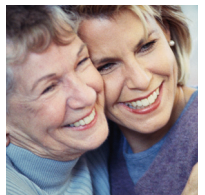
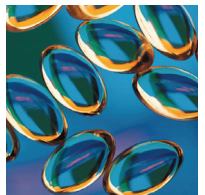


Targeting Cancer: Innovation in the Treatment of Chronic Myelogenous Leukemia



New England Healthcare Institute

NEHI Innovation Series

March 2004

ABOUT

Founded in 2002, the New England Healthcare Institute (NEHI) specializes in identifying innovative strategies for improving health care quality and reducing health care costs. NEHI conducts independent, high quality research that supports evidence-based health policy recommendations at the regional and national levels. Member representatives from the biotechnology, medical device, pharmaceutical, academic health center, research, provider, payer and employer communities bring an unusual diversity of talent to bear on NEHI's work. We collectively address critical health issues through our action-oriented research, education and policy initiatives.

Targeting Cancer:

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Authors: Valerie Fleishman and Robert Sayoc Nocon

Editors: Wendy Everett and Susan Klein

Graphic Design: Friskey Design

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Vincent Maffei, M.A., A.B.D., *Health Economist, Anthem Blue Cross and Blue Shield East*

Gerald Maxwell, Ph.D., *Professor of Neuroscience and Associate Dean of the Graduate School, University of Connecticut Health Center*

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Table of Contents

	List of Figures	ii
	Preface	1
	Executive Summary	3
	Introduction: Molecularly Targeted Drugs	7
	An Overview of Chronic Myelogenous Leukemia	9
	The Journey from Innovative Science to Patient Care	15
	Value Analysis	20
	Drivers and Barriers Analysis	28
	Lessons Learned	34
	Appendices	41
	Appendix 1: Data Sources	43
	Appendix 2: Clinical Care Pathways	44
	Appendix 3: Cost-Effectiveness Analysis	47
	Appendix 4: Experts Interviewed	50
	Appendix 5: Expert Panelists	52
	Appendix 6: Glossary	54
	Endnotes	57

List of Figures

Figure 0-1: NEHI's Innovation Research	8
Figure 1-1: New Cases of CML in New England.....	9
Figure 1-2: The Philadelphia Chromosome.....	10
Figure 1-3: Testing for CML	10
Figure 1-4: Treatment Goals	11
Figure 1-5: Gleevec.....	12
Figure 1-6: Comparison of Major CML Treatment Options.....	13
Figure 1-7: Clinical Pathways for Chronic Phase CML.....	14
Figure 2-1: Historical Timeline.....	16
Figure 2-2: Major Phases of FDA Review	17
Figure 3-1: NEHI's Value Analysis	20
Figure 3-2: Cost-Effectiveness Ratios.....	22
Figure 3-3: Stakeholder Value Analysis	24
Figure 3-4: Decrease In BMTs.....	26
Figure 4-1: Major Drivers and Barriers	28
Figure 4-2: Record Clinical Trials and Approval.....	30
Figure 4-3: Late Prescription Refills	32
Figure 5-1: Lessons Learned.....	34

Preface

This report is the first in a new *Innovation Series* to be published by NEHI. The goal of the *Innovation Series* is to identify opportunities to speed the adoption of highly valuable innovations that will benefit patients *and* help contain overall health care costs. Focusing on emerging innovations for the treatment of major diseases such as cancer, cardiovascular disease and diabetes, these reports will analyze specific classes of innovation to identify the value, drivers and barriers to their adoption as they move from initial concept into accepted clinical practice. NEHI will draw upon its industry-wide membership to guide the development of a policy action plan to drive change and facilitate the adoption of beneficial innovations.





Executive Summary

From drugs and medical devices, to information technology and care delivery, advances across the health care system have led to significant improvements in the quality and length of patients' lives. In recent years however, the relentless rise of health care costs has shifted our national attention toward the cost of innovation. Ultimately, the most successful path to improving the efficiency of our health care system lies in defining the value of innovative treatments and care processes, rather than measuring costs or benefits alone. We must work to find ways to identify valuable innovations and the mechanisms for getting them to patients as quickly as possible. We need to speed the adoption of cost-effective innovations to improve patient quality of life without increasing the aggregate costs of health care.

One area of advancement in health care where questions of value and efficient adoption are especially important is the area of molecularly targeted drugs, which are poised to fundamentally change the treatment of cancer as we know it. Advances in molecular biology and our understanding of the human genome have led to rational drug design, a process whereby scientists first identify molecular targets in the body that lead to disease and then develop drugs that selectively attack these targets. Although this is an emerging field, there are already examples of molecularly targeted cancer drugs that are dramatically improving patient outcomes and quality of life.

A prime example is Gleevec[®], a molecularly targeted drug introduced in 2001 for the treatment of chronic myelogenous leukemia (CML). CML is a cancer that affects a relatively small patient population, but with potentially life-threatening outcomes. The story behind Gleevec's development and adoption illuminates the critical issues health care system stakeholders face in bringing a scientific breakthrough to life. In particular, Gleevec highlights the challenges and opportunities involved in bringing drugs for rare diseases to market and reinforces the importance of examining the value, and not just the cost, of expensive therapies.

Targeting Cancer: Innovation in the Treatment of Chronic Myelogenous Leukemia identifies and analyzes these issues and their impact on major health care system stakeholder groups – patients, manufacturers, physicians, employers, payers and hospitals – and on society as a whole. It is intended to raise awareness of the specific challenges in bringing highly valuable innovations to patients and to identify opportunities to speed the adoption of new medical, information, and care technologies that dramatically improve patient care.

KEY FINDINGS

Gleevec has clearly made history as a medical, scientific and regulatory breakthrough. It has dramatically improved patients' lives. It has created excitement and hope for the future of molecularly targeted cancer treatments, and is a model for fast-track FDA approval. Taking into account all of the costs and benefits of adding Gleevec to the system of care for CML patients, it is a highly valuable innovation to society as a whole and valuable or neutral to major health



care system stakeholders. The fact that it has a positive or negligible impact on all industry sectors is one of the prime reasons behind its rapid adoption and uptake across the health care system.

Small markets can yield big rewards

Gleevec's developer, Novartis Pharma AG, was initially reluctant to make a major investment in a therapy that targets a small market. But thanks to a successful pricing strategy; the drug's use as a chronic, ongoing therapy; and the expansion of indications to include other diseases, Gleevec has become a "mini-blockbuster", generating 2003 global sales of \$1.1 billion. Given the deceptively large market potential presented by molecularly targeted therapies, large pharmaceutical companies should not be afraid to invest in therapies that are initially targeted at small and rare disease populations.

A winning combination can expedite U.S. Food and Drug Administration (FDA) approval

Four factors working in concert facilitated Gleevec's record approval time: (1) its clear efficacy and breakthrough nature; (2) an FDA policy of speeding up the regulatory and review process for life-saving therapies; (3) patient mobilization and involvement before and during clinical trials; and (4) a commitment from Novartis leadership to get Gleevec to market as quickly as possible.

Lack of Medicare coverage is a difficult barrier for patient access to innovations

Medicare's complex policies prohibit coverage of many orally administered, life-saving cancer therapies. The average annual cost for treatment with Gleevec—including the drug and clinician visits—is \$32,724 per patient. Novartis' patient assistance program enabled many CML patients to obtain Gleevec treatment, who would otherwise not have been able to afford the drug.

Variance in physician practice patterns can limit the efficacy of an innovation

After FDA approval, Gleevec treatment shifted from major medical centers, to oncologists and physicians in the community. High awareness of Gleevec in the oncology community led to rapid adoption of the therapy. However, manufacturer market research and NEHI's own analysis of claims data suggest that some patients were given sub-optimal dosages in this early period of adoption. Reasons for this may have included a lack of *specific* knowledge about the latest treatment standards due to the low incidence of CML and an unintended carryover of treatment protocol for previous therapies. This lag period between drug approval and consistent optimal dosing and monitoring is one of the more problematic aspects of assimilating new drugs into the health care system.

Patient activism can be a powerful driver of adoption

Patient demand was a major force behind Gleevec's rapid speed to market and its rate of adoption. Mobilizing through the Internet, patient activists eliminated roadblocks at several crucial points. They persuaded Novartis to accelerate production and make the drug more widely available; advocated enrollment in clinical trials; and helped disseminate information on proper dosing and treatment.



KEY HEALTH POLICY QUESTIONS

This case study of Gleevec raises important issues applicable to molecularly targeted cancer therapies and other emerging medical innovations.

Getting promising drug candidates for rare diseases off of the shelf

Large pharmaceutical firms face significant pressures to produce blockbuster drugs targeted at large patient populations. This business strategy almost derailed Gleevec and often deters investments in treatments for rare, life-threatening diseases.

- How can we make it more likely that promising drugs for small patient populations are not stalled or put on the shelf indefinitely?

Reducing FDA approval time

While the FDA has ramped up its commitment to accelerating approval of life-saving treatments, Gleevec, which was approved after a 72-day review, remains the benchmark for fast-track approval.

- How can the levels of communication that took place among regulators, researchers, physicians and patients throughout the FDA review process be fostered to maximize the efficiency of future reviews?

Value versus cost

Gleevec was priced within the range of less effective and higher risk existing treatments, and ultimately presented a cost-effective new treatment option. This pricing strategy allowed Novartis to gain coverage acceptance and maximize its return on investment for Gleevec without adding significant costs to the overall health care system.

- How will the various stakeholder groups react when an expensive, highly effective targeted therapy is approved for a more widespread disease? Could new therapies be priced according to the value they provide?

Improving the dissemination of new treatment knowledge

Experts hypothesize that molecularly targeted therapies will lead to sub-grouping of diseases to the extent that all cancers may be considered “orphan” diseases. Sub-grouping will make it increasingly difficult for any physician to stay current on the optimal treatment practices for the numerous cancer sub-groups likely to arise.

- Whose responsibility is it to ensure that patients are receiving the best, evidence-based practices? Should the responsibility lie with manufacturers, medical schools, professional organizations, patients or some combination thereof?

Patient communication and empowerment

Patient support groups and registries are often very effective for mobilizing patients suffering from rare and/or life-threatening diseases.

- How could patient support groups be leveraged to speed enrollment in clinical trials and encourage the dissemination of timely and accurate information?



THE NEED FOR ACTION

All sectors of the health care system, not just patients, stand to benefit from the rapid identification and efficient adoption of truly high-value medical innovations. Leaders in all sectors of the health care industry will need to be imaginative as we work together to create fresh answers to these questions. The ultimate need to develop a system of behavioral and financial incentives for physicians, hospitals, payers, and manufacturers that are directly aligned in the best interest of the patients should be the dominant driver in our discussions.

NEHI will continue to work with its membership to address these critical issues. We will educate the public and policymakers regarding the findings from this research and create specific policy recommendations to drive public and private sector change.



Introduction: Molecularly Targeted Drugs

As the first in NEHI's *Innovation Series*, this report uses a case study of Gleevec® (imatinib mesylate) to illustrate the value of the emerging class of molecularly targeted cancer drugs. While Gleevec is just one example in a single class of drugs, it highlights many critical issues that arise in the development and adoption of medical innovations. This case study analyzes the value and impact of Gleevec to society as a whole, as well as to six major stakeholders in the health care system: patients, manufacturers¹, physicians, employers, payers and hospitals. After exploring the value of the innovation, this study identifies the drivers and barriers to Gleevec's adoption and concludes with an examination of the broader policy issues and implications that may be relevant to other breakthrough innovations.

Among the earliest clinical applications to emerge from the human genome project—a major initiative to identify and catalogue human genes—are therapies that target the genes that cause specific diseases. While much of the project's promise has yet to be realized, the nascent science of genomics is already starting to transform the way we treat cancer.

These new molecularly targeted therapies have emerged from great advances in scientific understanding of the genetic basis of cancers.

Mainstream cancer therapies of the late 20th century (e.g. chemotherapy) indiscriminately kill all cells in their path. Today's emerging targeted therapies are designed to destroy specific cancerous cells and leave healthy cells intact. Early results of this approach show significantly fewer side effects and better patient outcomes than prior treatments.

The excitement surrounding these new therapies has been nothing short of extraordinary. Major media outlets have heralded molecularly targeted therapies as a “revolution in cancer therapy.”² Assessments among scientific circles have been equally enthusiastic.³ While only a handful of targeted cancer drugs are currently approved in the United States,⁴ translating the wealth of known genetic targets into new cancer treatments is high on the national health care agenda and one of the National Cancer Institute's central goals for 2004.⁵

A key reason for this optimism and investment is the widely cited success story of Gleevec, one of the first molecularly targeted therapies for cancer. Gleevec has truly transformed the treatment landscape for chronic myelogenous leukemia (CML), a rare, life-threatening disease that annually afflicts 4,300 new patients in the United States and 94,500 people worldwide.⁶

Developed in the 1990s by Ciba-Geigy, which later merged with Sandoz to form Novartis Pharma AG, Gleevec received U.S. Food and Drug Administration (FDA) approval in May 2001. It was awarded orphan drug status for its use in CML and

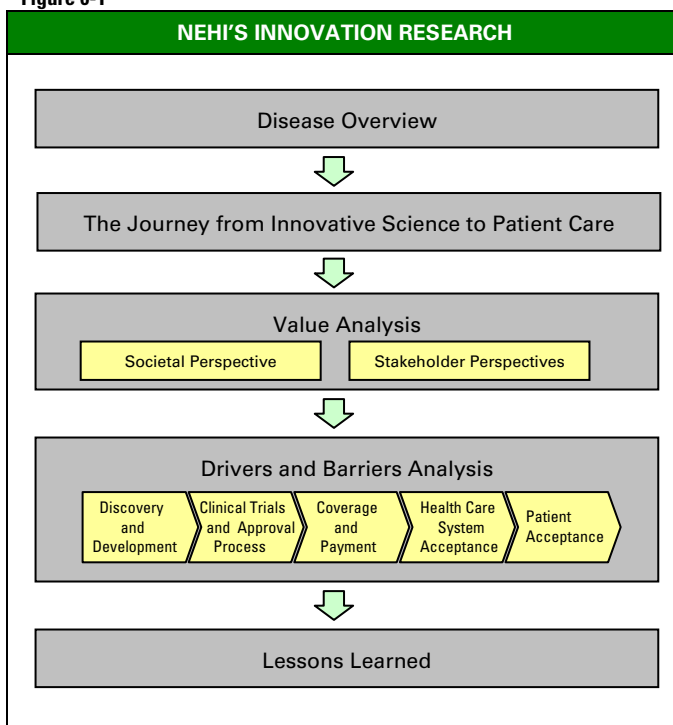
The remarkable story of Gleevec's development and commercialization illustrates the opportunities and challenges inherent in the adoption of breakthrough medical innovations.



another rare cancer, Gastro Intestinal Stromal Tumor (GIST), allowing for exclusive marketing protections, tax credits and other benefits.⁷ Today, Gleevec is marketed in 65 countries worldwide⁸ under the international brand name Glivec, with global annual sales of \$1.1 billion⁹. The remarkable story of Gleevec's development and commercialization illustrates the opportunities and challenges inherent in the adoption of breakthrough medical innovations.

This report has five chapters (Figure 0-1): (1) an overview of CML; (2) an account of Gleevec's journey from discovery to adoption; (3) an analysis of the value of Gleevec to major health care system stakeholders; (4) an examination of the drivers and barriers to the adoption of this innovation; and (5) a summary of lessons learned and the policy questions raised by this case study.

Figure 0-1



Source: NEHI



An Overview of Chronic Myelogenous Leukemia

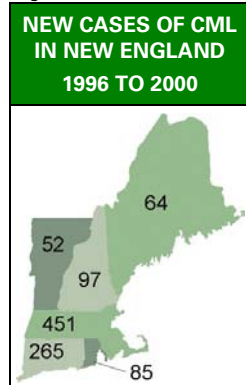
To appreciate the impact of a new innovation on disease treatment, it is important to understand basic facts about the disease itself and the treatment options available. This section provides an overview of CML, a rare and life-threatening disease, with a unique identifiable genetic marker.

LEUKEMIA AND CML

Leukemia is a cancer of the bone marrow in which the body produces large numbers of abnormal white blood cells that interfere with the usual functions of the blood. Three central processes maintain the right balance of cells in the body: cell reproduction, maturation and death. In normal cells, these three processes are in balance, allowing the body to continuously grow and lose cells while maintaining the right overall number. With leukemia, one or more of these processes malfunctions, and cells in the bone marrow cause the body to overproduce certain types of blood cells. CML (also known as chronic myeloid leukemia) is a subtype of leukemia that is characterized by the early presence of elevated white blood cell levels and minimal negative effect on patients in the early stage of the disease. Without treatment, the disease inevitably progresses to severely inhibit patient function and become fatal.

CML affects roughly 4,300 new patients annually in the United States and comprises 14 percent of all new leukemia cases.¹⁰ The median age of CML patients at diagnosis is 53 years old. Incidence increases with age, but all age groups are at some risk for the disease. The disease affects slightly more men than women (by a ratio of 1.4 to 1)¹¹ and does not occur disproportionately in any racial or ethnic group.¹² There are no known risk factors for CML.¹³ Seven percent of all new CML cases occur in New England (Figure 1-1), roughly consistent with the 5 percent of the U.S. population residing in the region.¹⁴ However, major New England cancer centers draw CML patients from around the world, and some of the key clinical investigative work takes place here.

Figure 1-1



Source: North American Association of Cancer Registries; Vermont Department of Health

IDENTIFIABLE GENETIC MARKER

Unlike most cancers, where the genetic basis of disease is unknown, the root of nearly all CML cases is a single, easily-identifiable genetic mutation.¹⁵ This mutation occurs in a gene that codes for a type of protein “on-off switch” for cell reproduction. In its normal state, the switch helps to ensure the right balance of cells in the bone marrow. When mutated, the switch becomes stuck in the on position and causes excessive proliferation of white blood cells. This same genetic mutation, known as the Bcr-Abl oncogene (Figure 1-2), is associated with a telltale change in the appearance of the cell’s chromosomes – the formation of a shortened, stubby-looking

The root cause of nearly all CML cases is a single, easily-identifiable genetic mutation.



chromosome. Scientists have dubbed this the “Philadelphia chromosome,” due to its discovery at the University of Pennsylvania. The Philadelphia chromosome is easily identifiable under a microscope and present in over 95 percent of CML patients, making it an excellent marker for detecting and monitoring the disease.

DIAGNOSIS

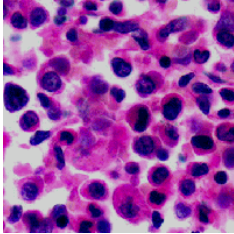
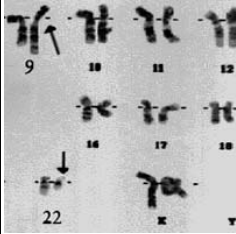
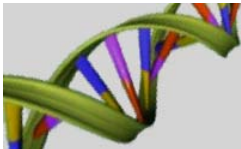
Due to the unobtrusive nature of the disease in its early phase, half of CML cases go undiagnosed until a physician notices a drastically elevated white blood cell level in a routine blood count. Other patients are diagnosed upon receiving a complete blood count as a result of minor symptoms, such as fatigue.¹⁶ The information provided by this blood count allows the physician to determine whether there are signs of CML at a hematologic level – meaning that the levels of each type of blood cell (e.g. white, platelet) are characteristic of CML. The diagnosis is confirmed if the Philadelphia chromosome is found by cytogenetic analysis, where a sample of blood cells is examined under a microscope. This testing verifies the disease at a chromosomal level. More rigorous techniques such as polymerase chain reaction (PCR) testing can further corroborate the presence of CML by counting the number of cells possessing the Bcr-Abl mutation (Figure 1-3). Detection of disease at the molecular level is the gold standard of testing.

Figure 1-2



Source: Howard Hughes Medical Institute

Figure 1-3

TESTING FOR CML			
	Least Accurate →		Most Accurate
Level of disease	Hematologic	Cytogenetic	Molecular
Measurement	Complete blood count	Cytogenetic testing	PCR testing
Object of Measurement	 Percent of immature blood cells (blasts)	 Percent of cells with the Philadelphia chromosome	 Number of cells with the Bcr-Abl oncogene

Source: Johns Hopkins Medical Institutions; Leukemia & Lymphoma Society; National Human Genome Research Institute (images)

COURSE OF THE DISEASE

There are three phases of disease progression in CML. Approximately 85 percent of newly diagnosed patients are in the early chronic phase of the disease, while the remaining 15 percent are diagnosed in the two advanced stages: accelerated and blast phases.¹⁷ Prior to the development of Gleevec, life-expectancy for newly



diagnosed patients was three to six years for those in chronic phase, one year for those in accelerated phase and three to six months for blast phase patients.¹⁸

Chronic phase: At the clinical level, many chronic phase patients have no outward signs of disease apart from high white blood cell counts. While some patients may experience fatigue, abdominal pain or weight loss, CML does not usually restrict their ability to carry out day-to-day functions. At the cellular level, these symptoms are associated with elevated white blood cell levels, elevated platelet counts, or reduced red blood cell levels, which result from uncontrolled reproduction of leukemic cells. In chronic phase, CML is not severely debilitating because the excess white blood cells and platelets still function normally and the patient is not significantly anemic.

Accelerated phase: For patients in accelerated phase, fatigue, abdominal pain and weight loss become increasingly common and more serious symptoms arise, such as frequent infection and bleeding. On the cellular level, their condition worsens as the leukemic cells develop further mutations.

Blast phase: In blast phase, CML becomes a fatal acute leukemia. Patients reach this stage when more than 30 percent of their marrow cells are blast cells – immature cells that have not developed the ability to carry out normal functions. These blast cells dominate the blood and marrow, crowding out healthy cells.

TREATMENT

The central goal of CML treatment is to improve the quality and length of patient's lives by eliminating cells with the Bcr-Abl mutation. The effectiveness of treatment can be measured at different levels, corresponding to the disease testing techniques available (Figure 1-4). A response to treatment means the number of leukemic cells has been reduced by the treatment. Remission means there are no signs of the cancer at the level of testing used (hematologic, cytogenetic or molecular). Thus, a patient exhibiting a *hematologic response* shows fewer immature cells in a complete blood count after treatment. A patient with a complete *cytogenetic remission* shows no cells with the Philadelphia chromosome when examined visually under a microscope. A patient with a *molecular remission* shows no trace of the Bcr-Abl oncogene in PCR testing. A sustained molecular remission is a good indication that a patient is cured of CML. If a patient shows a response or remission after therapy, but later loses that response or remission, the patient is said to have relapsed.

Figure 1-4

TREATMENT GOALS			
Level of Disease	Hematologic	Cytogenetic	Molecular
Response	Fewer immature myelogenous cells	Fewer cells with Philadelphia chromosome	Fewer cells with Bcr-Abl mutation
Remission	No immature myelogenous cells	No cells with Philadelphia chromosome	No cells with Bcr-Abl mutation

Source: NEHI



Bone marrow transplantation

The only known cure for CML is a bone marrow transplant (BMT). A BMT is usually a one-time procedure that involves regular long-term monitoring for disease relapse (Figure 1-6). The patient's marrow cells, both healthy and leukemic, are destroyed with high doses of chemotherapy. The patient then receives an infusion of healthy cells from a suitable donor. While the possibility of being cured makes BMT an attractive treatment option, it is also a high-risk procedure with a treatment-associated mortality of up to 20 percent for chronic phase patients over age 40.¹⁹ Moreover, not everyone is eligible for the procedure. Patients must have a suitable and willing donor, whose bone marrow is a good match. BMT outcomes vary significantly by factors such as age at transplantation, phase of disease and donor suitability.²⁰ Complications such as graft versus host disease (GVHD), an adverse immune response of the transplanted donor cells against the host cells of the patient, are also a major concern. Depending on donor suitability, as many as 26 percent to 49 percent of BMT patients face severe problems from GVHD. The risks and limitations of BMT generally limit eligibility to roughly 30 percent of the CML population.

Recombinant interferon alpha

Before Gleevec, recombinant interferon-alpha (IFN)²¹ was the primary drug therapy for patients with CML. This injectable drug is a synthetic human compound that inhibits cancer growth and promotes immune destruction of leukemic cells. According to aggregate clinical trials results, IFN induces hematologic remission for more than 50 percent of CML patients and cytogenetic response in about 20 percent. Only about 2 percent of patients experience a sustained molecular response to IFN,²² and molecular remissions are virtually unheard of. IFN is a toxic treatment generally associated with flu-like symptoms, diarrhea, psychological problems and fatigue, which persist as long as the patient is on the drug (usually indefinitely).

Gleevec (imatinib mesylate)

Gleevec (Figure 1-5), previously known as STI571, is an oral drug that inhibits the reproduction of leukemic cells by binding to the Bcr-Abl tyrosine kinase and permanently turning the malfunctioning cell growth and division switch to the "off" position. The drug's ability to bind specifically to the Bcr-Abl tyrosine kinase is central to the reduced treatment toxicity experienced by patients. Since Gleevec only affects the Bcr-Abl kinase and its downstream functions, fewer other functions of the cell are disrupted.

Evidence of Gleevec's efficacy has been overwhelmingly positive to date. Results published in May 2003 from the International Randomized Study of Interferon and STI571 (IRIS) study – a 1,106-patient Phase III clinical trial of Gleevec versus IFN for chronic phase CML – showed vastly improved disease response rates and lower toxicity for patients receiving Gleevec. Importantly, after a median follow-up of 19 months, 97 percent of patients

Figure 1-5

**GLEEVEC (IN 400MG
AND 100 MG TABLET
FORM)**



Source: Novartis



showed a hematologic remission with Gleevec and 87 percent had a major cytogenetic response. This compares with a 69 percent hematologic remission rate and 35 percent major cytogenetic response rate of IRIS trial patients treated with IFN. A December 2003 update of the trial at 30 months of follow-up showed that these response rates remain roughly consistent over time.²³ The IRIS trials showed that many more patients respond to Gleevec than IFN and that response occurs sooner when treated with Gleevec. Additionally, the improved rates of complete cytogenetic response suggest the likelihood of improved survival. While not as dramatic, there is also evidence of effectiveness in accelerated phase patients. In blast phase patients, although remission rates are better with Gleevec, neither Gleevec nor IFN significantly prolong survival.

Evidence of Gleevec's efficacy has been overwhelmingly positive to date.

While early data from the major Gleevec clinical trials are impressive, it is important to note that since Gleevec was first administered in human trials in 1998, only a few years of follow-up data exist. Nonetheless, most clinical experts expect overall improvement in long-term survival with Gleevec. Although the vast majority of patients experience improved outcomes, there is a small population for whom the drug has no clinical effectiveness. About 5 percent of patients develop resistance to treatment and must consider other options.

Figure 1-6

COMPARISON OF MAJOR CML TREATMENT OPTIONS			
Treatment	Bone Marrow Transplant (BMT)	Interferon Alpha (IFN)	Imatinib Mesylate (Gleevec)
Clinical Efficacy	Capable of obtaining sustained molecular remission – a true cure	Capable of obtaining cytogenetic remissions	Capable of obtaining molecular remissions (in less than 5 percent of patients)
Morbidity / Mortality	High treatment-related mortality. Risk of chronic GVHD.	Low mortality. High morbidity, associated with chronic flu-like symptoms, which can be alleviated through dose-reduction	Low mortality and low morbidity observed to date
Long-Term Cost	Costs are highly concentrated in first year of treatment	Regular, ongoing cost	Regular, ongoing cost

Source: NEHI

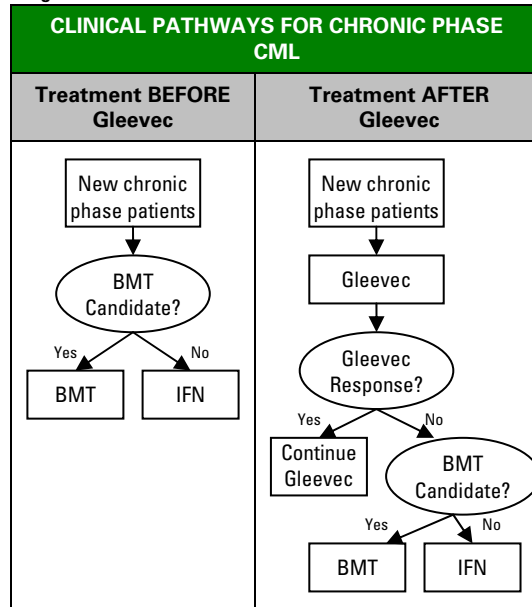


CLINICAL TREATMENT PATHWAYS FOR CML BEFORE AND AFTER GLEEVEC

Gleevec has dramatically changed the clinical pathway for CML. Before the adoption of Gleevec, there were two main treatment options that prevented progression of the disease: BMT and IFN. Patients who were BMT candidates received a transplant as soon as possible; those who were not began IFN treatment. Gleevec is now widely utilized as a first-line treatment for CML (Figure 1-7).²⁴ Patients who respond well remain on Gleevec treatment. The small minority of patients who do not respond well, or develop resistance or intolerance to the drug, then are candidates for BMT or IFN. Gleevec thus allows most patients to avoid or delay the high costs and risks of BMT and the difficult side effects and lower efficacy of IFN.

Although Gleevec has clearly become an established and effective treatment for CML, it did not arrive at this position without facing several challenges along the way. The next section of this report illustrates the challenges and opportunities in introducing a new innovation, following it from innovative science to patient care.

Figure 1-7



Source: NEHI



The Journey from Innovative Science to Patient Care

Much has been made of how rapidly Gleevec has transformed the treatment landscape for CML. Yet the full story spans approximately 40 years – from early research into the genetic origins of CML, to the development of the drug itself and ultimately to present-day issues surrounding proper use and new applications (Figure 2-1).

DISCOVERY AND EARLY DEVELOPMENT (1960 - 1998)

Identifying markers of the disease

In 1960, Peter Nowell, M.D., a pathologist at the University of Pennsylvania School of Medicine, and David Hungerford, M.D., of the Institute for Cancer Research at Fox Chase Cancer Center, conducted ground-breaking research that identified a genetic alteration (the Philadelphia chromosome) associated with CML. Thirteen years later, Janet Rowley, M.D., a researcher specializing in human genetics at the University of Chicago Medical Center, linked the Philadelphia chromosome to the Bcr-Abl oncogene, a gene that causes normal cells to become cancerous. Rowley's discovery was another major milestone in CML research.

In the late 1980s, Nobel Prize-winning virologist David Baltimore, Ph.D., a founding faculty member of the Whitehead Institute for Biomedical Research, and Owen Witte, M.D., a professor of microbiology, immunology and molecular genetics at UCLA's Jonsson Cancer Center, isolated the Bcr-Abl tyrosine kinase as the cause of CML.

At the same time, researchers at the Swiss pharmaceutical giant Ciba-Geigy were studying tyrosine kinase inhibitors, looking for early drug candidates. Led by staff scientists Alex Matter, M.D., and Nick Lydon, Ph.D., they focused on kinases in major cancers such as solid tumors of the lung, breast and prostate. The impetus to focus on CML – in spite of the small target patient population – came in 1988 from Brian Druker, M.D., at the Dana-Farber Cancer Institute who convinced the staff scientists that successful tyrosine kinase inhibition in CML would serve as “proof-of-concept” for cancer therapies based on targeted drug design and tyrosine kinase inhibition.

Identifying a drug candidate

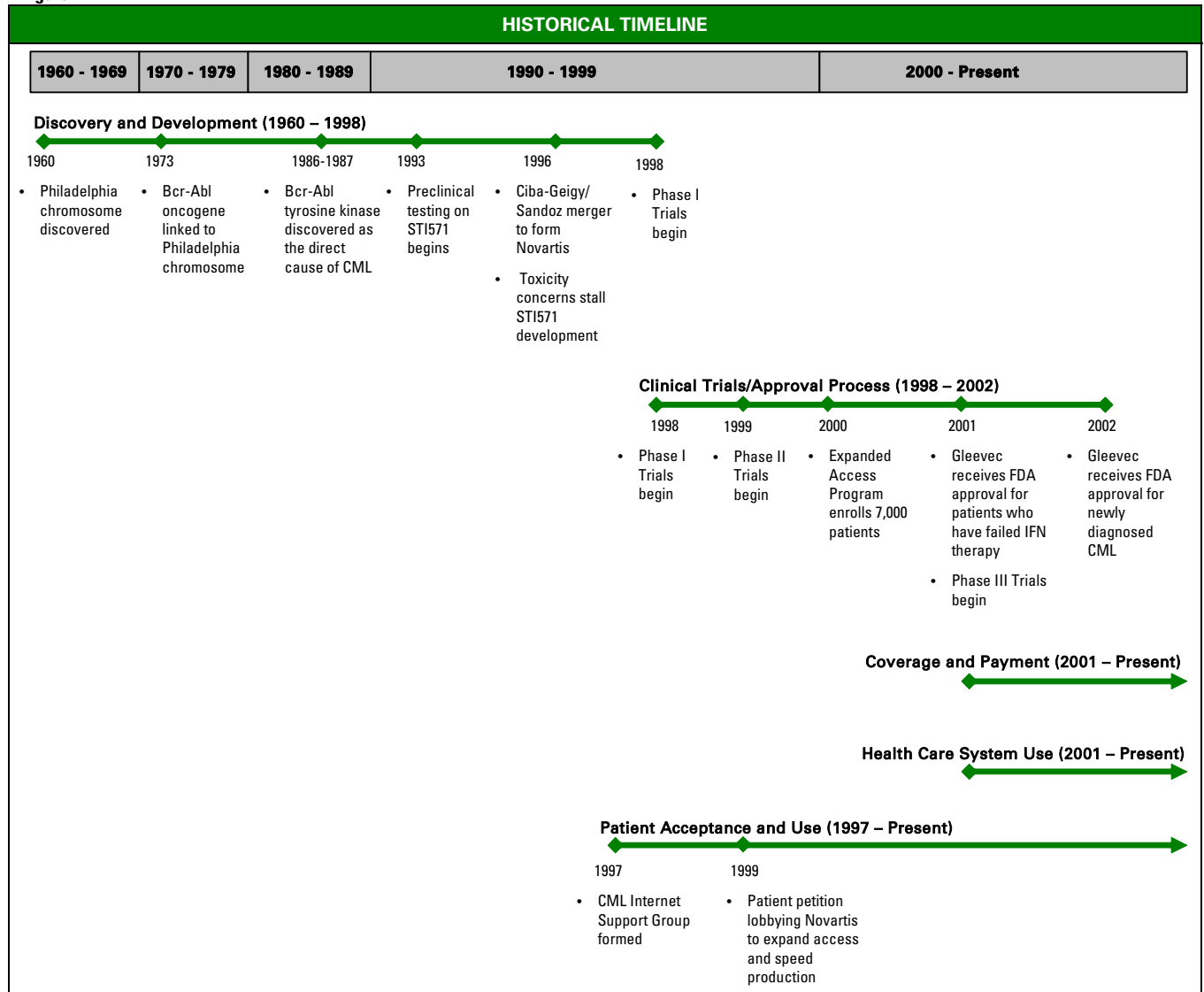
In 1993, the Ciba-Geigy scientists identified a promising drug candidate, which they labeled “STI571,” later to be known as Gleevec. They enlisted Druker, by then at the Oregon Health and Science University, who demonstrated in 1994 that STI571 inhibited the Bcr-Abl tyrosine kinase in vitro, raising hopes about the drug's potential in humans.

After the Ciba-Geigy and Sandoz merger in 1996 (creating Novartis), it became apparent that higher-than-expected toxicity levels were occurring in animals. These troublesome results, along with a post-merger re-prioritizing of initiatives, exacerbated Novartis' ongoing concerns about investing in a program unlikely to produce sufficient returns. Despite Novartis' initial hesitance to develop the drug,



The Journey from Innovative Science to Patient Care

Figure 2-1





Druker pursued his research of STI571 and in 1998, successfully persuaded Novartis to commence Phase I trials of STI571 in humans.

CLINICAL TRIALS AND FDA APPROVAL PROCESS (1998 - 2001)

In June 1998, Phase I trials (Figure 2-2) for STI571 began. Less than one year later, investigators saw strong indications that Gleevec could be a highly efficacious therapy. Realizing that STI571 represented a potential breakthrough therapy, Novartis consulted with the FDA to find out if a Phase II trial – assuming strong results – could be sufficient for approval, given the severity of the disease. The FDA worked with Novartis on the design of protocols for the Phase II trial and took the step of acknowledging that if such response rates held during the Phase II trial, fast-track approval might be warranted.

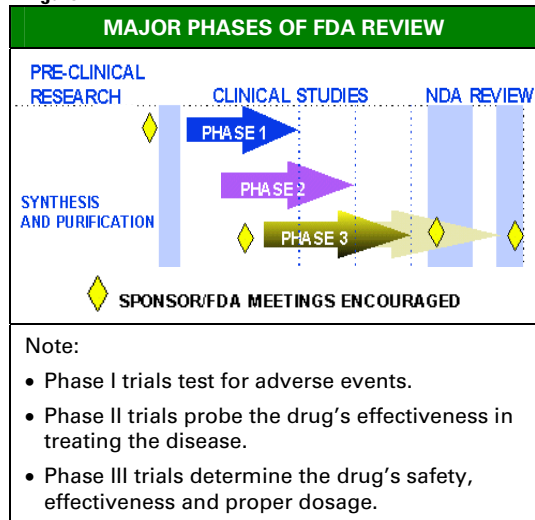
Word of the unprecedented Phase I results spread quickly throughout the patient community, through an active Internet CML support group. Desperately wanting access to this breakthrough therapy, patients mobilized to create a tidal wave of demand for the treatment. In October of 1999, they sent Novartis a 3,030-signature petition and deluged the company with letters, e-mail and calls – pressuring the manufacturer to scale up production of STI571.

With promising Phase I trial results and aggressive patient demand, Novartis made a critical decision to expand Phase II trials and accelerate production of the drug. This decision required a significant, high-risk investment in a therapy with only Phase I results. In 1999, Novartis took the unusual measure of enrolling more than 1,000 patients at sites in the United States and Europe in the STI571 Phase II trial and later in 2000 launched an expanded access program to provide the drug to an additional 7,000 patients prior to FDA approval.

In February 2001, only 32 months after the first dose had been administered to humans, Novartis filed a new drug application (NDA) with the FDA and was granted priority review status on March 26, 2001, cutting the normal 10 to 12 month review period to six months.

On May 10, 2001, a mere three years from the start of the Phase I trial, Gleevec was granted FDA approval for the treatment of CML. As a condition of accelerated approval, Novartis was also bound to continue longer term clinical trials on Gleevec to gain a deeper understanding of the effects of the drug. To

Figure 2-2



Source: Food and Drug Administration



date, results from these trials have remained positive, with the Phase III IRIS trial providing the most compelling evidence for the clinical efficacy of the drug.

COVERAGE AND PAYMENT (2001 - PRESENT)

Despite the record approval time, Novartis faced two primary challenges in obtaining coverage and payment for Gleevec from public and private health care insurers. First, with the exception of some drugs that have an intravenous equivalent, the U.S. Medicare program does not cover oral cancer treatments. Second, from an absolute dollar standpoint, Gleevec is expensive. While patients and physicians hailed the efficacy of the drug, Novartis' pricing of Gleevec at just under \$30,000 per year did come under criticism.

To address this issue and reduce the cost burden for Medicare-eligible patients and for the uninsured, Novartis established a sliding-scale patient assistance program to subsidize Gleevec for patients who could not otherwise afford the drug. Patients with annual family incomes under \$43,000 receive Gleevec for free. Those earning between \$43,000 and \$100,000 pay at most 20 percent of their annual income for the drug. Patients with family incomes higher than \$100,000 pay the full price of the drug. While Novartis has made a strong commitment to enabling access through this patient assistance program, for those patients who are not fully subsidized, the cost of therapy (20 percent of total income or \$29,844) can be a difficult expense to bear.

HEALTH CARE SYSTEM ACCEPTANCE (2001 - PRESENT)

Unlike many cutting-edge therapies, Gleevec experienced rapid, widespread adoption among oncologists due to the strength of clinical results, its reputation as a breakthrough in cancer therapy and widespread media attention. Once Gleevec was approved in May 2001, treatment of CML patients shifted away from major medical centers – the central sources of treatment during clinical trials. Because Gleevec is administered orally, both administration and patient monitoring spread to more numerous, smaller medical facilities in the community, allowing for greater patient access and convenience.

While general knowledge of Gleevec was widespread, detailed knowledge of proper use and administration of the drug may not have been as pervasive. Although Novartis conducted an extensive marketing and physician education effort, it soon became apparent that dosing of Gleevec varied widely among the many physicians who did not frequently see CML patients, despite guidelines and recommendations from clinical trials. While experts vary in their assessment of practice variation, data indicate that some patients - perhaps as many as 25 percent according to survey research by the drug's manufacturer- were given less-than-effective doses of Gleevec in the first six months to one year after FDA approval.

PATIENT ACCEPTANCE AND USE (1997 - PRESENT)

Patient demand and empowerment was a major force behind Gleevec's unprecedented speed to market. In addition to lobbying Novartis in 1998 to ramp up production for Phase II trials and provide financial

Patients educated patients on proper dosing and treatment.



assistance for expanded access, patients also leveraged online support groups to speed enrollment into clinical trials and disseminate the latest information and data on Gleevec. Patients educated patients on proper dosing and treatment.

NEW AND EMERGING ISSUES WITH CML AND GLEEVEC

Even with the excellent progress in CML therapy over the past several years, the scientific community is still working vigorously to improve CML treatment. Key areas of research include long-term molecular testing of Gleevec patients to assess the drug's potential as a curative therapy; improvement in therapy for those patients who relapse while on Gleevec; and improvement in response rates by increasing dosage or combining it with other therapies.

In addition, several new treatments are currently in development and clinical trials. One area of significant interest is less debilitating BMTs, called non-myeloablative or "mini" transplants. Combination therapies are also now being tested in humans. Researchers are evaluating, for instance, whether Gleevec can have a complementary effect on other drugs that have a long track record of effectiveness, such as IFN. In addition, there are ongoing clinical trials on CML vaccines that encourage the body's own immune system to recognize and destroy cancerous cells.

Beyond its indications for CML treatment, Gleevec is FDA approved for GIST, a rare cancer of the abdomen, and its uses are currently being explored for illnesses such as prostate cancer, hypereosinophilia, polycythemia vera, acute lymphoblastic leukemia and glioblastoma.

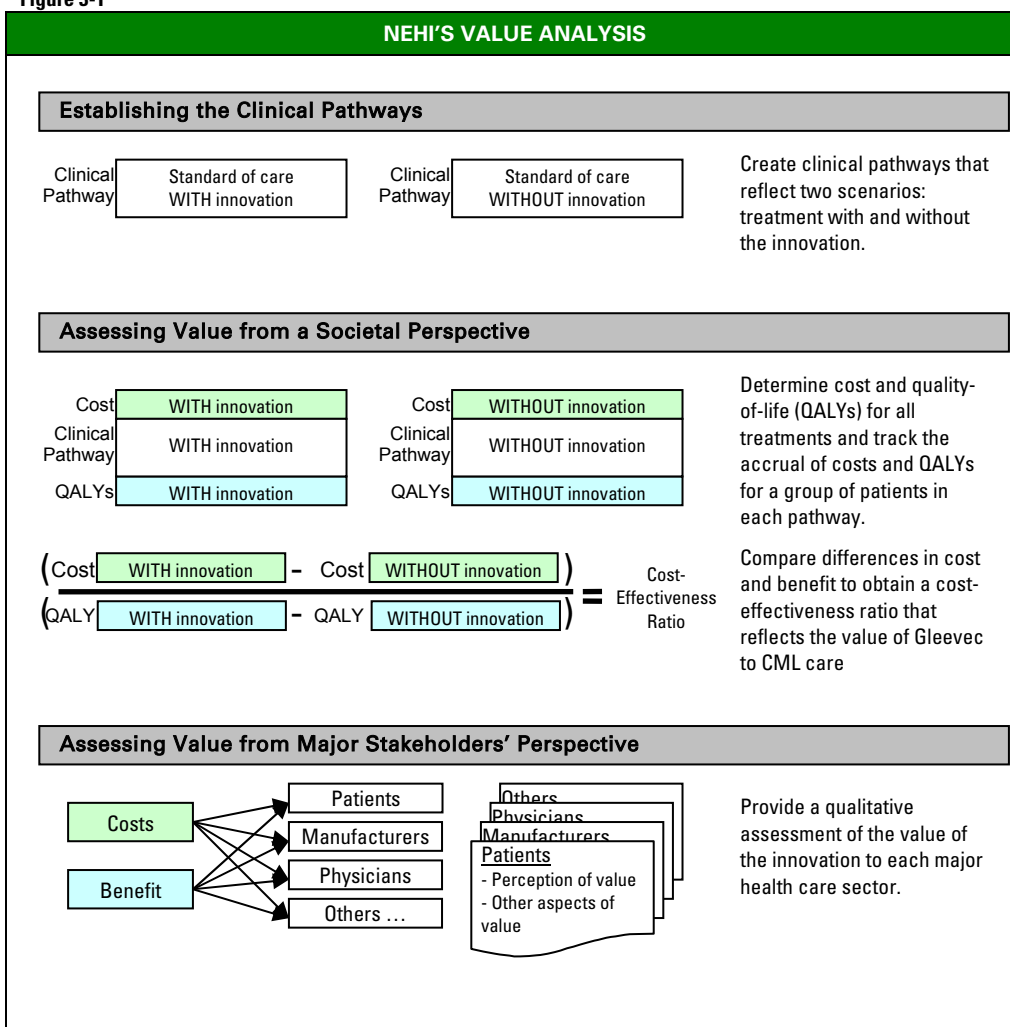
The story behind Gleevec's development and adoption encapsulates the critical issues health care system stakeholders face in bringing a new scientific breakthrough to life. In particular, Gleevec highlights the challenges and opportunities involved in bringing drugs to market for rare diseases and reinforces the importance of examining the value, not just the cost of expensive therapies.

The next section of this report examines the full value of Gleevec, as an example of the emerging class of molecularly targeted therapies. It analyzes the value of this innovation to society and to major stakeholders in the health care system.



Value Analysis

Figure 3-1



Source: NEHI



Value Analysis

OVERVIEW

Gleevec's clinical efficacy was the central driving force behind its success. Yet, in an era of escalating health care costs, clinical efficacy is essential – but not sufficient – to justify the widespread adoption of a new treatment. The concept of value has become increasingly important to the nation's dialogue on health care. However value in health care can be difficult to define. Attempts to determine value immediately raise such questions as “Value to whom?” and “How is it measured?”

To address these issues, NEHI's Value Analysis (Figure 3-1) draws upon traditional methods of cost-effectiveness analysis to compare the costs and health benefits that accrue to patients before and after the incorporation of Gleevec into the system of CML care. We then assess how costs and benefits accrue to specific sectors of the health care community.

The concept of value has become increasingly important to the nation's dialogue on health care.

ASSESSING VALUE

Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) is a standardized method of evaluating health care interventions by comparing the costs and benefits of competing treatment strategies (for a more detailed explanation of cost-effectiveness analysis, please see Appendix 3). To assess the value of adding an innovation to the system of care, a standard approach is to calculate a cost-effectiveness ratio.

In this analysis of CML, the cost-effectiveness ratio compares the total system of CML treatment with Gleevec (mainly Gleevec, BMT, and IFN) to the total system of treatment without Gleevec (mainly BMT and IFN). The cost-effectiveness ratio is calculated by dividing an estimate of the incremental cost of adding Gleevec to CML care (measured in dollars) by an estimate of the incremental improvement in health as a result of Gleevec (measured in Quality Adjusted Life Years, or QALYs). According to the literature on cost-effectiveness, treatments with a cost-effectiveness ratio above \$100,000/QALY are not considered cost-effective, those between \$50,000 and \$100,000 are marginally cost-effective, and those below \$50,000/QALY are the most cost-effective.²⁵

Since these estimates depend on factors that are inherently uncertain (e.g. future outcomes of treatment, or the quality of patient health) we conducted a sensitivity analysis to understand the effect that changes in our assumptions have on our final conclusion.

Value to Society

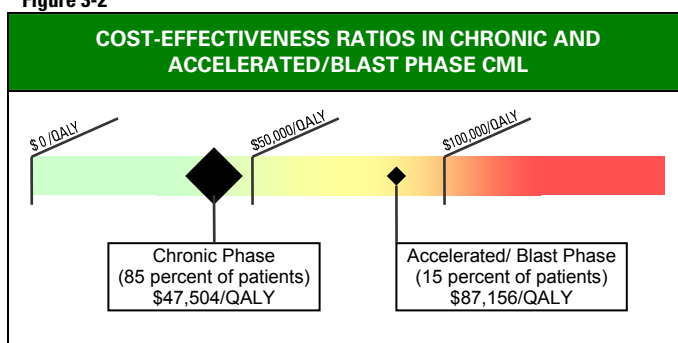
Treatment with Gleevec improves the quality and length of patient lives. These benefits, however, do come at a higher overall dollar cost. The benefit of treatment is measured by the QALY, a figure that captures the treatment's effect on both length and quality of life. From a cost perspective, accounting for both



drug and other direct health care costs on an annual, per patient basis, Gleevec costs \$32,724 compared with \$28,159 for IFN. On average, BMT costs an estimated \$196,000 in the first year of treatment and \$12,000 each year thereafter.²⁶

The comparison of CML treatment with Gleevec versus without Gleevec leads to a cost-effectiveness ratio that, at \$47,504, is below the traditionally utilized thresholds for cost-effectiveness and implies that the cost of Gleevec is warranted for most CML patients (Figure 3-2). For accelerated and blast phase patients, that amount rises to \$87,156 per QALY,²⁷ indicating that, while less certain, the drug is likely still cost-effective in late-stage disease (See Appendix 3 for further detail).

Figure 3-2



Source: NEHI



ASSESSING VALUE FROM MAJOR STAKEHOLDERS' PERSPECTIVES

Cost-effectiveness analysis (CEA) is a necessary, but not sufficient method of determining the value of innovations. Although it calculates the overall value of an innovation from a particular perspective, it does not capture the effect of a new innovation on each specific part of the health care system. NEHI's Value Analysis adds an examination of the costs and benefits of CML innovation from the perspective of six key health care stakeholders to the classic CEA: patients, manufacturers, physicians, employers, payers and hospitals. Informed by expert opinion, this sector-based analysis provides a more nuanced understanding of how an innovation affects each constituent it touches. This knowledge of sector-specific effects allows us to identify critical drivers and barriers that will speed or impede the adoption of innovation.

The fact that every stakeholder either benefits from, or is net neutral to the advent of Gleevec has been one of the critical factors behind the drug's rapid adoption and uptake across the health care system.

Gleevec is a cost-effective and highly valuable treatment for CML patients. It is also an important innovation for the majority of stakeholders in the health care system (Figure 3-3). The fact that every stakeholder either benefits from or is net neutral to the advent of Gleevec has been one of the critical factors behind the drug's rapid adoption and uptake across the health care system.

High value

First and foremost, patients yield the highest value from Gleevec. The benefits are clear. As an oral therapy that can be taken at home, with strong efficacy and few side effects, Gleevec has dramatically improved patient quality of life and productivity. Patients themselves have remarked...

on the difference between Gleevec and IFN...

"People talk about having 'interferon brain'. It makes you unclear, stupid, and eventually depressed. It's not a pleasant thing...it was very nice to stop it when Gleevec became available."²⁸

on general quality of life...

"My psychological response to this is... great! I am still alive... My quality of life is back... I awake each morning. I am here. Each new day I don't think about the cancer any more, where it used to play a very important part of my life. It was probably 90 percent of my thinking time. It's not there now."²⁹



ASSESSING VALUE FROM MAJOR STAKEHOLDERS' PERSPECTIVES

Figure 3-3

STAKEHOLDER VALUE ANALYSIS			
Stakeholders	Net Value	Benefits	Costs
Patients	+++	<ul style="list-style-type: none"> - Vastly improved quality of life, improved outcomes and lower side effects - Convenience of pill versus intravenous delivery, fewer physician office visits, treatment at home - Higher productivity - Empowerment and optimism 	<ul style="list-style-type: none"> - Co-pays - High costs for some Medicare and uninsured patients
Manufacturers	+++	<ul style="list-style-type: none"> - First example of rational drug design - Commercial success for Novartis with 2003 global sales of \$1.1 billion 	<ul style="list-style-type: none"> - Significant investment of resources in accelerated development, trials and production, and expanded access programs
Physicians	++	<ul style="list-style-type: none"> - "Proof of concept" and boost to research on molecularly targeted cancer drugs - CML patients are doing well and living longer 	<ul style="list-style-type: none"> - Less revenue from reduced office visits
Employers	+/Neutral	<ul style="list-style-type: none"> - Increased productivity as patients can go back to work 	<ul style="list-style-type: none"> - Increased costs in extended years of life
Payers	+/Neutral	<ul style="list-style-type: none"> - Improved predictability of costs, fewer large one-time claims 	<ul style="list-style-type: none"> - Negligible overall impact due to small patient base and substitution pricing
Hospitals	Neutral/-	<ul style="list-style-type: none"> - Minimal to none 	<ul style="list-style-type: none"> - Fewer BMTs / less revenue from CML

Scale:

+++ to - - -

Source: NEHI



on increased productivity...

“...I went from having a hard time even getting out of my bed some days to going back to work full time.”³⁰

In addition to these quality of life and productivity benefits, Gleevec slows disease progression and may increase survival rate as well. Since all of these benefits accrue directly to patients and most patients in the insured population bear a relatively small portion of the total cost of treatment, Gleevec is clearly a highly valuable innovation from the patient perspective.

Gleevec is also of very high value to its manufacturer, Novartis. Despite initial concerns about developing a drug targeted to a small market like CML, Novartis has yielded significant value from Gleevec. Certainly one reward to Novartis has been the high-profile therapeutic and clinical success of the drug. In addition, Gleevec has provided a strong financial boost to the company.

Although Novartis invested significant resources in getting the drug to market quickly and incurs ongoing production and marketing costs, Gleevec has clearly exceeded the company's financial expectations. In the words of Novartis Chief Executive Officer, Daniel Vasella, M.D., in 2002, “Gleevec is on its way to becoming a commercial success, which nobody expected.” Today, as Novartis' second-largest pharmaceutical product, with over \$1.1 billion in 2003 worldwide sales³¹, Gleevec has indeed become a “commercial success.”

Although it is difficult to quantify the total costs Novartis has incurred for Gleevec, the company has clearly made an enormous investment in the drug, spanning 15 years of research, development and production. The Tufts Center for the Study of Drug Development estimates that pre-clinical and clinical production costs for global pharmaceutical companies developing new drugs average \$802 million per drug, rising to \$897 million with the inclusion of post-approval research.³² In order for a company to remain competitive, expenditures for failed drug discovery ventures must be offset by revenue from successful products. Based on the Tufts estimates, it appears that Gleevec, with \$1.1 billion in annual sales is making a solid return on investment for Novartis and likely providing significant subsidies toward current research and development efforts. Although IFN manufacturers have lost CML market share due to Gleevec, the relative impact has been less significant due to the use of IFN in several larger disease states.

Moderate value

For physicians, Gleevec's rewards are strong, yet intangible. For oncologists treating CML patients or for those involved in the development of Gleevec, patient outcomes have been tremendously rewarding.

Moreover, Gleevec has provided physicians and researchers with “proof of concept” for the class of molecularly targeted cancer drugs which, in turn, has given a strong boost to scientific research in oncology. Richard Silver, M.D., a

...so for us in the trenches it has been a very heartwarming, glorious experience.



pioneer in CML research, expressed how the availability of effective treatment options affects the treating physician as well as the patient:

“The impact of Gleevec for me has been a very personal one because we have seen people who would otherwise have died, now live gainful lives...So for us in the trenches it has been a very heartwarming, glorious experience.”³³

The words of Dr. Brian Druker, an instrumental figure in the development of Gleevec, illustrates just how rewarding it is to see one’s scientific work affect the lives of patients:

“Words can't describe how gratifying this has been for me. I've dreamed of doing something like this since I was a medical student. I've worked on the project for 10 years, on this drug for six, and now I get to see it work in patients.”³⁴

Despite the high intangible value, the overall financial value of Gleevec to physicians, however, is uncertain. While clinical trial data indicate a 38 percent reduction in annual physician office visits, increased survival may mitigate this reduction by providing each physician with more patients overall.

Modest value

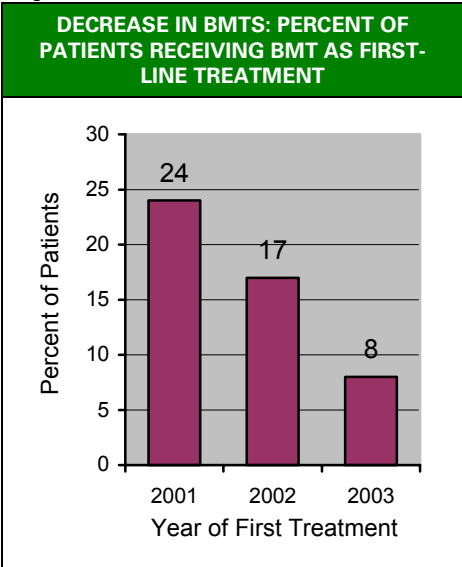
Because of its small patient population, the value of Gleevec to employers, third-party payers and hospitals is minimal.

While employers of CML patients clearly benefit from Gleevec through increased productivity from patients who return to work, some of that benefit is offset by the health care costs that the employer must bear in the extended years of patient life. Ultimately however, with so few CML patients (one in 67,000 people), only a small percentage of businesses are likely to have an employee with the disease.

To hospitals, the net impact of Gleevec is neutral to slightly negative. Based on national registry data and information from a major cancer center, the number of CML-related BMTs has declined in recent years. NEHI’s analysis of claims data shows fewer patients receiving first-line BMT over time (Figure 3-4). Although BMTs are typically a highly profitable procedure for major hospitals, demand for BMTs to treat other conditions has in many cases filled the void left the success of Gleevec.

To third-party private payers the value of

Figure 3-4



Source: NEHI



Gleevec is neutral to slightly positive. With its small patient base, the net benefits and costs of treating CML with Gleevec are minimal to any one payer and although the total cost of Gleevec therapy is high at \$32,724 per year, the relative costs vis a vis IFN are minimal.³⁵ Third party payers also benefit from the increased predictability of costs. With fewer patients receiving BMTs at a high, up-front cost, payers are less likely to pay for a procedure now that will produce health benefits at a later time when the patient is no longer their member.

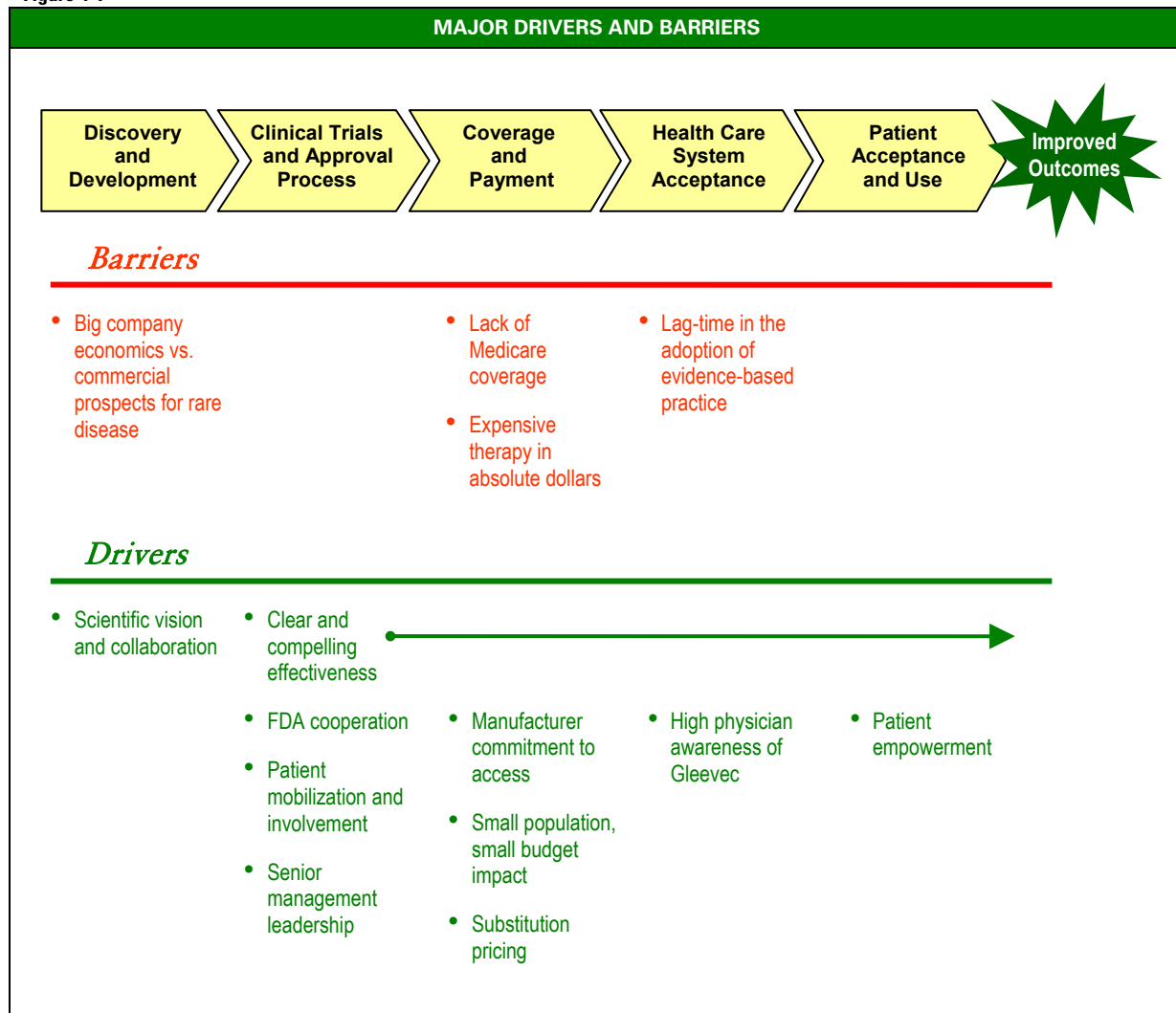
In summary, Gleevec is a highly valuable innovation. In addition to being cost-effective to society, it is valuable to patients, manufacturers and physicians and, at a minimum, neutral to payers, employers and hospitals.

Valuable new innovations, however, are not always immediately adopted; it typically requires additional critical success factors to speed adoption. In this next section, we examine both the drivers and barriers to Gleevec's adoption through its journey from discovery to diffusion, a journey of highs and lows, not uncommon to those faced by many new and innovative therapies.



Drivers and Barriers Analysis

Figure 4-1



Source: NEHI



Drivers and Barriers Analysis

The story of Gleevec's journey, from innovative science to patient care, highlights the major drivers and barriers to one drug's adoption in the health care system (Figure 4-1). Many of these drivers and barriers, however, are not unique to Gleevec; rather they are indicative of the challenges and opportunities faced by many other breakthrough innovations.

DISCOVERY AND EARLY DEVELOPMENT

Barriers

Big Company Economics vs. Commercial Prospects of Rare Disease

During the 1980s and 1990s large pharmaceutical companies like Ciba-Geigy and Novartis could not rationally pursue all interesting scientific paths for drug development. It was difficult to justify spending research and development resources on potential drugs for small patient populations that were unlikely to yield major financial returns. Even when it was becoming evident that STI571 was a promising drug candidate, the CML market was just too small to warrant management attention or significant research and development spending. For five years – from 1993, when STI571 was first discovered and tested, until 1998 when the Phase I trial began – Gleevec development stumbled and the drug candidate languished on the shelf.

For five years...Gleevec development stumbled and the drug candidate languished on the shelf.

Drivers

Scientific Vision and Collaboration

Had it not been for the passionate commitment of the corporate scientists and for Druker's vision and stewardship, Gleevec might never have made it out of the lab. Moreover, unlike most drugs and therapies that are typically developed by in-house leadership at a pharmaceutical company *or* under academic leadership in a research setting, Gleevec is a prime example of an innovation developed through deep, sustained collaboration between industry and academic champions of the drug.

CLINICAL TRIALS AND FDA APPROVAL PROCESS

Drivers

Breakthrough Therapy with Evidence-Based Efficacy

The most fundamental force behind Gleevec's rapid approval was strong evidence-based data from clinical trials. Gleevec's clinical trials demonstrated definitively and early on that this new therapy was safe and significantly benefited patients.



FDA Cooperation

Gleevec’s record approval time (Figure 4-2) required far-reaching cooperation from the FDA. From helping Novartis design protocols for the Phase II trial to expediting the review process, the FDA clearly demonstrated its commitment to fast-tracking safe and efficacious treatments for life-threatening diseases.

Patient Mobilization and Involvement

Patients played a vital role in advocating and justifying the rapid approval of Gleevec. The formation of the CML support group, an online chat room for CML patients, is a prime example of patient unification and empowerment through the Internet. During clinical trials, this support group leveraged its collective strength to pressure Novartis into speeding up Gleevec production and expanding Phase II trials. This patient support group also spurred enrollment in clinical trials.

Senior Management Leadership

In 1999, Gleevec finally caught the attention of senior management. Novartis’ chief executive officer responded personally to the patient petition and committed the company to stepping up investment in, production of, and access to Gleevec for CML patients worldwide.

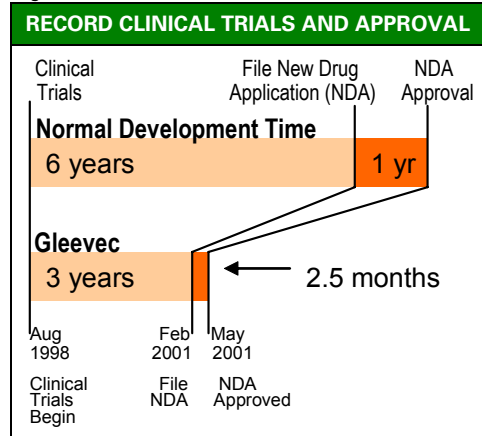
COVERAGE AND PAYMENT

Barriers

Lack of Medicare Coverage

When Novartis decided to develop an oral formulation of Gleevec, the company knew it would be difficult to get Medicare to cover the treatment. Since most cancer drugs are delivered intravenously by physicians, payment has traditionally fallen under the Medicare-covered classification of drug use that is “incident to” a physician visit. When legislators began to realize the growing importance of oral drugs in cancer treatment, coverage was partially expanded to include oral drugs with an intravenous equivalent. This partial expansion left a gap in coverage for a handful of oral cancer drugs that do not have an intravenous equivalent. Gleevec is the highest-profile of these uncovered therapies; others include Iressa™ for non-small cell lung cancer, tamoxifen for breast cancer and flutamide for prostate cancer. While these drugs in many cases are more effective than an injectable alternative, they are, nonetheless, not covered by Medicare.

Figure 4-2



Source: Adjusted from Novartis Annual Report, 2001



Expensive Therapy in Absolute Dollars

Despite Gleevec's clinical efficacy and prospects for displacing costly existing treatments, Novartis was concerned about the perception and impact of the drug's high cost. In his 2003 book, *Magic Cancer Bullet*, Dr. Daniel Vasella explains Novartis' pricing strategy: "We agree with those who say that the price we have set for Gleevec is high. But given all the factors, we believe it is a fair price."³⁶ Ultimately, Novartis put a price on Gleevec roughly equivalent to the full cost of treatment with IFN: \$29,844 for a year's worth of treatments.

Drivers

Manufacturer Commitment to Access

To address potential gaps in coverage, Novartis made a strong commitment to ensure that patients had access to Gleevec — particularly the uninsured and those on Medicare. It established a patient assistance program that enabled eligible CML patients to get the drug for free or at a significant discount. This program has helped make Gleevec available to the uninsured and those covered by Medicare. While the cost of treatment is clearly still burdensome for those without financial assistance, Novartis' commitment to patient access has reduced the cost barrier for those with the greatest need.

Small Patient Population, Small Budget Impact

When assessing the impact of new therapies on coverage and payment policies for new therapies, third-party payers have two main considerations. First and foremost is evidence-based clinical efficacy. Second is the budget impact, namely, the overall financial impact of a new therapy once it is added to the system of care. The budget impact is a function of the number of potential plan members treated with the new therapy and the total increase in costs associated with the therapy. Third-party payers would ordinarily consider \$29,844 per patient per year a high price for a chronic medication taken over the span of many years. But the overall budget impact of Gleevec to third-party payers is minimal because the patient population is so small. As a single drug for a small patient population, coverage and payment for Gleevec never truly became an issue for large private payers.

Substitution Pricing

Novartis priced Gleevec so that it was essentially cost neutral to third-party payers. In addition to documenting clinical efficacy, budget estimates given by Novartis to payers³⁷ demonstrated that, while pharmacy costs may be slightly higher than those for IFN, overall medical costs would be lower because patients treated with Gleevec required fewer outpatient visits and hospitalizations, as demonstrated in clinical trials. By pricing Gleevec as cost neutral on net to IFN and significantly less — initially — than BMTs, Novartis made sure that payers would not suffer financially and Novartis could reap a maximum return on its investment in a drug with a small patient base.



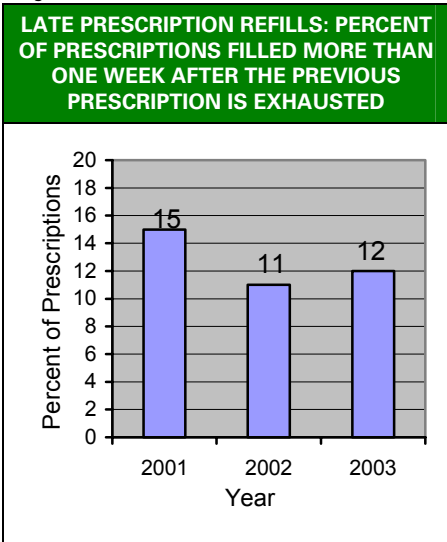
HEALTH CARE SYSTEM ACCEPTANCE

Barriers

Lag-time in the Adoption of Evidence-Based Care

Data from surveys conducted by Novartis suggest that as many as 25 percent of chronic-phase patients were prescribed dosages lower than the demonstrated effective level.³⁸ Our own analysis of health plan claims data (Figure 4-3) also shows that in the first year of FDA approval, 15 percent of prescription refills were made more than one week later than would be expected based on standard treatment dosage. While there are no hard data to explain the rationale behind this under-dosing phenomenon, some have speculated that physicians may have been incorrectly administering Gleevec in a manner similar to common practice with IFN – using an initial dose and subsequently lowering it according to side effects. Another hypothesis suggests that under dosing was caused by physicians being caught off-guard by minor side-effects when media hype and expectations implied there would be none. Despite widespread awareness of Gleevec within the oncology community, there appears to have been a delay in the use of optimal treatment dosage. Some experts have also noted difficulty in ensuring widespread adequate monitoring of CML patients. This delay in the dissemination of treatment knowledge corresponds to a pattern affecting many novel therapies.

Figure 4-3



Source: NEHI

Drivers

High Awareness

As one of the first molecularly targeted cancer therapies with remarkable clinical results, Gleevec was the subject of extensive mainstream and medical press coverage, which in turn prompted rapid acceptance by the health care system. New therapies, particularly those for rare diseases, typically suffer slow adoption rates due in part to lack of awareness. Gleevec benefited from high awareness of the therapy within the oncology community, even when the specifics of dosage and monitoring may not have been as widely known.

PATIENT ACCEPTANCE AND USE

Drivers

Patient Empowerment

In *The Magic Cancer Bullet* Dr. Vasella states that “no other group of cancer patients benefited as much from the ubiquity and the immediacy of the Internet as did CML patients.”³⁹ This small but passionate group of CML patients leveraged the Internet to become true activists for Gleevec at critical junctures in the drug’s



development. Intent on getting the drug in time to save their own lives, they mounted a campaign beginning in a chat room in 1997 that ultimately pressured Novartis to make a significant early investment in Gleevec. Their efforts were so successful in driving patient registration in clinical trials that investigators reluctantly had to turn patients away.

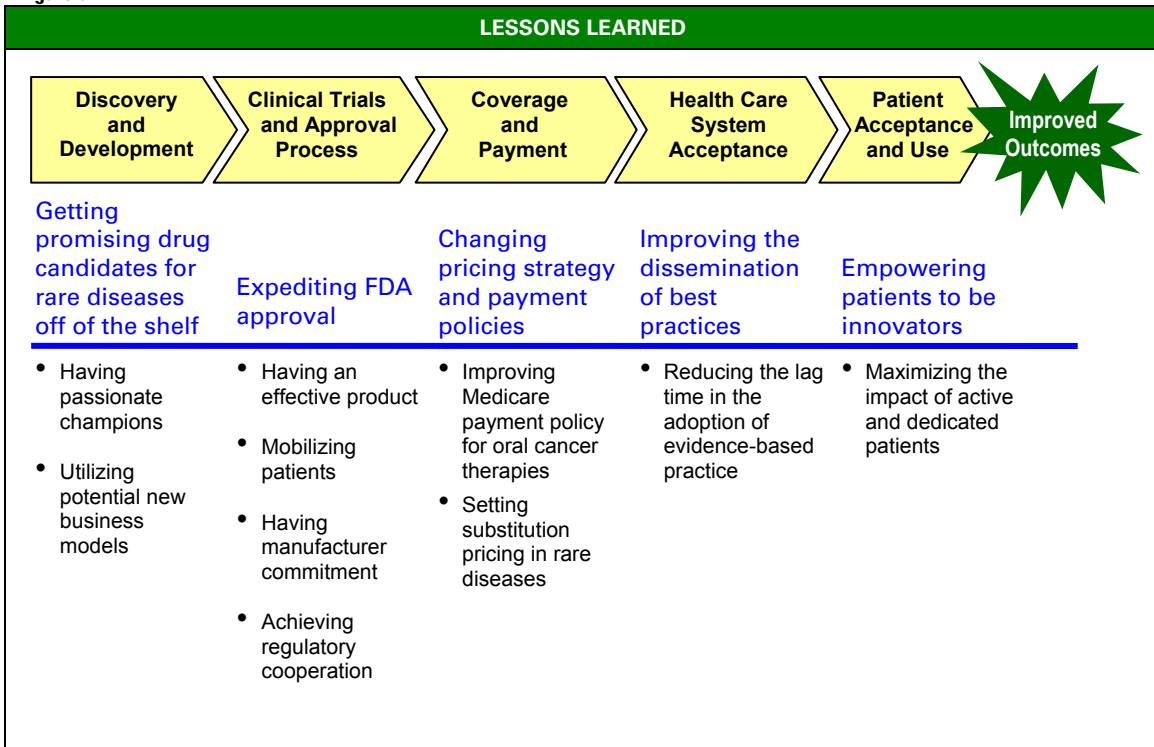
Moreover, after Gleevec's approval, as clinical data was released and published, patients who were involved in this network were often better informed about Gleevec than their physicians and even felt compelled to suggest changes to the care they were receiving. In essence, patients began taking responsibility for their own care. As one patient, Judy Orem, advocated:

“Be part of the team with your doctor. You may find that your doctor isn't as knowledgeable because he doesn't have any other patients with CML. Get second opinions if you're not happy with what's going on.”⁴⁰



Lessons Learned

Figure 5-1





Lessons Learned

This report examines both the successes and challenges in Gleevec's journey from an innovative concept to patient adoption, as well as its value to the health care system. The lessons learned from this case study of Gleevec (Figure 5-1) raise several critical questions and issues that are applicable to future molecularly targeted cancer therapies and to other emerging medical innovations at large. In this section, we identify the findings of the case study and pose several key policy questions. As the pace of medical innovation accelerates, these policy questions must be addressed to ensure patient access to the most highly valuable and medically necessary care.

OVERVIEW OF FINDINGS

NEHI's Value Analysis demonstrates that Gleevec is cost-effective to society as a whole and very valuable to three out of the six major health care system stakeholders. Gleevec has clearly made history as a scientific and medical breakthrough and as a model for fast-track FDA approval. Most importantly, however, it has dramatically improved patients' lives, creating excitement and hope for the future of molecularly targeted cancer treatments. The fact that Gleevec is cost-effective to society, highly advantageous to patients, manufacturers and physicians and at worst, cost-neutral to payers, employers and hospitals is one of the prime reasons behind its rapid adoption and uptake across the health care system.

Specific findings reveal that:

- Targeted therapies for small patient populations can yield commercial successes.
- FDA approval can be expedited for breakthrough drugs with industry leadership and patient participation.
- Lack of Medicare coverage is a difficult barrier to patient access, overcome in this instance by Novartis' willingness to pay for the drug.
- Substitution pricing strategies can enable the adoption of innovations.
- Variance in physician practice patterns can limit the efficacy of an innovation
- Patient activism can be a powerful driver of adoption.

The following section provides more depth and detail about each of these findings.



DISCOVERY AND DEVELOPMENT

Getting promising drug candidates for rare diseases off the shelf

Findings:

The Gleevec story demonstrates the financial success of a targeted therapy for a small patient population and the dynamics that can sustain revenue. Large pharmaceutical firms face significant pressures to produce correspondingly large blockbuster drugs – pressures which often operate against investment in treatments for rare, life-threatening diseases. In counterpoint to this scenario, revenue generation with Gleevec has occurred by virtue of four real-world market characteristics: (1) the drug’s usage as a chronic, ongoing treatment; (2) increases in patient life span that engender a longer average revenue period per consumer; (3) global reach, which enlarges the marketplace; and (4) the expansion of Gleevec indication into other markets such as GIST, expanding the consumer base.

Thus, while targeted therapies may command less revenue than typical blockbuster drugs, these avenues for revenue growth demonstrate the potential for “mini-blockbusters” such as Gleevec. Despite Novartis’ initial concerns that a major investment in a small disease population was less likely to yield significant returns, the company has demonstrated that returns can be made on investments in small markets. Large pharmaceutical companies like Novartis should not be afraid to invest in life-saving treatments for small markets. In fact, several biotechnology companies like Genzyme and Transkaryotic Therapies have built highly successful franchises by focusing on therapies for rare diseases.

Key policy questions to be addressed:

- How can we make it more likely that promising drugs for small patient populations are not stalled or put on the shelf indefinitely?
 - Are there novel or underused “option” arrangements to transfer such technologies to smaller companies, perhaps with targeted government support?
 - How does the potential for “foster homes for orphan drug candidates” affect patents or other intellectual property processes?
- Could communication among the scientific community, senior management at major pharmaceutical companies and government be improved to foster *ad hoc* consortia aimed at specific therapeutic opportunities?
- How will drug development companies electing to pursue targeted therapies have to adapt their business models to target smaller initial markets?
 - Could they find similar ways to make a return on smaller target markets – perhaps through reduced development time and/or partnerships?



- Are there ways of encouraging “champions” within major pharmaceutical companies, from both scientific and business disciplines, who can effectively advocate for promising drugs?

CLINICAL TRIALS AND APPROVAL PROCESS

Expediting FDA approval

Findings:

There were four critical success factors that enabled Gleevec’s record approval time: (1) the breakthrough nature of the drug and its clear efficacy; (2) the FDA’s cooperation in speeding up the regulatory and review process for a life-saving therapy; (3) patient activism and involvement before and during clinical trials; and (4) a commitment on the part of Novartis leadership to get Gleevec to market as quickly as possible. While each of these alone is important, in the case of Gleevec, these four forces converged leading to record FDA approval.

While the FDA has ramped up its commitment to accelerate approval of life-saving treatments⁴¹, Gleevec, nonetheless, remains the benchmark for fast-track approval.

Key policy questions to be addressed:

- Why has no other drug to date made it through the approval process as rapidly as Gleevec?
 - Assuming safety and breakthrough clinical effectiveness, what barriers have blocked other promising new innovations in the clinical trials or approval process?
- What might happen to the FDA fast-track process of review if a drug candidate, unlike Gleevec, were to have controversial scientific or marginal clinical results?
- How can other areas of the health care system best respond to more frequent accelerated approvals in ways that minimize bottlenecks and deploy innovation more effectively?

COVERAGE AND REIMBURSEMENT

Changing pricing strategy and payment policies

Findings:

Lack of coverage stymies patient’s access to an innovative drug. Medicare’s complex policy on coverage of oral cancer therapies means Medicare beneficiaries receive no coverage for Gleevec. Medicare currently covers similarly priced, less effective injectable therapies like IFN. But it does not provide coverage for oral cancer drugs when there is no injectable equivalent. With the high median age of onset for CML, many patients could not afford Gleevec without Novartis’ patient assistance program. The Medicare bill, passed in November 2003 and scheduled to take effect in 2006, will allow coverage for Gleevec. The bill includes a demonstration program (from 2004-2006) that would provide a transitional benefit covering certain oral cancer drugs such as Gleevec. This coverage would end when the new Medicare benefit takes effect in 2006. At that time, Gleevec will



be covered under the newly established benefit structure. Even with this coverage, current estimates suggest that Medicare patients will still be required to pay \$5,000 - \$6,000 out-of-pocket for treatments like Gleevec.

Novartis' substitution pricing strategy for Gleevec, while controversial at the time, proved to be crucial to the Gleevec success story. For many patients, Gleevec directly replaces existing treatments for CML. By setting a price for the drug that is roughly cost equivalent on net to IFN and significantly less than the initial cost for BMTs, Novartis maximized its return on investment for Gleevec *without* raising the annual cost of treatment. Novartis' substitution pricing strategy enabled it to win crucial coverage acceptance from third-party payers. In addition to substitution pricing, two other distinct aspects of the drug and pricing strategy led to its relatively unobtrusive adoption by commercial payers. First, the overall magnitude of any potential cost increase was small on a system-wide scale, given the small CML population. Second, clear clinical benefits and improved patient outcomes justified the case for a high price. In concert, these three factors led to little overall scrutiny of Gleevec's price and value. The absence of any one of these three factors, however, would likely trigger greater scrutiny and resistance from payers. As Medicare enters the debate with the new prescription drug benefit and early demonstration projects, it is likely that cost will become even more of an issue in the months and years to come.

Key policy questions to be addressed:

- Should there be a provision for subsidizing patient cost-sharing under the new Medicare drug benefit?
- What happens if new therapies are not direct substitutes for existing ones, such as Gleevec generally is for IFN and BMT?
- Could these new therapies be priced according to the *value* they provide? What are appropriate ways to meaningfully and specifically price drugs according to value?
- How will stakeholder groups react when an expensive, highly effective targeted therapy is approved for diseases with much larger patient populations?
 - Will the size of such markets cause delay in adoption simply because of resistance to system cost increases?
 - Alternatively, will the development of more drugs for small populations cause payers and policy makers to examine the value of each one more carefully?
- How will payers ensure that the right therapies are used for the right disease sub-groups when the diagnostic tools to accurately identify appropriate patients may lag in development?



HEALTH CARE SYSTEM ACCEPTANCE

Improving the dissemination of best practices

Findings:

As the locus of treatment shifted from major cancer centers out to community oncologists and physicians after Gleevec was approved by the FDA, some data suggest that a subset of patients were receiving sub-optimal dosages. While a clear majority of physicians administered the recommended dosage, data indicate that ensuring widespread adoption of proper dosing and adequate patient monitoring was a challenge early on. Finally, the low incidence of CML means that most physicians rarely see CML patients, making it difficult to stay up-to-date on the latest CML treatments.

This problem is not unique to Gleevec. Many drugs experience an initial period of suboptimal use after regulatory approval. There will be many highly effective breakthrough therapies in the next decade emanating from advances in genomics. Given that prospect, it is critical that our health care system delivers these therapies in accordance with the latest evidence-based guidelines and best practices. Experts hypothesize that molecularly targeted therapies ultimately will cause the sub-grouping of diseases such that all cancers may be considered “orphan” cancers. This redoubles the difficulty for physicians to stay current on the best treatment practices for each sub-group. In the case of Gleevec, the educational challenges were overcome through a combination of educational campaigns by Novartis and an empowered and educated patient population that took an active role in ensuring proper treatment. It is unclear whether such combinations will arise spontaneously in the future.

Key policy questions to be addressed:

- Is it realistic to expect physicians, who do not focus their practice on rare diseases such as CML, to stay abreast of all the latest treatment innovations?
- What processes could be put in place to improve the dissemination of knowledge about new therapies for rare diseases?
- Whose responsibility is it to ensure that patients are treated with the best, evidence-based practices?
 - Should the responsibility lie with manufacturers, medical schools, medical societies, patients, or some combination thereof?
- How can we reduce the time lag commonly seen in the dissemination of innovative technologies and improve the use of best practices?
 - What mechanisms should be put in place, if any, to monitor education and adoption processes? How would such mechanisms square with the independent professional model of physician practice in the United States?



- Are there ways to use telemedicine technology to efficiently educate non-specialist physicians about the evidence base and clinical experiences relevant to rare diseases?

PATIENT ACCEPTANCE AND USE

Empowering patients to be innovators

Findings:

Patient demand was a major force behind the unprecedented speed to market and rapid adoption of Gleevec. Although patient support groups and registries exist for many disease states and conditions, it is often those for rare and/or life-threatening diseases (e.g. AIDS, breast cancer, CML) that are most effective in mobilizing patients. That said, there are few examples of patient support groups that have played as critical a role in bringing forth an innovation as the CML support group did for Gleevec.

Leveraging an Internet support group, patients mobilized to lobby Novartis to accelerate development and production and expand patient access to the therapy. They drove rapid enrollment in clinical trials and educated fellow patients on proper dosing and treatment. This small, but passionate group of CML patients became true activists for Gleevec at critical junctures in its development and adoption.

Key policy questions to be addressed:

- How could patient support groups be leveraged to speed enrollment in clinical trials of other innovations and encourage the dissemination of timely and accurate data and information?
- How could patients with other rare diseases take an active role in ensuring that they receive the best possible treatment, whether it is through support groups, Internet communities or other knowledge-sharing organizations?

THE NEED FOR ACTION

All sectors of the health care system, not just patients, stand to benefit from the rapid identification and efficient adoption of truly high-value medical innovations. Leaders in all sectors of the health care industry will need to be imaginative as we work together to create fresh answers to these questions. The ultimate need to develop a system of behavioral and financial incentives for physicians, hospitals, payers, and manufacturers that are directly aligned in the best interest of the patients should be the dominant driver in our discussions.

NEHI will continue to work with its membership to address these critical issues. We will educate the public and policymakers regarding the findings from this research and create specific policy recommendations to drive public and private sector change.

APPENDICES

Appendix 1: Data Sources

MEDICAL LITERATURE

The primary source of data for the cost-effectiveness analysis comes from the IRIS Phase III clinical trial. As the first major clinical trial investigating the use of Gleevec as a first-line treatment for CML, the IRIS study was initiated in 2001 and enrolled 1,106 patients who had little or no prior treatment for their disease. The study treated patients with either Gleevec or IFN and recorded key clinical outcomes, health care utilization and quality of life. In the case of both IFN and BMT, this study's estimates of treatment outcome draw upon several CML medical literature analyses which cover numerous observational and controlled studies initiated since 1980.⁴² In addition, four cost-effectiveness analyses of CML treatment published prior to the advent of Gleevec⁴³ were also used as key data sources.

CLAIMS DATA

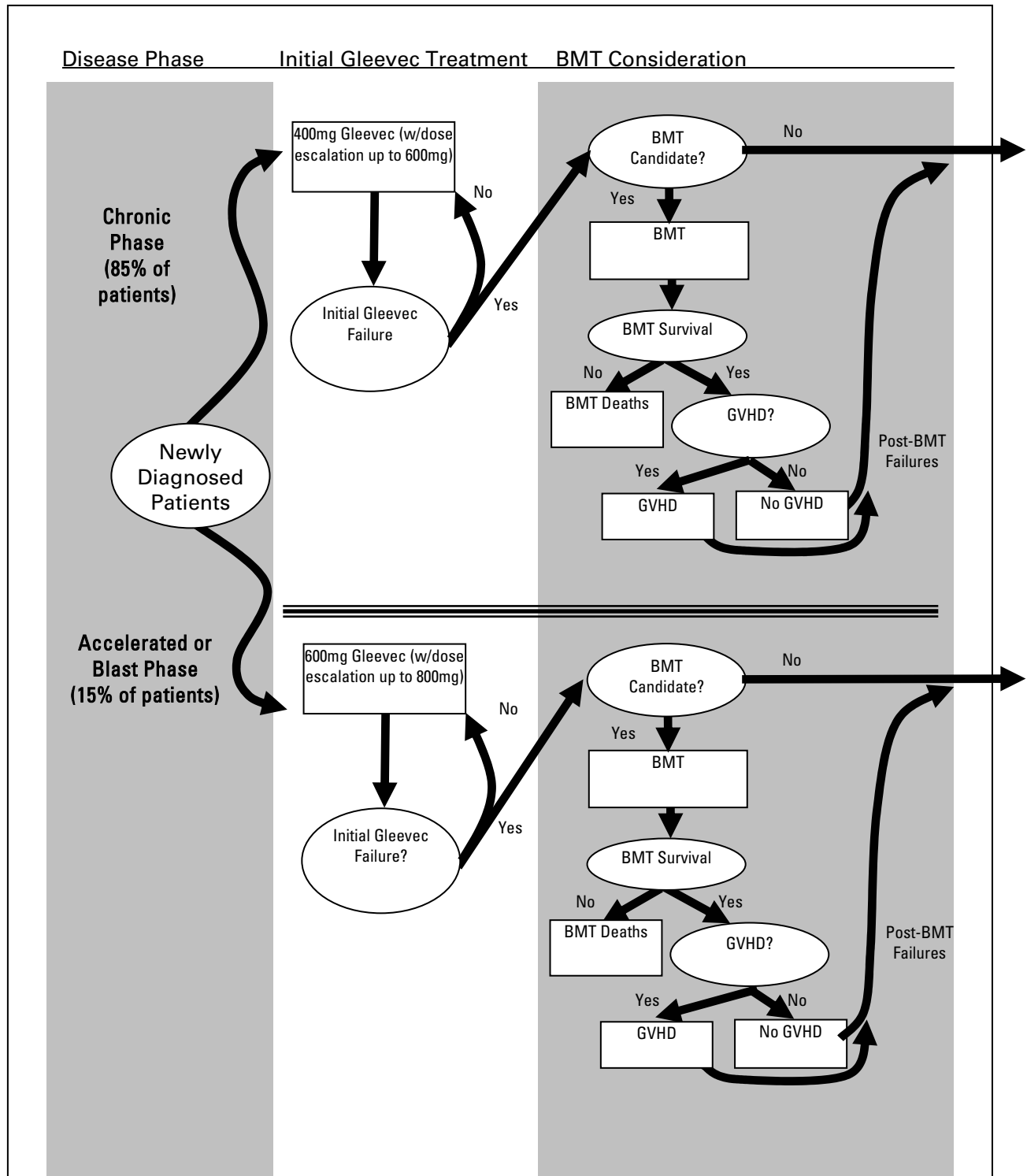
Data regarding current clinical practice was obtained from three large health plans. The data covers patients from four New England states and a range of health insurance products. Each health plan provided de-identified pharmacy, inpatient, and outpatient claims data on all patients who have ever had an ICD-9 diagnosis code for CML.

EXPERT INTERVIEWS AND PANEL DISCUSSION

The primary data sources utilized for the clinical care pathway and the sector-based Value Analysis were expert interviews, literature review and information obtained through an eight-member expert panel discussion conducted by NEHI in November of 2003. Interviews were conducted with nationally recognized experts on health care and CML treatment, with individuals representing the patient, provider, payer, manufacturer, policy and research perspectives.

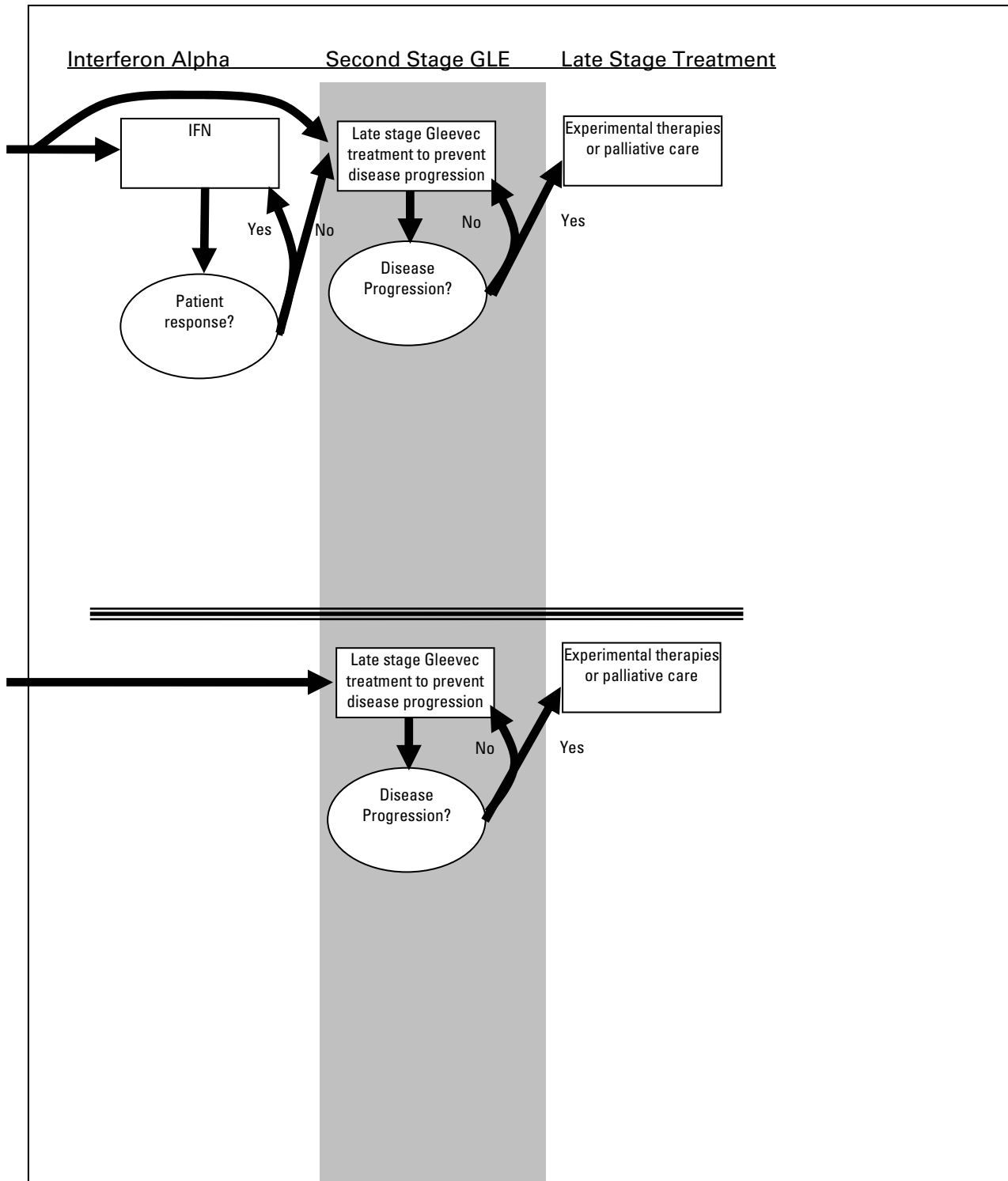
Appendix 2: Clinical Care Pathways

WITH GLEEVEC

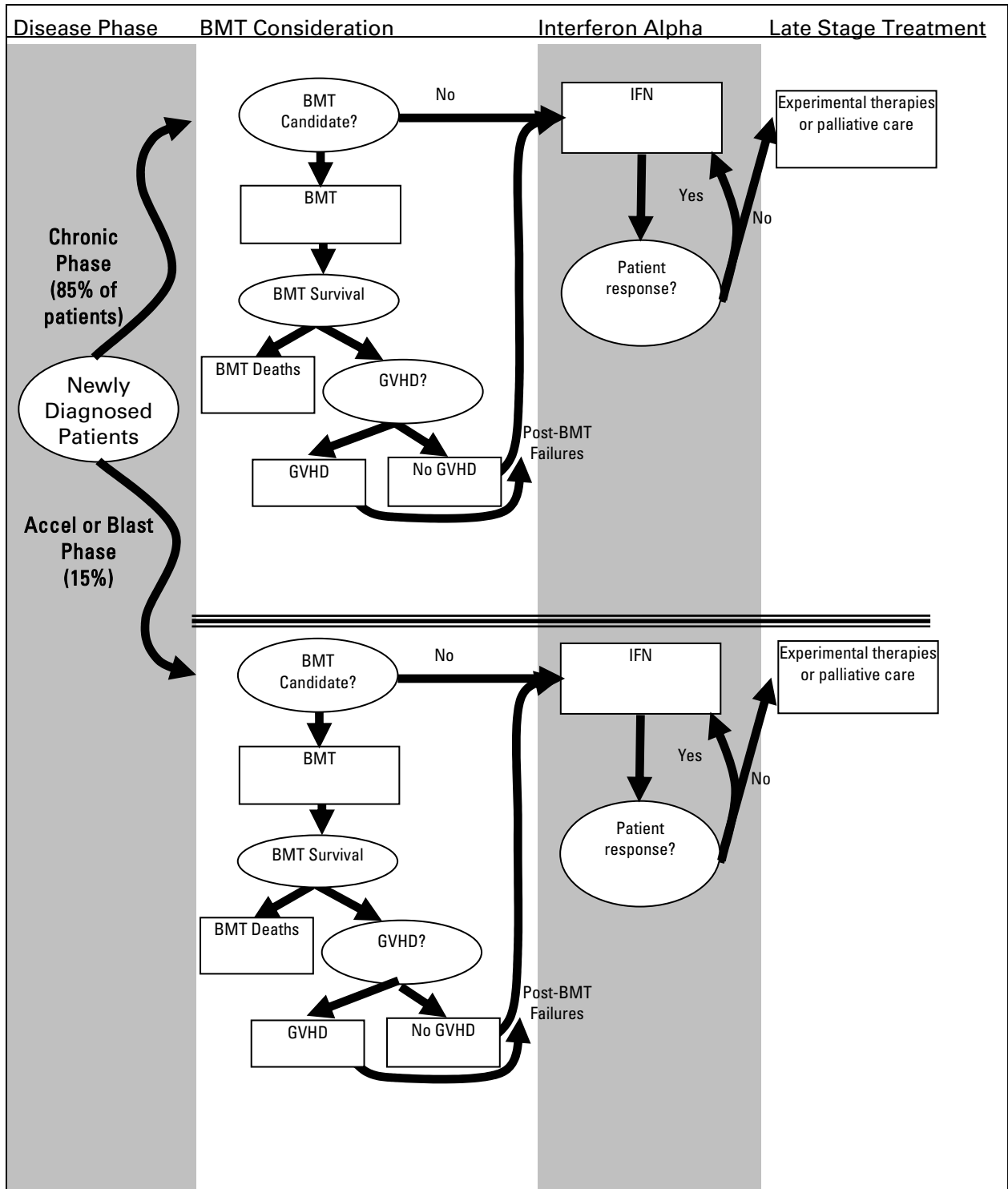


Source: NEHI

WITH GLEEVEC (Continued)



WITHOUT GLEEVEC



Source: NEHI

Appendix 3: Cost-Effectiveness Analysis

COST-EFFECTIVENESS ANALYSIS

Cost-effectiveness analysis (CEA) provides a means of determining whether the benefits of a health care intervention are worth the costs. The net costs and benefits of a new strategy of treatment relative to the status quo are expressed in a cost-effectiveness ratio (CER), which can be compared with CERs for other interventions to gauge the relative value of a change in treatment strategy, such as a new innovation. Incorporating published literature, expert opinion, and reasonable estimates, CEA enables the estimation of costs and benefits across a system of care, incorporating the whole treatment strategy as opposed to solely viewing single first-line treatments in isolation.

METHODS

This study conducts two parallel analyses of Philadelphia chromosome-positive CML patients from the societal perspective, one comparing treatments for chronic phase patients and another for advanced stage disease (accelerated and blast phase). This comparison required the simulation of four hypothetical patient cohorts:

Chronic phase CER: chronic phase patients treated WITH Gleevec
vs.
chronic phase patients treated WITHOUT Gleevec

Accel/blast phase CER: accel/blast patients treated WITH Gleevec
vs.
accel/blast phase patients treated WITHOUT Gleevec

Disease Progression

Based on the clinical pathway developed for CML (Appendix 2), we constructed a multi-state Markov model that reflected major health states and treatment options. States and transitions that were not clinically meaningful and those that did not affect the conclusion of cost-effectiveness were removed from the model. The model was run at one month cycles and allowed to run to failure (until all simulated patients died). To estimate the outcomes of treatment and progression through the model, our analysis utilized data on response and survival from the published literature. Published response rates were converted into monthly progression probabilities and incorporated into the model.

Quality of Life and Cost

The benefit of treatment is defined in terms of the length and quality of life for CML patients undergoing treatment. This benefit is reflected by a measure called the Quality Adjusted Life Year (QALY), a figure that quantifies patient quality of life on a scale of 0 (lowest quality) to 1 (highest quality) and uses that number to assign lower values for years spent in poor health and higher values for years spent in good health. Utility estimates were reviewed with physician experts. The costs considered in this analysis include expenditures for health care services (i.e. direct costs such as the cost of a drug or physician visit).

To account for uncertainty in all of these estimates, we conducted single variable sensitivity analyses in which baseline estimates of each factor are varied.

ANALYSIS

Cost and Utilities

The clearest benefit of Gleevec to society is the superior quality of life for CML patients. QALY estimates from the literature were derived from either direct preference elicitation using the Euro-Qol 5D (in the case of IFN in chronic phase and Gleevec) or physician assignment of utility (BMT and IFN in advanced stage disease). Since IFN was the commonly measured treatment across studies, estimates from all previous studies were normalized to the values observed in the IRIS study. Estimated utilities for each health state are reflected in table below.

Costs were assigned to treatment with IFN and Gleevec based on the IRIS study and BMT based mainly on the range of values observed by Lee et al. (1996). The average annual estimated drug cost is \$29,844 for Gleevec and \$21,235 for IFN. The IRIS study demonstrates that patients treated with Gleevec average six fewer physician visits (16 vs. 10), four fewer nurse or therapist visits (six vs. two), and three fewer days of hospital stay (five vs. two) per year compared with patients on IFN. This utilization decrease translates into a \$4,044 annual savings in medical services for patients treated with Gleevec. The comparison of costs between Gleevec and IFN on a comprehensive annual basis (both drug and health care utilization costs), therefore are \$32,724 and \$28,159, respectively.

The majority of BMT costs are incurred in the first year of treatment, when the procedure and highest cost follow-up occur. On average BMT costs an estimated \$196,000 in the first year of treatment and \$12,000 each year thereafter.

COSTS AND UTILITIES		
Health State / Treatment	Cost / Month	Utility
Gleevec in Chronic Phase	\$2,734	0.838
Gleevec in Accelerated or Blast Phase	\$3,982	0.440
Chronic Phase BMT	\$150,000	0.000
Accelerated or Blast Phase BMT	\$200,000	0.000
Post BMT w/o GVHD	\$983	0.864
Post BMT w/ GVHD	\$1200	0.785
Interferon in Chronic Phase	\$2,347	0.781
Interferon in Accelerated or Blast Phase	\$2,758	0.140

RESULTS AND DISCUSSION

In chronic phase, our model calculated an average health benefit of 5.6 QALYs per patient, at an increased cost of \$264,423 per patient. The cost-effectiveness ratio for chronic phase patients is \$47,504/QALY. For accelerated and blast phase patients, that amount rises to \$87,156/QALY, indicating that the drug is less cost-effective in late-stage disease.

To test how sensitive these results are to changes in base case assumptions, such as cost of treatment or quality of life, we performed sensitivity analyses across a range of reasonable values. The results in chronic phase were consistent over a wide variation in assumptions, however the estimate of accelerated and blast phase cost-effectiveness was highly sensitive to variation from the base case.

According to the literature on cost-effectiveness, treatments with a cost-effectiveness ratio below \$100,000/QALY are considered cost-effective, those between \$50,000 and \$100,000 are marginally cost-effective, and those below \$50,000/QALY are the most cost-effective. Based on these guidelines Gleevec is clearly cost-effective for chronic phase CML treatment and marginally cost-effective in accelerated and blast phase treatment.

For further information on this cost-effectiveness analysis of CML, including a full sensitivity analysis and list of progression probabilities, contact NEHI.

CHRONIC PHASE SENSITIVITY ANALYSES			
Sensitivity in Cost-Effectiveness Ratios (\$/QALY)			
Input Varied	Baseline	Range	0 50,000 100,000
Gleevec Cost/Year	\$32,724	\$24,543–\$40,905	31,542 — 63,457
Gleevec QALYs	0.854	0.790–0.940	41,075 — 53,824
Interferon Cost/Year	\$28,154	\$21,119–\$47,870	41,706 — 49,975
GLE Annual Mortality	0.5%	0.5%–5.0%	47,504 — 56,000
			Cost-Effective Marginally Cost-Effective Not Cost-Effective

Appendix 4: Experts Interviewed

NEHI is very grateful to each of the experts who generously gave us their time and provided us with valuable input into our research and analyses.

AMERICAN CANCER SOCIETY

David Rosenthal, M.D., *Past President*

ANTHEM BLUE CROSS AND BLUE SHIELD EAST

Vincent Maffei, Ph.D., *Health Economist*

BIOGEN IDEC

Burt Adelman, M.D., *Executive Vice President of Development*

BRIGHAM AND WOMEN'S HOSPITAL

Grace Chang, M.D., *Associate Physician*

BROWN UNIVERSITY/MIRIAM HOSPITAL

Alan Rosmarin, M.D., *Associate Professor*

DALBY & DALBY, LLC

Michael Dalby, Ph.D., *Managing Director*

DANA-FARBER CANCER INSTITUTE

Joseph Antin, M.D., *Chief, Stem Cell Transplant Program*

Amy Emmert, *Program Administrator, Hematologic Malignancies*

Arnold Freedman, M.D., *Associate Professor*

Stephanie Lee, M.D., M.P.H., *Assistant Professor*

Jerome Ritz, M.D., *Director, Cell Manipulation and Gene Transfer Lab*

Richard Stone, M.D., *Clinical Director, Adult Acute Leukemia Program*

Jane Weeks, M.D., M.Sc., *Chief, Division of Population Science*

DUKE CLINICAL RESEARCH INSTITUTE

Kevin Anstrom, Ph.D., *Assistant Professor, Biostatistics*

Shelby Reed, Ph.D., *Assistant Professor, Health Economics*

FOOD AND DRUG ADMINISTRATION

Martin Cohen, M.D., *Medical Officer, Oncology, Center for Drug Evaluation and Research*

HARVARD SCHOOL OF PUBLIC HEALTH

Milton Weinstein, Ph.D., *Professor of Health Policy and Management and Biostatistics*

HEALTH COMMONS INSTITUTE

Richard Rockefeller, M.D., Ed.M., *Founder and President*

HEALTH TECHNOLOGY CENTER

Charles Wilson, M.D., M.H.S.A., Sc.D., *Senior Fellow*

LEUKEMIA & LYMPHOMA SOCIETY

George Dahlman, *Vice President of Public Policy*

Alan Kinniburgh, Ph.D., *Vice President of Medical and Scientific Affairs*

MASSACHUSETTS GENERAL HOSPITAL

David Ryan, M.D., *Physician, MGH Cancer Center*

NORTHWESTERN UNIVERSITY

Deborah Dobrez, Ph.D., *Research Assistant Professor, Institute For Health Services Research and Policy Studies*

Elizabeth Hahn, M.A., *Director, Biostatistics and Data Management Systems, Center on Outcomes, Research and Education (CORE)*

NOVARTIS

Brenda Blanchard, *Vice President of Public Affairs*

Dan Casserly, *Director, Government Relations*

Deborah Dunsire, M.D., *Senior Vice President and North American Region Head of Oncology*

Wanda Toro, Pharm.D., *Gleevec Brand Team*

OREGON HEALTH SCIENCES UNIVERSITY

Brian Druker, M.D., *Chair of Leukemia Research*

TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT

Janice M. Reichert, Ph.D., *Senior Research Fellow*

TUFTS UNIVERSITY MEDICAL SCHOOL

Harris Berman, M.D., *Chairman, Department of Family Medicine and Community Health*

UNIVERSITY OF CONNECTICUT HEALTH CENTER

Gerald Maxwell, Ph.D., *Professor of Neuroscience and Associate Dean of the Graduate School*

WEILL MEDICAL COLLEGE OF CORNELL UNIVERSITY

Richard Silver, M.D., *Director, Center for Leukemia and Myeloproliferative Disorders*

Appendix 5: Expert Panelists

On November 5, 2003 the New England Healthcare Institute's (NEHI) first panel discussion of the value of emerging health care innovations brought together a range of experts to discuss the impact of treatment innovation in CML.

NEHI would like to offer special thanks to all participants in our Expert Panel who so generously gave us their time, feedback and valuable input in our research and analysis.

Joseph Antin, M.D.

Dr. Antin heads the Stem Cell Transplant Program of the Department of Medical Oncology at the Dana-Farber Cancer Institute. He is a professor of medicine at Harvard Medical School and a founding member and president of the American Society of Blood and Marrow Transplantation.

Harris Berman, M.D.

Dr. Berman is chairman of Tufts School of Medicine's Department of Family Medicine and Community Health. He had previously served as Chief Executive Officer of Tufts Health Plan for more than 17 years. Under his leadership, Tufts Health Plan grew in membership from 60,000 in 1986 to more than 900,000 in 2003, and the plan became one of the first Health Maintenance Organizations to offer preventive benefits. Prior to his time at Tufts Dr. Berman was a co-founder, medical director, then executive director of the Matthew Thornton Health Plan in Nashua, New Hampshire, the first HMO in northern New England.

Deborah Dunsire, M.D.

Dr. Dunsire is senior vice president and North American region head of oncology for Novartis, where she is responsible for all functions that drive the commercial oncology business in the United States. She serves as a member of the global Oncology Business Unit Executive Coordinating Committee and the Novartis Pharmaceuticals Corporation Executive Committee. Dr. Dunsire joined the oncology group in the United States in 1994. In 1997, she formed and headed the Oncology Business Unit at Novartis Pharmaceuticals Corporation, taking on all commercial functions, including sales, marketing, new product commercial planning, scientific field operations, medical affairs and business relations.

Robert Mittman, M.S., M.P.P. (Moderator)

Mr. Mittman is founder of Facilitation, Foresight, Strategy. As an experienced moderator, he brings a multidisciplinary perspective to emerging technology and health care forecasting and planning. Mr. Mittman specializes in developing innovative approaches to modeling and forecasting under conditions of little or conflicting data. He is co-author of *The Future of the Internet in Health Care: A Five-Year Forecast*. He was also a contributing author of the Institute for the Future's annual *Health Care Outlook* report and of *The Future of American Health Care, Vol. IV, Transforming the System: Building a New Structure for a New Century*.

Richard Rockefeller, M.D., Ed.M.

Dr. Rockefeller is founder and president of the Health Commons Institute, a group dedicated to improving shared decision making by patients and doctors through the wise use of computer technology. He is a clinical instructor of family medicine at Maine Medical

Center-Mercy Hospital and he also serves on numerous national, regional, and state boards, including the board of directors of Rockefeller University and the U.S. advisory board to Doctors without Borders.

David Rosenthal, M.D.

Dr. Rosenthal is a past president of the American Cancer Society (ACS) and currently serves as Director of Harvard University Health Services (HUHS) and professor of medicine at Harvard Medical School. Dr. Rosenthal has led HUHS since 1990, coordinating the care and management of 35,000 members of the Harvard University community. As a volunteer with ACS, Dr. Rosenthal is a representative of organization's New England Division Board of Directors, National Board of Directors and National Assembly. He is also an active member of numerous ACS committees including the national committees on research and clinical investigation, public issues/public policy, and medical affairs.

Richard Silver, M.D.

Dr. Silver directs the Center for Leukemia and Myeloproliferative Disorders at the Weill Medical College of Cornell University. He was a principal investigator in the world trials of Gleevec and was one of the first to use interferon in the treatment of chronic myeloid leukemia. Dr. Silver was a pioneer in the development of courses to train physicians in the biopsy of bone marrow and interpretation of the results. Dr. Silver chaired the International Congress on Myeloproliferative Diseases and Myelodysplastic Syndromes in 2001 and 2003. In 2000, Cornell endowed the Richard T. Silver Distinguished Professorship of Hematology and Medical Oncology in his honor.

Milton Weinstein, Ph.D.

Professor Weinstein is a renowned expert on the methods of cost-effectiveness analysis in health care and serves as professor of health policy and management and biostatistics at the Harvard School of Public Health, and professor of medicine at the Harvard Medical School. He also directs the Program on Economic Evaluation of Medical Technology in the Harvard Center for Risk Analysis. His research uses the methodologies of decision analysis, mathematical modeling and cost-effectiveness analysis to address resource allocation decisions at the clinical, institutional and societal levels. He has extensive experience in the evaluation of cancer therapies. Professor Weinstein was co-chairman of the U.S. Panel on Cost-Effectiveness in Health and Medicine and is a member of the Institute of Medicine and its committee on priorities for new vaccine development.

Charles Wilson, M.D., M.S.H.A., Sc.D.

Dr. Wilson is professor emeritus of neurosurgery at the University of California, San Francisco (UCSF), a senior fellow at the Institute for the Future and a senior advisor at the Health Technology Center. For 25 years he served as chairman of the Department of Neurosurgery and director of the Brain Tumor Research Center at UCSF. He has authored 600 scientific publications and is a member of the Institute of Medicine. He serves on the governing board of the Tulane University Health Sciences Center and Tulane University's board of administrators. At the Institute for the Future, his areas of expertise are emerging medical technologies and the impact of genomic medicine on health and health care. At the Health Technology Center he works to create forecasts of future medical technologies and the impact of their introduction into the health care system.

Appendix 6: Glossary

Glossary entries are from the National Cancer Institute (NCI) Dictionary. The NCI dictionary can be found online at: <http://www.nci.nih.gov/dictionary>

accelerated phase

Refers to chronic myelogenous leukemia that is progressing. The number of immature, abnormal white blood cells in the bone marrow and blood is higher than in the chronic phase but not as high as in the blast phase.

blast

An immature blood cell.

blast crisis

The phase of chronic myelogenous leukemia in which the number of immature, abnormal white blood cells in the bone marrow and blood is extremely high. Also called blast phase.

blast phase

The phase of chronic myelogenous leukemia in which the number of immature, abnormal white blood cells in the bone marrow and blood is extremely high. Also called blast crisis.

bone marrow

The soft, sponge-like tissue in the center of most large bones. It produces white blood cells, red blood cells, and platelets.

bone marrow transplantation

A procedure to replace bone marrow that has been destroyed by treatment with high doses of anticancer drugs or radiation. Transplantation may be autologous (an individual's own marrow saved before treatment), allogeneic (marrow donated by someone else), or syngeneic (marrow donated by an identical twin).

cancer

A term for diseases in which abnormal cells divide without control. Cancer cells can invade nearby tissues and can spread through the bloodstream and lymphatic system to other parts of the body. There are several main types of cancer. Carcinoma is cancer that begins in the skin or in tissues that line or cover internal organs. Sarcoma is cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. Leukemia is cancer that starts in blood-forming tissue such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the bloodstream. Lymphoma is cancer that begins in the cells of the immune system.

cell differentiation

The process during which young, immature (unspecialized) cells take on individual characteristics and reach their mature (specialized) form and function.

chemotherapy

Treatment with anticancer drugs.

chromosome

Part of a cell that contains genetic information. Except for sperm and eggs, all human cells contain 46 chromosomes.

chronic myelogenous leukemia

CML. A slowly progressing disease in which too many white blood cells (not lymphocytes) are made in the bone marrow. Also called chronic myeloid leukemia or chronic granulocytic leukemia.

chronic phase

Refers to the early stages of chronic myelogenous leukemia or chronic lymphocytic leukemia. The number of mature and immature abnormal white blood cells in the bone marrow and blood is higher than normal, but lower than in the accelerated or blast phase.

complete blood count

CBC. A test to check the number of red blood cells, white blood cells, and platelets in a sample of blood. Also called blood cell count.

cytarabine

Also known as Ara-C. An anticancer drug that belongs to the family of drugs called antimetabolites.

cytogenetics

The study of chromosomes and chromosomal abnormalities.

differentiation

In cancer, refers to how mature (developed) the cancer cells are in a tumor. Differentiated tumor cells resemble normal cells and tend to grow and spread at a slower rate than undifferentiated or poorly differentiated tumor cells, which lack the structure and function of normal cells and grow uncontrollably.

GIST

Gastrointestinal stromal tumor. A type of tumor that usually begins in cells in the wall of the gastrointestinal tract. It can be benign or malignant.

graft-versus-host disease

GVHD. A reaction of donated bone marrow or peripheral stem cells against the recipient's tissue.

hematologist

A doctor who specializes in treating blood disorders.

imatinib mesylate

A drug that is being studied for its ability to inhibit the growth of certain cancers. It interferes with a portion of the protein produced by the bcr/abl oncogene. Also called Gleevec and STI571.

interferon

A biological response modifier (a substance that can improve the body's natural response to infections and other diseases). Interferons interfere with the division of cancer cells and can slow tumor growth. There are several types of interferons, including interferon-alpha, -beta, and -gamma. The body normally produces these substances. They are also made in the laboratory to treat cancer and other diseases.

intravenous

Injected into a blood vessel.

leukemia

Cancer that starts in blood-forming tissue such as the bone marrow, and causes large numbers of blood cells to be produced and enter the blood stream.

morbidity

A disease or the incidence of disease within a population. Morbidity also refers to adverse effects caused by a treatment.

mutation

Any change in the DNA of a cell. Mutations may be caused by mistakes during cell division, or they may be caused by exposure to DNA-damaging agents in the environment. Mutations can be harmful, beneficial, or have no effect. If they occur in cells that make eggs or sperm, they can be inherited; if mutations occur in other types of cells, they are not inherited. Certain mutations may lead to cancer or other diseases.

myelogenous

Having to do with, produced by, or resembling the bone marrow. Sometimes used as a synonym for myeloid; for example, acute myeloid leukemia and acute myelogenous leukemia are the same disease.

oncogene

A gene that normally directs cell growth. If altered, an oncogene can promote or allow the uncontrolled growth of cancer. Alterations can be inherited or caused by an environmental exposure to carcinogens.

oncologist

A doctor who specializes in treating cancer. Some oncologists specialize in a particular type of cancer treatment. For example, a radiation oncologist specializes in treating cancer with radiation.

palliative care

Care given to improve the quality of life of patients who have a serious or life-threatening disease. The goal of palliative care is to prevent or treat as early as possible the symptoms of the disease, side effects caused by treatment of the disease, and psychological, social, and spiritual problems related to the disease or its treatment. Also called comfort care, supportive care, and symptom management.

phase I trial

The first step in testing a new treatment in humans. These studies test the best way to give a new treatment (for example, by mouth, intravenous infusion, or injection) and the best dose. The dose is usually increased a little at a time in order to find the highest dose that does not cause harmful side effects. Because little is known about the possible risks and benefits of the treatments being tested, phase I trials usually include only a small number of patients who have not been helped by other treatments.

phase II trial

A study to test whether a new treatment has an anticancer effect (for example, whether it shrinks a tumor or improves blood test results) and whether it works against a certain type of cancer.

phase III trial

A study to compare the results of people taking a new treatment with the results of people taking the standard treatment (for example, which group has better survival rates or fewer side effects). In most cases, studies move into phase III only after a treatment seems to work in phases I and II. Phase III trials may include hundreds of people.

Philadelphia chromosome

An abnormality of chromosome 22 in which part of chromosome 9 is transferred to it. Bone marrow cells that contain the Philadelphia chromosome are often found in chronic myelogenous leukemia.

polymerase chain reaction

PCR. A laboratory method used to make many copies of a specific DNA sequence.

preclinical study

Research using animals to find out if a drug, procedure, or treatment is likely to be useful. Preclinical studies take place before any testing in humans is done.

progression

Increase in the size of a tumor or spread of cancer in the body.

progression-free survival

One type of measurement that can be used in a clinical study or trial to help determine whether a new treatment is effective. It refers to the probability that a patient will remain alive, without the disease getting worse.

remission

A decrease in or disappearance of signs and symptoms of cancer. In partial remission, some, but not all, signs and symptoms of cancer have disappeared. In complete remission, all signs and symptoms of cancer have disappeared, although cancer still may be in the body.

white blood cell

WBC. Refers to a blood cell that does not contain hemoglobin. White blood cells include lymphocytes, neutrophils, eosinophils, macrophages, and mast cells. These cells are made by bone marrow and help the body fight infection and other diseases.

Endnotes

¹ This report uses the term “manufacturers” to refer specifically to the manufacturers of the health care innovation. The discussion surrounding the effects of the innovation on manufacturers will focus on how changes in the use of their product affect the organization. For discussion of how all companies are affected by general trends in health care costs, see the discussion of “employers”.

² ‘Revolution’ in Cancer Treatment: A Chat with Cancer Expert Dr. Brian Druker. New York, NY: ABC News, 2002. (accessed January 27, 2004, at http://www.abcnews.go.com/sections/community/2020/chat_leukemia0409.html). See also, Skin cancer 'gene' breakthrough. London, England: BBC News, 2002. (accessed December 9, 2002, at <http://news.bbc.co.uk/1/hi/health/2035051.stm>)

³ Chabner B. The Oncologic Four Minute Mile. *The Oncologist*. 2001; 6: 230-232; Abbot A. Cancer research: On the offensive. *Nature* 2002; 416: 470–474.

⁴ These include AstraZeneca PLC's Iressa™ (gefitinib) for non-small cell lung cancer and Genentech, Inc.'s Herceptin® (trastuzumab) for metastatic breast cancer.

⁵ Plans & Priorities for Cancer Research. Bethesda, MD: National Cancer Institute, 2002. (Accessed February 15, 2004, at <http://plan2004.cancer.gov/discovery/targets.htm>)

⁶ For U.S. incidence see: Cancer Facts and Figures. Atlanta, GA: American Cancer Society, 2003:4. Worldwide incidence estimate is based on 1.5 new CML cases per 100,000 people and a world population of 6.3 billion.

⁷ Orphan drug status is conferred by the Food and Drug Administration (FDA) for treatments directed toward a patient population of fewer than 200,000 patients (prevalence). The major benefits of orphan drug status designation to manufacturers are: a seven year period of exclusivity during which the FDA will not grant approval to new drugs for the same use unless the competitor can prove clinical superiority; tax credits of up to 50 percent of the cost of conducting human clinical trials; and research grants for the testing of new therapies. Cohen, Moses, and Pazdur. Gleevec for Treatment of Chronic Myelogenous Leukemia. *The Oncologist*, 2002; 7: 390–392.

⁸ Brookes L. Imatinib Mesylate Therapy in CML and GISTs. 38th Annual Meeting of the American Society of Clinical Oncology, May 18 - 21, 2002, Orlando, Florida. (Accessed February 15, 2004, at <http://www.medscape.com/viewarticle/434205>)

⁹ Novartis 2003 Financial Results. Basel, Switzerland: Novartis Pharma AG, 2004.

¹⁰ Cancer Facts and Figures, 2003, pg 4.

¹¹ *Ibid.*, pg 4.

¹² See table 1.1: Invasive Cancer Incidence Rates by Primary Site in Almon L, Friedman C, et al. *United States Cancer Statistics: 2000 Incidence*. Atlanta, GA: Centers for Disease Control and Prevention, 2003; pg 20.

¹³ High doses of irradiation may cause a slight increase in risk for the Bcr-Abl mutation in a very small portion of patients. *Chronic Myelogenous Leukemia*. Mamaroneck, NY: Leukemia and Lymphoma Society, 2003: 8.

¹⁴ Demographic Profile of New England. Boston, MA: Federal Reserve Bank of Boston, 2003. (Accessed February 15, 2004, at <http://www.bos.frb.org/economic/regional/profile/demographic/dall.htm>)

¹⁵ Five percent of CML patients do not have the Philadelphia chromosome. Kolibaba K, Druker B. Current Status of Treatment for Chronic Myelogenous Leukemia. *Medscape General Medicine* 2000; 2.

¹⁶ What is Chronic Myelogenous Leukemia? *Advances In Oncology*, 2001. (Accessed March 1, 2004, at http://www.advancesinoncology.com/webcast_transcript.asp?f=aio_cml&c=cml_whatiscml&b=aio)

¹⁷ Faderl S, Talpaz M, Estrov Z, Kantarjian H. Chronic Myelogenous Leukemia: Biology and Therapy. *Annals of Internal Medicine* 1999; 131:207-219

¹⁸ *Ibid.*, pg 208

- ¹⁹ Gratwohl A, Hermans J, et al. Risk assessment for patients with chronic myeloid leukaemia before allogeneic blood or marrow transplantation. *Lancet*, 1998 ; 352: 1087.
- ²⁰ Weisdorf, Anasetti, Antin, et al. Allogeneic Bone Marrow Transplantation for Chronic Myelogenous Leukemia: Comparative Analysis of Unrelated versus Matched Sibling Donor Transplantation. *Blood*, 2002; 99: 1973-4.
- ²¹ Interferon Alpha is produced under the brand names Roferon and Pegasys, by Roche Pharmaceuticals and Intron-A by Schering Corporation. It is sometimes delivered in conjunction with another drug known as Cytarabine, or Ara-C. Since the price increase from adding Ara-C is minimal and there is only a questionable difference in effectiveness, this study does not differentiate between Interferon used alone and Interferon used in conjunction with Ara-C. The abbreviation "IFN" will be used to refer to both cases.
- ²² Hughes T, Kaeda J, et al. Frequency of Major Molecular Responses to Imatinib or Interferon Alfa plus Cytarabine in Newly Diagnosed Chronic Myeloid Leukemia. *New England Journal of Medicine*, 2003; 349: 1423.
- ²³ Cervantes F. Durability of Responses to Imatinib in Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia (CML): 30-month Update from the IRIS Study. American Society of Hematology 45th Annual Meeting, December 2003.
- ²⁴ While some experts recommend early BMT without prior Gleevec treatment (especially for young patients diagnosed early on in their disease) most that we interviewed agreed that even early BMT candidates were likely to receive Gleevec to obtain a remission prior to transplant and these patients may remain on the drug depending on their response.
- ²⁵ Several authors have utilized this standard as a reference for assessing cost-effectiveness. For the use of the standard in CML, see Lee S, Anasetti C, et al. The Costs and Cost-Effectiveness of Unrelated Donor Bone Marrow Transplantation for Chronic Phase Chronic Myelogenous Leukemia. *Blood* 1998; 92:4047; Liberato NL, Quaglini S, Barosi G. Cost-effectiveness of interferon-alpha for chronic myelogenous leukemia. *Journal of Clinical Oncology* 1997; 15: 2673-2682.
- ²⁶ Lee S, Anasetti C, et al., pg 4050.
- ²⁷ Accelerated / blast phase results were highly sensitive to several variables.
- ²⁸ Vasella D. *Magic Cancer Bullet*. New York, NY: Harper Collins, 2003: 215.
- ²⁹ *New Horizons in the Treatment of CML*. Mamaroneck, NY: Leukemia & Lymphoma Society. (Accessed March 1, 2004, at <http://www.cancereducation.com/cancersyspagesnb/transcripts/lls/25/aava.pdf>)
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- ³¹ Novartis 2003 Financial Results.
- ³² Total Cost to Develop a New Prescription Drug, Including Cost of Post-Approval Research, is \$897 million. Boston, MA: Tufts Center for the Study of Drug Development, 2003. (Accessed March 1, 2004, at <http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=29>)
- ³³ NEHI Expert Panel Discussion, November 2003.
- ³⁴ *Leukemia Drug Heralds Molecularly Targeted Era*. Bethesda, MD: National Cancer Institute, 2000. (Accessed March 1, 2004, at <http://www.nci.nih.gov/clinicaltrials/developments/molecular-target-drug0400>)
- ³⁵ Formulary Submission Dossier For Gleevec. East Hanover, NJ : Novartis Oncology, 2003 : 56-68.
- ³⁶ *Magic Cancer Bullet*, pg 180.
- ³⁷ Formulary Submission Dossier For Gleevec.
- ³⁸ Novartis internal survey data.
- ³⁹ *Magic Cancer Bullet*, pg 123.
- ⁴⁰ Will Gleevec be effective in the long-term? *Advances In Oncology*, 2001. (Accessed March 1, 2004, at http://www.advancesinoncology.com/webcast_transcript.asp?f=aio_cml&c=cml_gleevecfficacy&b=aio)
- ⁴¹ FDA Sees Rebound in Approval of Innovative Drugs in 2003: New Innovation Initiative Anticipated to Speed Approvals in Years Ahead. Washington, D.C.: Food and Drug

Administration 2004. (Accessed March 1, 2004, at <http://www.fda.gov/bbs/topics/NEWS/2004/NEW01005.html>)

⁴² See Silver RT. Chronic Myeloid Leukemia. *Hematology/Oncology Clinics of North America* 2003; 17: 1159-1173. See also, Farderl S, Talpaz M, et al. Chronic Myelogenous Leukemia: Biology and Therapy. *Annals of Internal Medicine* 1999; 131: 207-219.

⁴³ Kattan MW, Inoue Y, Giles FJ, et al. Cost-effectiveness of Interferon-a and conventional chemotherapy in chronic myelogenous leukemia. *Annals of Internal Medicine* 1996; 125: 541-548. See also, Messori A. Cost-effectiveness of interferon in chronic myeloid leukemia: Analysis of four clinical studies. *Annals of Oncology* 1998; 9: 389-396; Lee S, Anasetti C, et al, 1998; and Liberato NL, Quaglino S, Barosi G, 1997.



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