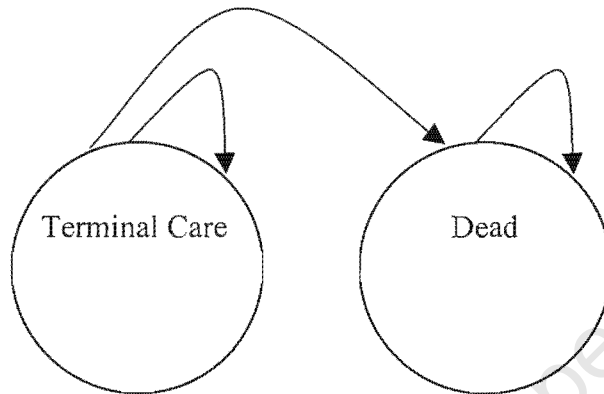


Figure 8. Health States, Allowable State Transitions, and Structure of Markov Model Under the Assumption of FDA DENIAL of Gefitinib (Iressa).

Allowable State Transitions Under the Assumption of FDA Denial



Markov Model Based on Above

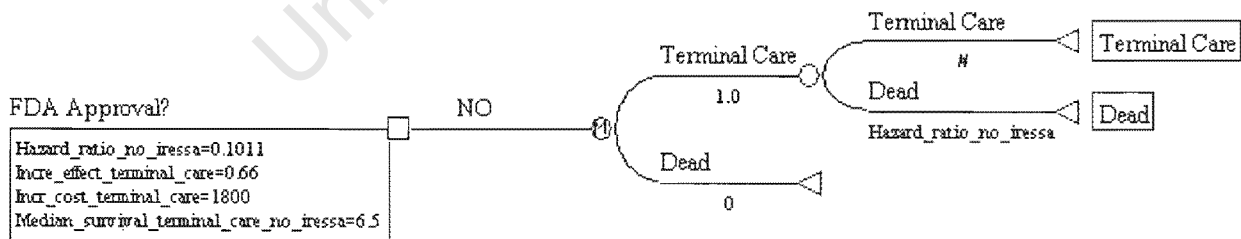


Figure 9. Markov Probability Analysis under the Assumption of FDA Approval of Gefitinib

Markov Probability Analysis

