



Value-Based Oncology **BENEFIT DESIGN**TM

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Target Audience

This activity was developed for pharmacists and other healthcare professionals practicing in a managed care environment who wish to enhance their knowledge concerning the implementation of a value-based benefit design for cancer care.

Learning Objectives

At the completion of this educational activity, participants should be able to:

- Identify the intersection of epidemiologic shifts in the American cancer patient population.
- Identify new cancer drug costs and define the role of value (cost, quality, access) in the new value-based healthcare system, as well as the incentives of payers and purchasers to meet each of these 3 aspects of value in cancer care.
- Define how new diagnostic measures may help determine how to better achieve value-based clinical cancer treatment outcomes and determine how clinical practice treatment guidelines are aiding all stakeholders in attaining value-based cancer care amidst rising new product costs.

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Mission Statement

Value-Based Oncology Benefit Design provides payers and others involved in overall healthcare resource allocation with the information they need to make competent formulary and benefit design decisions. The sharp escalation in the cost of cancer care is threatening the financial stability of the healthcare system and has become a major area of strategic focus for payers, purchasers, government, and other stakeholders. New cancer therapies must meet a triad of qualities to find acceptance by payers—cost, quality, access—the value proposition for all healthcare interventions.

Cancer Care Market Indicators: Implications of Changing Demographics and New Treatment Choices for Today's Health Plans

Gary M. Owens, MD

Adapted from a presentation at the Academy of Managed Care Pharmacy meeting, April 2009.

The goal of this special supplement is to provide payers and purchasers insight on balancing cost, quality, and access needs for patients with cancer. We have seen major changes in the approach to cancer patients and in treatment advances, but these have been accompanied by unprecedented increases in the cost of care.

This article presents examples in breast cancer, non-small-cell lung cancer (NSCLC), and multiple myeloma (MM) to raise some questions that must be considered to be able to manage cost, quality, and access to cancer care. We must continue to raise the questions of what should we do, and what types of information do we need, for benefit design to provide affordable cancer care yet keep the system intact.

It is well known that heart disease is the number 1 killer in the United States and cancer is the number 2 killer. With the aging population, the number of cancer cases is continuing to grow. More than 500,000 cancer deaths occurred in the US population in 2008, according to data from the American Cancer Society.¹ Solid-organ tumors lead the way in cancer frequency. In women, breast cancer is the most common cancer, followed closely by lung and colorectal cancer. In men it is prostate cancer, also followed by lung and colorectal cancer.¹ If we add up the lung cancer cases in men and women, this makes it the number 1 cancer across the total population.¹

Most cancers are seen in people aged 55 and older,¹ and the baby boom population is reaching that age. With a large mass of population becoming 55 and older, this alone is a major driver for increasing the number of cancer cases. And the numbers are astounding. Estimated new cases for 2009 for prostate cancer and for breast cancer are more than 180,000 each.¹ Almost 100,000 men and about 70,000 women will likely die of lung cancer in the coming year.¹

Demographics (eg, the aging population, types of cancer) are not the only drivers of cancer care costs. Although cancer cases are increasing, the cost per case is greater than ever before. Much of that is driven by new technology that

helps to more precisely diagnose and stage cancer and to find metastases. But this comes with a cost. The new technologies that drive cancer care cost include:

- Diagnostic imaging: magnetic resonance imaging, positron emission tomography scans
- Radiation oncology: gamma knife, proton beam therapy
- Genetic testing: we are on the verge of being able to treat cancer based on individual genetic differences
- Pharmaceuticals, especially biotechnology products.

There was about a 17% increase from 2007 to 2008 in specialty drug costs.² Cancer was by far the largest driver of the specialty drug trend, with almost one third of the cost, as can be seen in the **Figure**.²

The cost of cancer care to health plans is only going to increase with the aging population, increasing cancer cases, and new technologies.

Breast Cancer

Worldwide, more than 1 million new cases of breast cancer occur each year. Adjuvant chemotherapy with cyclophosphamide, methotrexate, and fluorouracil (CMF) has increased the 10-year survival rate by as much as 7% to 11% compared with surgery alone³; CMF is now a standard of care. Because of the number of new cases every year and the prolonged survival, the approximate 2.4 million Americans who are affected by breast cancer are either currently under treatment, having had treatment and are now in remission, or are actively in a progressive form of the disease.^{4,5}

The past 3 decades have witnessed a notable improvement in metastatic breast cancer treatment with the use of anthracyclines, antiestrogen agents, cyclophosphamide, platinum-containing agents, and taxanes.

In addition, we now have biologics, such as trastuzumab, for the treatment of human epidermal growth factor type 2 (HER2)/*neu* overexpression breast cancer. In this type of patient, the response rate to trastuzumab alone is from 11% to 26%.^{6,7} The use of trastuzumab with chemotherapy has increased survival and response rate, compared with trastuzumab alone, and reduced the risk of relapse in the adjuvant setting by 50%.^{6,7}

Amplification of HER2/*neu* occurs in about 20% to 30% of early-stage breast cancers,^{6,7} which is likely an underestimate. This percentage could be larger at later-stage breast

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cancers. HER2/*neu* expression promotes invasion of the cancer cells by enhancing cell survival, as well as cancer cell angiogenesis.

Results of one study showed that about 10% of those using trastuzumab relapsed as opposed to about a 17% relapse rate among those who did not use that drug.⁷ However, almost 5 of 6 patients would not have developed a recurrence during the study, regardless of trastuzumab, because of the natural history of the disease, and almost 1 of 10 patients relapsed despite the treatment.⁷ This is the type of things that health plans struggle with—patients who get a drug that the plan has no way of knowing in advance whether it would be effective. About 1 patient in 13 receives additional benefit from trastuzumab for preventing cancer recurrence, if we subtract those who would not have a recurrence and hence would not benefit.⁷

That is balanced against trials in which between 25 and 100 patients needed to be treated to prevent 1 death in 2 to 4 years.⁸ For each life saved, from 10 to 25 patients will develop some form of heart disease, which will kill some of them.⁸ The excess heart disease associated with this treatment offsets some of the treatment effects, meaning that we have to treat up to 100 patients to save 1 single life in a 2-year period.⁸

How do we direct this treatment to patients who are going to benefit from it most? HER2/*neu* overexpression is known at the time that the tumor is removed, but are there other ways that can help direct treatment to avoid giving trastuzumab to women who probably would not benefit from it?

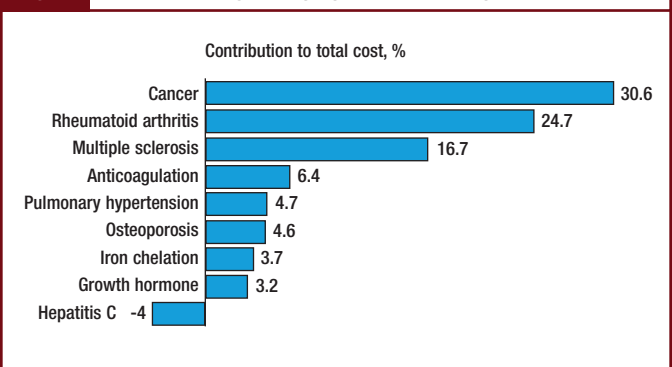
In 2008, the US Food and Drug Administration (FDA) approved bevacizumab for breast cancer treatment. Although an advisory panel voted 5 to 4 against this approval, its recommendation was overruled by the FDA; the panel was concerned that the data did not show increased quality of or prolonged life, but 2 important benchmarks of the trial—tumor volume reduction and increased progression-free survival—were achieved.⁹ These 2 end points are important for people with late-stage breast cancer, and this type of controversy may become an issue for health plans that need to have clear coverage positions based on FDA labeling and other sources (eg, compendia and guidelines).

The addition of biologics to cancer care has done wonders for selective patients, but the question is how can we direct that toward the right patients?

Non–Small-Cell Lung Cancer

As noted, lung cancer is the second most common cancer in men and women in the United States.¹⁰ More than 175,000 new cases of lung cancer are projected for 2009. NSCLC is the most frequent histologic type of lung cancer, accounting for 86% of all lung cancer cases. Advanced NSCLC stage IIIb and stage IV cannot be resected, and chemotherapy is recommended.^{11,12}

Figure Cost of Biologics, by Type of Therapy/Condition



Source: Medco. 2008 Drug Trend Report. Franklin Lakes, NJ: Medco Health Solutions; 2008.

In addition to standard chemotherapy, small-molecule treatments include gefitinib, which has some issues, and erlotinib, which targets the epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor that is overexpressed in mutated NSCLC. In phase 3 clinical trials, erlotinib improved survival in the treatment of lung cancer patients.^{13,14} But after a period of 8 to 12 months, cancer cells became resistant to treatment, most likely because of recruiting the mutated insulinlike growth factor 1 receptor.^{13,14} Not every patient will respond to erlotinib. In addition, measuring EGFRs has not determined the best way to direct this agent toward the right patients.

The addition of biologics to cancer care has done wonders for selective patients, but the question is how can we direct that toward the right patients?

Bevacizumab is also indicated for NSCLC and is the mainstay of treatment in advanced nonsquamous NSCLC. Bevacizumab received FDA approval for lung cancer in 2006, to be used in combination with standard first-line chemotherapy—a platinum-based combination doublet, typically. The Eastern Cooperative Oncology Group study showed a 2-month improvement in overall survival in patients with stage IIIb and stage IV NSCLC.^{15,16} Although this is not a long period, overall outcomes in this very progressive disease are dismal, and even small incremental gains in overall survival may be significant to selected patients.

Bevacizumab is not indicated for use in the squamous variety of NSCLC, because of the significant amount of severe pulmonary hemorrhage; it should be directed toward the nonsquamous NSCLC patient. Beyond this limitation,

Table Survival in Multiple Myeloma, by Disease Stage

Staging	Median survival probability
Stage I: Beta-2-microglobulin <3.5, albumin ≥3.5	62 month
Stage II: Beta-2-microglobulin <3.5, albumin <3.5 or beta-2-microglobulin 3.5 to <5.5	44 month
Stage III: Beta-2-microglobulin ≥5.5	29 month

Sources: National Cancer Institute. Multiple myeloma and other plasma cell neoplasms treatment (PDQ). November 6, 2008; Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. *J Clin Oncol*. 2005;23:3412-3420.

we have virtually no evidence to allow more refined targeting of patients with NSCLC for specific agents or combinations of agents to produce the best outcomes.

Multiple Myeloma

The second most common hematologic malignancy, after non-Hodgkin's lymphoma, is MM. Between 5 and 7 patients per 100,000 individuals annually have MM, meaning that a typical 1-million-member health plan will have between 50 and 70 new cases of MM in the course of 1 year. Almost 60,000 patients currently live with MM in the United States. In 2008, according to the American Cancer Society, about 20,000 new cases were diagnosed and 10,000 deaths were caused by this type of cancer.^{17,18}

Smoldering (asymptomatic) myeloma needs to be distinguished from progressive myeloma, because the treatment can be symptomatic for smoldering myeloma.

There have been significant improvements in the prognosis of this disease, with the many new therapies, including pulsed corticosteroids—dexamethasone, thalidomide, bortezomib, and lenalidomide—and stem-cell transplantations, that have changed the outcomes of patients with MM.

The median survival varies dramatically, depending on the stage of the disease, from about 62 months for patients with stage I MM to about 29 months for patients with stage III disease¹⁹ (Table). MM is often a rapidly progressive disease, but it also can be a lingering illness. The initial choice of treatment, therefore, is based on whether the patient is a transplant candidate; selecting the most aggres-

sive therapy is dependent on whether the patient is a candidate for transplantation.

Smoldering (asymptomatic) myeloma needs to be distinguished from progressive myeloma, because the treatment can be symptomatic for smoldering myeloma. Asymptomatic patients who do not have lytic bone lesions and have normal kidney function can be observed initially, and treated symptomatically (except in the context of a clinical trial). However, aggressive treatment should be given to patients with symptomatic advanced disease or with advanced-stage disease. Treatment should be directed at reducing the tumor-cell burden and reducing complications, such as kidney failure, hyperviscosity, or hypercalcemia.

Since the mid-1980s, dexamethasone has been a standard of care for induction therapy with a pulse-dose of 40 mg orally for 4 consecutive days. A regimen containing vincristine, doxorubicin, and dexamethasone (VAD) can also be administered in the same pulse-dose therapy. The 60% to 70% response rates in previously untreated patients is similar to responses with VAD.¹⁸ In a prospective trial of 488 patients older than 65 years, participants were randomized to dexamethasone alone, to dexamethasone plus methotrexate, or to dexamethasone plus interferon alfa, followed by methotrexate plus prednisone. Median follow-up of 7.1 years showed no difference in overall survival with these treatment regimens (median survival, 32-40 months).²⁰

Patients receiving a dexamethasone-based regimen, although in itself a very inexpensive therapy, had more infections, more glucose intolerance, and other side effects common to steroids.¹⁸ Several new agents have been introduced in the past 10 years for the treatment of MM that have changed the course of therapy. The first is thalidomide, the drug that in the past had very untoward results in the unborn but was later reborn as a treatment not only for MM but also for leprosy.

Eight randomized prospective studies involving more than 3000 patients have been published about the use of thalidomide for induction therapy in MM.¹⁸ All the trials reported improved response rates with thalidomide, and no hematopoietic damage. Thalidomide allows stem-cell collection when applicable, and the ability to progress to transplantation, while stabilizing the disease. But only 2 of 8 randomized studies reported a survival advantage with thalidomide.

Lenalidomide had much smaller studies. A prospective study randomized 351 patients with relapsed myeloma to high-dose dexamethasone plus lenalidomide versus high-dose dexamethasone plus placebo. The lenalidomide combination showed a significantly greater time to tumor progression—11.3 months versus 4.7 months—a significant difference ($P < .001$).²¹ But the lenalidomide-based arm also had more deep-vein thrombosis,²¹ again, showing advantages and disadvantages of using the newer agents.

The third agent is bortezomib. A randomized study of

669 patients with relapsing myeloma who had been previously treated with steroids were randomized to intravenous bortezomib versus high-dose oral dexamethasone.²² The overall survival at 1 year favored bortezomib, 80% versus 66% with oral dexamethasone, a significant difference ($P = .003$). One of the complications was peripheral neuropathy, which appears to be reversible in most patients after dose reduction or treatment discontinuation.¹⁸

In another study, 646 previously treated patients were randomized to bortezomib plus pegylated liposomal doxorubicin or to bortezomib alone.²³ The combination therapy resulted in better time to disease progression, 9.3 months versus 6.5 months, and in better overall survival of up to 82%, compared with 75% with bortezomib alone.²³ A subgroup of patients with unfavorable molecular cytogenetics showed no difference in progression-free survival; the benefit of bortezomib appeared to be maintained across all the risk groups.²³

Implications for Health Plans

How do health plans work with this type of information? Which treatment should be first-line? Which is the most effective clinically, as well as the most cost-effective treatment regimen? How do plans balance cost, quality, and access across multiple treatment options?

New cancer treatments, including biologics, have changed the lives of many plan members. Coverage of new drugs for cancer is essential. Plans have to provide access, but this major cost driver ultimately may result in problems with access for any health benefit design. As medical costs go up, premium costs go up, and as premium costs go up, the patient's ability to afford healthcare coverage goes down, and membership potentially goes down.

A new era of costs has emerged, driven by the shift from the use of cancer care agents as short-term therapies to chronic long-term therapies. With many new cancer care therapies costing in excess of \$50,000 annually, health plans need to use management strategies that balance access to these treatments, while preserving affordability by ensuring appropriate use.

Health plans must reassess their benefit designs to ensure that access is preserved and adequate management is possible. Health plans must be able to assess the comparative effectiveness of agents to provide relatively open access for superior treatments. They also need better information on treatment guidelines and on comparative clinical outcomes to properly structure benefits and management programs. There is much work to be done.

Creating value-based benefits for cancer care is a logical next step, but multiple issues must be overcome to get to that step. ■

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Cancer Drug Development: Barriers to Benefit Design in a Value-Driven Healthcare System

Al B. Benson, III, MD, FACP

Adapted from a presentation at the Academy of Managed Care Pharmacy meeting, April 2009.

Delivering quality healthcare to our patients with cancer involves vast complexities of issues that oncologists, providers, payers, and patients face today, much of which can be gleaned from Peter Bach's recent article.¹ We went from many decades of being able to offer little for our patients with cancer, outside of perhaps surgery in oncology, to a current vast collection of agents that is rapidly increasing. It is estimated that there are at least 850 agents today under development just for oncology. Recent data on the monthly and median costs of cancer drugs clearly demonstrate that cost has skyrocketed¹ and is therefore a subject of great interest to many stakeholders, including lawmakers in Washington.

As the saying goes, it's déjà vu all over again. In the 1990s there was a great deal of concern about off-label use of drugs, which is a critically important practice in oncology. Most of the combinations we use today have not received US Food and Drug Administration (FDA) registration for these uses. But our extensive networks of clinical trials have shown that many of these combinations are, indeed, efficacious and have entered into the routine care of cancer patients.

Because of the concern for off-label use, state societies were formed in the 1990s, representing medical oncologists and other practitioners in an effort to help create legislation to provide patients access to a variety of treatments, even if those have not been registered by the FDA outside of much narrower indications. This legislation and the legislation supporting the use of clinical trials in oncology were important efforts to expand treatment options for patients.

The cost of healthcare is the dominant force driving policy, legislation, reimbursement decisions, and discussions today. A battle is going on as to whom should determine the care that is provided. Many would argue that the clinician-patient interaction is the most important determinant of care. But we are seeing a great deal of friction between the providers of healthcare and those who pay for it.

The Economics of Cancer Care

One area of enormous tension is the economics of healthcare versus the providing of a critical human service. Be-

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cause healthcare is a giant industry, it is a very important part of the US economy. It also offers opportunity to promote innovation of new concepts and new treatments. We export a great deal of what we develop in healthcare; the pharmaceutical industry is perhaps one of the best examples of product exploration.

This use of healthcare as a tool to promote our economy through exports is significant. Healthcare is also important in terms of construction—healthcare facilities age rapidly and must be renewed. The healthcare industry is also a critical education tool that cannot be ignored as an economic force.

Another key issue is, what price for survival? A common question made about clinical trials is whether 2 months' survival really makes a difference. Clearly, if we are going to make substantial improvements in survival, we have to focus on prevention. If we can prevent serious disease, in the end we would save a lot of money.

Survival of patients with chronic illnesses, such as cancer, also relates to cost. Although cost analysis is generally focused on the intervention, if a patient receives much benefit from a therapy, that individual may continue employment, which should also be considered when doing the cost analysis of the therapy.

We also have to define the goals of therapy for individual patients and the strategy for healthcare delivery that should reflect those goals. If the goal is cure, then the cost benefit of survival could be enormous, and patients could enjoy many years of productive lives. Even in chronic diseases, we need to define our goals and the potential benefits to patients from selected intervention. For example, in my area of colorectal cancer, we more than doubled the survival of patients with advanced disease in less than a decade.

One very difficult area is the end of life, where an important aspect of cost is the last 6 months of life. As an oncologist I often have no idea if a patient is going to survive 6 months. Nonetheless, it is an area that requires a great deal of attention and significant education for our patients, for healthcare providers, and for policymakers to ensure that when we deliver care to patients at the end stages of their disease, we are providing appropriate service and not spending millions or billions of dollars on interventions that will not have any meaningful impact for that individual patient.

Policy Concerns

The cost of delivering healthcare has skyrocketed on

many fronts. Oncologists certainly face innumerable regulations, which are also important barriers to clinical trial development and participation. There may be good intentions when these regulations are created, but rarely is anyone going back to study a regulation to see if it accomplished what it was intended to do. And if it did not, it should be eliminated, or at least amended. Too often what we see is regulation upon regulation, and no one is checking to determine if we are getting what we intended.

Obviously technology is an important driver of cost. As technology evolves, construction and renovation are going to be critically important. For example, in the inpatient arena, we used to have as many as 16 patients or more in 1 giant room. Now we have individual patient rooms, and for good reasons, but this has certainly raised the cost of care. Other drivers of cost are competitive forces and the number of personnel we require to deliver what we think is appropriate oncology care.

Comparative Effectiveness Analysis

Comparative effectiveness is the new buzzword in Washington, and there is little doubt that the government will take major steps in this arena. And yet, this subject is very complicated. Many people see comparative effectiveness in terms of simply looking at large numbers of patients, comparing treatment X versus treatment Y, and then figuring out what works best. That is definitely not the direction oncology is moving toward. We are much more interested now in the individual factors that contribute to differences in clinical outcomes, such as:

- Comorbidities
- Drug–drug interactions
- Host genetics
- Race or ethnic diversity
- Tumor genetics
- Tumor heterogeneity.

Cancer is often perceived as if it were one entity, but each disease represents a collection of different tumor cells that may differ in individual patients. Tumor heterogeneity is very complex in terms of developing treatment strategies for patients. Increasingly we are focusing on tumor genetics and the individual patient host genetics to inform us of the processes of carcinogenesis and to design drugs to treat patients.

Therefore, many factors come into play in cancer outcomes, including tumor biology; patient biology; pathologic features, such as lymph node status; surgical techniques, which can be highly variable; and also critically important is patient access to care and how that may affect outcome (Figure 1). Geography can make a major difference in access to care; someone who lives in a very rural area may have difficulty getting to a healthcare facility compared with someone in a large urban environment.

In the not-too-distant past, when we thought of cancer as one entity (and we still do this to a large degree), we tended

Figure 1 Determinants of Cancer Outcomes/Patient Response to Treatment

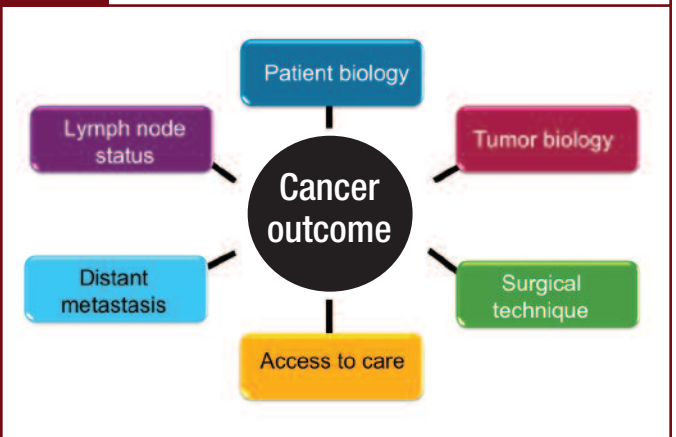
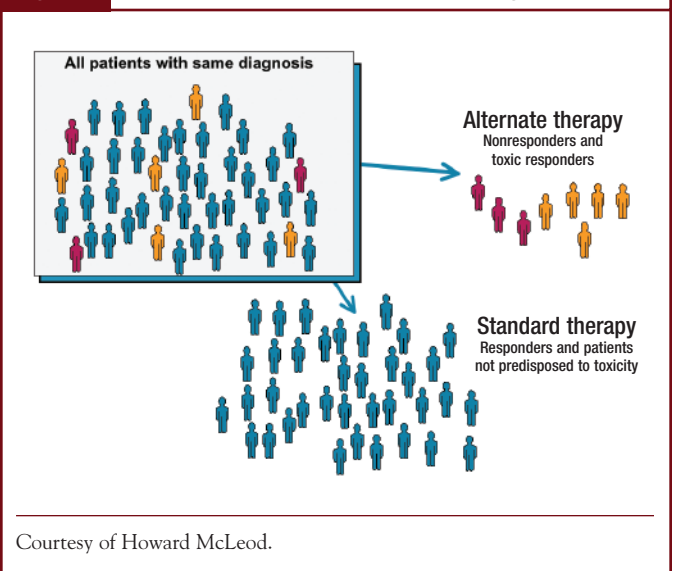


Figure 2 The New Approach to Cancer Therapy



to lump patients together as if they were all the same, and that certainly has been done in clinical trials. There are very few stratification factors to differentiate patients with stage IV colorectal cancer; but we have now learned that this collection of patients with the same diagnosis represents a variable population of individuals. Therefore, our new treatment strategy, which will affect concepts such as comparative effectiveness, is to take this group of patients who have the same diagnosis and segregate them according to what would be the most appropriate intervention, based on tumor genetics, host genetics, or other features. Our goal is to segregate out those who may be good candidates for the current therapeutic strategies, and then find alternative possibilities for the patients for whom we would predict no benefit from standard therapy (Figure 2).

Information technology is going to be very significant for

comparative effectiveness and will involve a variety of issues. It will require taking a large series of different databases to figure out how to get these databases to talk to one another. It will take private and public coordination of data collection, integration of clinical research networks, and utilization of healthcare databases. We currently are not able to link the different databases, but this has enormous potential in helping to isolate subsets of patients who may need different treatment strategies.

We hope that electronic health records will help create databases that will allow us to look at individual patient characteristics. But to optimize how we treat patients, it is necessary to integrate biologic markers in these databases.

Research methodology is going to take novel statistical analyses, computer modeling, and so forth, all of which will be very expensive. No single entity will be able to pay for this; it will require diverse funding, including funding from our insurance carriers.

Other issues relevant to comparative effectiveness are influenced by variable reimbursement strategies, the availability and timeliness of access, the quality of the ancillary services provided, and differences between care delivered in the tertiary care centers, such as large academic institutions, versus the community.

The NCCN Paradigm

The National Comprehensive Cancer Network (NCCN), which was founded in 1995 and now represents 21 of the leading cancer centers in the United States, offers a unique paradigm in cancer management. I currently serve as the chair of the board of directors of the NCCN. One of the reasons I was attracted to the NCCN concept is that it is one of the few examples where academic physicians meet on a regular basis to develop strategies to inform healthcare decisions, which is what the NCCN is all about.

There are now 110 NCCN clinical cancer guidelines that cover 98% of all cancer patients. The goal is to integrate clinical data and expert judgment into the real-world clinical experience, using an evidence-based approach when the evidence is available, and evidence-based expert consensus when high-level evidence is lacking. So a recommendation that is based on a lower level of evidence has to have uniform consensus among the panel members.

The NCCN guidelines are designed to address the entire continuum of cancer care, from initial diagnosis to the end of life. It is comprehensive across all stages of cancer and describes all modalities of treatment. The panel members are multidisciplinary, as appropriate for a given disease. Using an algorithm presentation is unique to the NCCN, making it quite easy to review the guidelines, although there are also very detailed manuscripts that discuss ongoing controversies and provide additional information, with references.

It is critically important that this process is a continuum that is updated constantly. The failure of many guidelines is

the lack of resources to keep the guidelines timely. The NCCN panels meet often on an ad-hoc basis when new data emerge. When new data are appropriate to integrate into care delivery, the NCCN guidelines and compendium are simultaneously revised.

What is important about the *NCCN Drug & Biologics Compendium* is that it is directly linked to the guidelines, and when the guidelines change, the compendium is updated when appropriate. We also have special task forces to look at a variety of different issues, such as positron emission tomography scans. Another critical decision has been to make the NCCN guidelines available free to everybody online, at www.nccn.org.

The NCCN paradigm is to have disease-specific and symptom-specific guidelines, which are linked to the compendium. A unique feature of the compendium process is the development of drug templates that are linked to the compendium and the guidelines; we believe these templates are very important for safe drug administration. The NCCN also has extensive database projects, where we are looking at, for example, concordance with the guidelines at our respective member institutions.

It is important to emphasize that the NCCN guidelines are not prescriptive. We do not expect 100% concordance. Patients are obviously variable. The NCCN is a voluntary effort, with more than 900 clinician volunteers, and it is multidisciplinary. When any guideline is up for review, it is sent to each of the 21 institutions, where additional experts get to review the algorithms and make comments. The guideline process is further informed by a variety of meetings, including our regional symposia, annual meeting, and international collaborations.

The Future: Genetic Testing

Oncology is moving away from empiric clinical trial design to molecular analysis of tumors and patients to drive the choice of treatment. For example, in myeloma and in the hematologic malignancies in general, a very strong focus has been on understanding the genetics of the disease. A host of different strategies to treat myeloma are available, including the introduction of new agents, which Dr Owens discusses in this supplement.

But what also has emerged is the ability to use molecular tests to identify high-risk disease. Molecular tests for myeloma include:

- Gene-expression profiling:
 - Arkansas 70-gene model to identify very high-risk disease (about 15% of patients)
- Identification of certain high-risk chromosomal abnormalities:
 - 13/13q-
 - t(4;14)
 - 17p-
 - 1p/1q changes.

These chromosomal changes have treatment implications. For example, in patients with 13q abnormalities, some therapeutic strategies may be particularly beneficial: bortezomib alone or in combination with lenalidomide may overcome adverse influences. In patients with 17p-, the use of thalidomide-based therapy may not be the best treatment option. And lenalidomide-bortezomib combination may overcome adverse influences in patients with t(4;14). So molecular biology can inform us not only what may be the right thing to do but, equally important, what is the wrong thing to do.

The Economic Implications of KRAS Testing in Metastatic Colorectal Cancer study, conducted by our cancer center at Northwestern University, was first presented in January 2009 at the Gastrointestinal Cancer Symposium.² This simple model of KRAS genetic testing informs us as to the importance of appropriate patient selection and the potential to save many healthcare dollars. The KRAS testing alone cost about \$452. When appropriate KRAS testing is done, there is an opportunity to save millions of dollars, as illustrated in Figure 3, by offering this therapy to the appropriate patients only (ie, those with the wild-type KRAS gene but not those with mutated KRAS).²

This was an analysis of patients with metastatic colorectal cancer, a disease for which cetuximab has clearly demonstrated benefit as a first-, second-, and third-line treatment for colorectal cancer patients. But recent retrospective analyses across many trials produced very consistent results, showing that the patients who will benefit from cetuximab are those with tumors of the wild-type KRAS compared with those with the mutated KRAS gene.² Although this tumor genetic testing has not been incorporated yet into the drug's package label, it has been now fully integrated into oncology practice and oncology guidelines as a standard test before cetuximab or panitumumab administration.

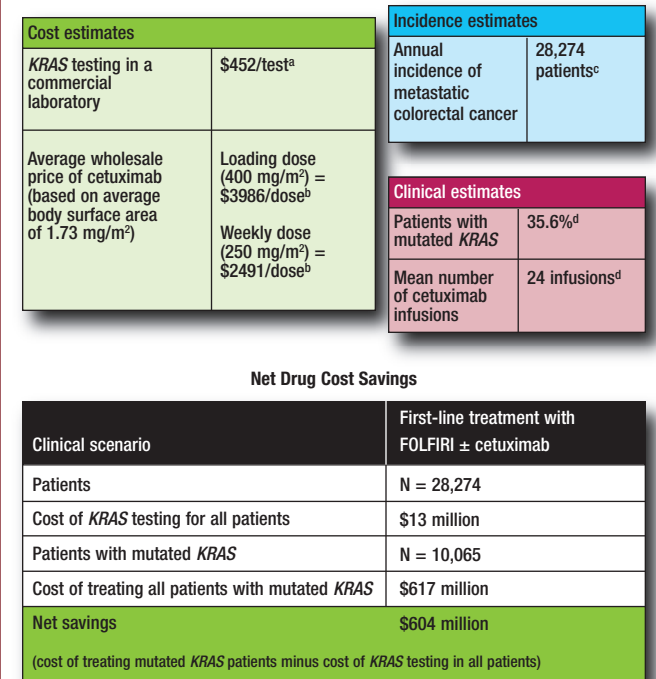
As a current clinical research strategy, the patients with mutated KRAS are being segregated out for alternative therapies, because clearly they are not going to benefit from cetuximab therapy.

Northwestern's 4R Approach to Value-Based Care

Also at our cancer center in Northwestern University we are developing a value-based healthcare program designated "the 4R approach": the Right information and Right care to the Right patient at the Right time, and this involves support by appropriate financial structures and incentive systems. Our cancer center is partnering with Northwestern University's Kellogg School of Management, as well as with the Center for Business Models in Healthcare, to look at new strategies of healthcare delivery that take into account many of the issues mentioned earlier and address barriers to the 4R healthcare approach. We are targeting breast cancer and colorectal cancers initially.

For example, from the breast cancer patient's perspective, there are multiple complexities associated with the

Figure 3 KRAS Testing Saves Drug Costs



^aGenzyme Corporation, Cambridge, MA.

^b2008 Red Book. *Pharmacy's Fundamental Reference*. Montvale, NJ: Thomson Healthcare; 2008.

^c*Cancer Facts and Figures*, 2008. Atlanta, GA: American Cancer Society; 2008.

^dVan Cutsem E, Lang I, D'haens G, et al. KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with FOLFIRI with or without cetuximab: the CRYSTAL experience. *J Clin Oncol*. 2008;26(May 20 suppl):Abstract 2.

FOLFIRI indicates fluorouracil, leucovorin, and irinotecan.

Source: Shankaran V, Bentrem DJ, Mulcahy ME, et al. Economic implications of KRAS testing in metastatic colorectal cancer (mCRC). 2009 Gastrointestinal Cancers Symposium. January 2009, Abstract 298.

treatment process, from the acute phase to recovery, as well as the long-term sequelae. In fact, cancer survival now is a topic of enormous importance but has not received sufficient attention. At the NCCN, for example, we are now integrating survival strategies in our guidelines.

The list of healthcare practitioners and other ancillary services that are involved with a breast cancer patient is enormous, resulting in clinical complexity, care delivery complexity, and business complexity of the practice infrastructure—all of which could lead to failure of integration of these critically important services.

This complexity also acknowledges the fragmentation and variability in cancer care delivery. Cancer care may be one thing at a place like Northwestern University, where we have a clinical cancer center and many healthcare providers in one setting, compared with a community practice, where

the oncology office, the hospital, and the infusion center are each in a separate place. Therefore, integrating the patient's care can be very problematic, resulting in misalignment of care or in poor communication that can lead to significant gaps in care, where diagnostic and treatment decisions are out of sequence, or test results are not available at the time of treatment decision. Such inconsistencies in clinical decision-making can be the cause of suboptimal outcomes.^{3,6}

Barriers to the 4R healthcare approach in breast cancer diagnosis are enormous:

- Who should decide when to test the patient?
- Which test and which laboratory to use?
- Who interprets the results?
- How do costs influence the choice of test to use?

The complexity of just ordering a fairly standard test can affect a cancer patient's treatment outcome. For example, with regard to testing for human epidermal growth factor receptor type 2 (HER2), which is critically important for informing the patient's decision on treatment, there are a host of interactions involved, and a failure in any of these can lead to inconsistencies in the care delivered, as has been shown in several studies.^{3,6} Two studies suggest that some eligible patients do not receive HER2 testing, or their testing is not documented.^{3,6} Testing, including the HER2/*neu* gene testing, can have variability in the assays and interpretation, which also need to be taken into account.

Therefore we have to look at the care fragmentation barriers, the lack of comparative assessments, as well as the economic dilemmas. For example, only about 25% of breast cancer patients benefit from trastuzumab, and the annual cost of the drug is up to \$50,000.⁷ But results of another study showed that 4% of patients receiving trastuzumab had not been tested for HER2 status, and 8% of patients have negative HER2 status.⁴ This also emphasizes the importance of comparative effectiveness and the integration of these diagnostic testing and molecular markers for segregating out the appropriate subpopulations for treatment.^{8,9}

The host of healthcare providers that are needed to optimize a breast cancer patient's overall care leads to highly variable reimbursement strategies, and many of these services are not reimbursed at all, further demonstrating the need to integrate and appropriately reimburse these services.^{3,10} There are many barriers that entail behavioral changes, economics, and the health outcomes impact on benefit designs. More evidence is needed to construct an effective oncology reimbursement solution.^{11,12} Effective provider reimbursement in oncology should also incorporate value-added services and practice infrastructure.

The 4R care model will be built at Northwestern University as a vehicle for personalized medicine, with continuation of patient care coordination. It will involve not only the initial medical practice initiative but also medical home initiatives, looking at a variety of shared medical decision-making disciplines, and at how best to create a model that will enhance

care delivery to patients routinely. Our goals are to:

- Eliminate the gaps and redundancies in diagnostic services and other care events
- Integrate personalized medicine and related services into the care delivery
- Connect academic and community physicians, services providers, and the patient into an effective structure
- Improve the overall care that is delivered and reduce cost, by delivering more appropriate care.

Conclusion

Off-label use of cancer drugs is a critical component of care, and it must be protected. However, many people do not understand this concept. The media coverage lately has suggested that off-label use represents experimental treatment and should not be reimbursed. We need to better inform policymakers, regulators, insurance carriers, and patients about the role off-label agents plays in cancer care and the evidence that supports such use. As mentioned, the cost of healthcare is the dominant force driving policy, legislation, and a host of decisions. The result is the current controversy between the economics of medicine and a critical human service. If we are going to get closer to evidence-based medicine and integrate it into routine practice, we need to focus on approaches such as provided by the NCCN. Finally, we need models to consider appropriate subsets of patients for treatment strategies, as well as appropriate care strategies. ■

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A Viable Value-Based Oncology Benefit Design

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Adapted from a presentation at the Academy of Managed Care Pharmacy meeting, April 2009.

What is value? Value in healthcare should reflect both cost and quality. It is similar to the concept of cost-effectiveness that is discussed in this supplement. Much of the value is measured by a societal perspective, and it does not assume that high quality and low cost are the end results. Rather, a value-based initiative is a collective consideration of cost and quality, where quality equates with outcomes.

What are some of the general concepts of value-based design? Benefit design based on value could be viable even with increased costs, if we add patients' productivity gains and disability savings (associated with successful, albeit expensive, therapies), or if we target treatments to patients more effectively. As more biomarkers are being added to cancer therapy, for instance, we could have very expensive therapies that are nevertheless cost-effective, because the overall treatment is more effective. Such benefit design would have value (reflecting cost and quality).

Components of Benefit Design

The focus in benefit design should not be just on saving money, but rather on an overall value-based perspective related to the outcome of each specific service. For example, even if lowering copays does not save money, applying the principles of value-based insurance designs can improve health outcomes, which in turn could have cost-savings opportunities downstream.

Some of the components of benefit design in oncology include:

- National guidelines
- Personalized medicine
- Supportive care, including hospice and social services.

Many clinical guidelines in oncology have been issued by the major cancer organizations in the country. For the purposes of this discussion, the focus is on the National Comprehensive Cancer Network (NCCN) guidelines. In addition to what Dr Benson mentioned in this supplement, it is important to note that the NCCN guidelines include screening and preventive care, as well as supportive care components. The NCCN guidelines represent the best evidence available at the time they are constructed, and unlike some guidelines that have quarterly or annual updates, these are updated continuously as new information becomes available.

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The guidelines are based on level of evidence consensus, classified by the quality of the evidence and the level of consensus¹:

- Category 1: high-quality evidence; uniform consensus
- Category 2A: lower-quality evidence; uniform consensus
- Category 2B: lower-quality evidence; nonuniform consensus
- Category 3: any quality evidence; major expert disagreement.

The majority of products and treatment guidelines fall into category 2A, which has a lower quality of evidence but a uniform consensus among panel members.

Personalized Medicine

Personalized medicine is a key component in oncology benefit design and is not confined to areas where money can be saved. In some cases, personalized medicine can be expanded to include care areas with high value, but also with high cost. For example, increasing numbers of first-line oncology therapies that receive US Food and Drug Administration (FDA) approval add value, but they also are rather expensive, and therefore the cost of therapy, on a per-patient basis, is increasing.

Personalized medicine in oncology is based to a large degree on biomarkers, which are identified through genomics, proteomics, and metabolics. Even though we do not yet have all the potential biomarkers we wish for, personalized medicine is one of the main features of a benefit design in oncology. Current biomarkers can be used to determine safety surrogates, dose regimen, optimization of therapy, or efficacy. In most cases, when a new drug becomes available, one of the first questions for many stakeholders is whether a biomarker is associated with this product, because the availability of a biomarker offers the opportunity to target that therapy to the right patient for the best outcomes.

The "poster child" of personalized medicine was the human epidermal growth factor receptor type 2 (HER2) marker. This biomarker determines which patients with breast cancer can use the drug trastuzumab. The label of trastuzumab requires patients to be tested for the presence of HER2 mutation before the administration of this drug. Patients with breast cancer who do not have this mutation are not supposed to receive trastuzumab.

Other markers or targets in cancer therapy currently available are listed in **Table 1**. The number of biomarkers is still limited but is constantly expanding.

Table 1 Cancer Targets and Therapies**Angiogenesis**

- VEGF inhibitors (bevacizumab, sunitinib)

Apoptosis

- TNF- α -related apoptosis-inducing ligand death receptor molecules

Endless replication

- Chemotherapy

Invasion/metastasis

- MMPi
- VEGF inhibitors (bevacizumab, sunitinib)

Self-sufficient growth signals

- Tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib)

Insensitive to antgrowth signals

- Tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib)

Estrogen receptors

- Tamoxifen
- Aromatase inhibitors
- Fulvestrant

HER2

- Trastuzumab
- Lapatinib
- Pertuzumab (investigational)

Epidermal growth factor receptors

- Cetuximab
- Panitumumab
- Erlotinib
- Gefitinib

HER2 indicates human epidermal growth factor receptor type 2; MMPi, matrix metalloproteinase inhibitors; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

Oncology Benefit Design

An oncology drug benefit design can incorporate the NCCN guidelines and their categories of evidence and consensus to specific health and drug benefits, using the following parameters:

- The lowest copay would apply to benefits with the highest consensus (category 1)
- The medium copay would apply to benefits with the lower level of evidence but with a uniform consensus (category 2A)
- The highest copay or coinsurance would apply to benefits with the lowest consensus, a nonuniform level of consensus (category 2B)
- No coverage (or for those who want to cover all benefits, coinsurance) would apply to benefits with any quality of

Table 2 Future Trends: Specialty Pharmacy Continues to Grow

Year	2002	2006	2007	2011
Specialty pharmacy, \$ billions	29.7	44.7	60+	100 ^a
Annual increase, %	–	50	34	67 ^a

^aEstimated.

Source: Pyenson B, Murphy-Barron C. *Realizing the Value of FDA-Approved Therapies*. New York, NY: Milliman; March 31, 2007.

evidence but also with a major disagreement on the level of consensus (category 3).

In addition, the benefit design should include incentives for hospice and social services. In some cases, supportive care includes drug therapies, but those drugs are already covered, normally within the general plan benefit. Those could be incentivized from a copay differential to ensure that patients' persistency and adherence to supportive care is high.

Drug Benefit Misalignment

One of the challenges of a value-based benefit design is the current drug benefit misalignments; that is, the way drugs are covered by payers. Drugs may be covered either under the medical benefit or the pharmacy benefit, and therefore they have different reimbursement patterns, different member cost-sharing, different clinical review processes, and different utilization management.

One of the challenges of a value-based benefit design is the current drug benefit misalignments; that is, the way drugs are covered by payers.

The benefit components may further vary based on the site of administration or distribution, which leads to misalignment of financial and utilization practices. The Medicare fee schedule applies the average sales price (ASP) plus 6% strategy to many organizations. Although it is a uniform reimbursement philosophy, it also may encourage a greater use of high-cost drugs, because of the greater margin associated with the ASP plus 6% reimbursement approach for the more costly drugs.

Oncology drugs distribution has a variety of distribution channels, such as a retail pharmacy for oral drugs, a

home-delivered pharmacy, a specialty pharmacy, a physician's office, an outpatient hospital, or home infusion. Within these distribution and service areas, patients' benefits today can vary greatly—in terms of copays and utilization management.

Specialty Pharmacy

A value-based program is further challenged by the growth of specialty pharmacy, not only in terms of the number of new drugs being added in that area but also in the growing number of FDA approvals and new indications, followed by increased utilization once these products receive FDA approval for any indication and are on the market. This increased utilization can be the result of the increase in FDA indications, but also the increase in use of these oncology medications outside of their immediate FDA-approved indications (and therefore not always supported by appropriate evidence).

Specialty pharmacy has been growing consistently since 2002, with an annual increase of 50% in 2006, 34% in 2007, and an estimated 67% growth in 2011 (Table 2).²

The specialty pharmacy marketplace has become a prominent force in the delivery of specialty medications. The estimated total spending on therapeutic innovations is expected to be \$100 billion or more by 2011.

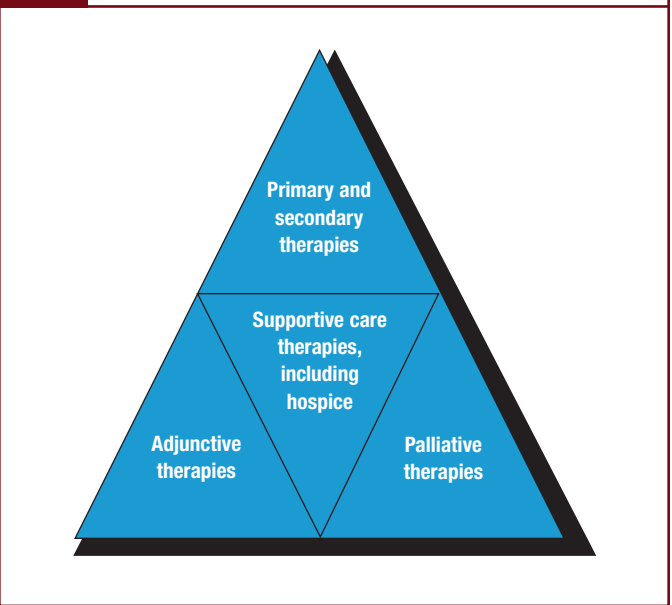
When large manufacturers such as Pfizer indicate that they are no longer going to do cardiovascular research, and their focus is instead going to be on biologics, this suggests where the emphasis of the pharmaceutical industry is, and the growth in the number of FDA approvals in oncology is reinforcing that trend.

Overall, specialty pharmacy has grown to \$60 billion and more annually.² The specialty pharmacy marketplace has become a prominent force in the delivery of specialty medications. The estimated total spending on therapeutic innovations is expected to be \$100 billion or more by 2011.²

Cancer Therapy Approach

The modern approach to cancer therapy is shaped like a pyramid (Figure), where the primary and secondary therapies are at the top, and the middle should be (but may not be emphasized in this manner) supportive care therapies, including hospice and social services. Those services, particularly hospice services, tend to focus more on the end of

Figure Modernized Oncology Therapy Approach



life, where, as has been mentioned previously, the largest cost of care is within the last 6 months.

These services need to be introduced earlier in the overall approach, so that a patient's care plan can incorporate these services earlier. The social worker and social services need to be incorporated within those support services, with hospice services introduced very early in the patient's treatment choices and discussions. Potentially, this can significantly reduce the end-of-care oncology drug therapies that are being used for palliative care.

Practical Implications

- When designing health benefits, waive or keep copays low for very appropriate screening, or for any cancer prevention activities
- Also waive fees or reduce copays for therapies with high evidence and with a high level of consensus
- Use higher copays or coinsurance for low-value care
- Introduce hospice and other supportive services earlier in the course of therapy and review
- When looking at the different distribution and service channels, it is useful to streamline the process and have a consensus, so that the patient is not disadvantaged or conceivably penalized based on what distribution channels are being utilized. ■

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