



# Considering Reimbursement for Cancer Preventive Agents

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## I. Foreword

In June 2006, C-Change, convened the Cancer Prevention Research Summit - a meeting of scientists, oncologists, pharmaceutical researchers, governmental representatives, public policy experts, and patient advocates to discuss the barriers to research and development of chemoprevention drugs and unleash the potential of this promising field. Four major barriers were identified as deterrents to progress: uncertain reimbursement for new agents; limitations in current patent law and intellectual property (IP) protection; emerging science and an uncharted clinical trial design and drug approval processes; and limited public participation in clinical trials. Proceedings from the summit were published in *Cancer Research* 66(24) December 15, 2006, "Cancer Chemoprevention and Cancer Preventive Vaccines - A Call for Action: Leaders of the Diverse Stakeholder Groups Present Strategies for Overcoming Multiple Barriers to Meet Urgent Need."

Following this groundbreaking meeting, three complementary efforts ensued to propose solutions to these financial, legal, and scientific/regulatory barriers impeding the field. This document reports on the work and recommendations of the Chemoprevention Reimbursement Committee. C-Change believes the findings and recommendations of the three task forces, when viewed as a whole, will address the major barriers and provide solutions to this multi-faceted challenge – unleashing lifesaving potential through the research, development, and delivery of chemoprevention agents.

The purpose of this paper is provide payers and advocates in the cancer community with information about emerging chemopreventive agents so they can more clearly consider the value of these new treatments in the context of a complex health environment. If traditional practices are used to determine coverage and reimbursement - the real contrast is between inertia and evaluation, not different methods - significant value may be overlooked. This paper identifies, frames, and suggests ways to consider challenges posed by cancer chemopreventive agents with realistic consideration for the financial burdens facing the public, employers, and payers; safety and quality expectations by consumers; and concepts for making informed decisions about prevention and treatment value. This information provides a foundation to begin a dialogue among advocates, private, and public payers, researchers, and investors to address the following issues:

1. Identify policy and conceptual obstacles to payers covering chemopreventive agents in past decision-making patterns, policy documents, and regulations
2. Define the concept of a “chemopreventive class” for formularies
3. Determine the characteristics of a chemopreventive agent that would make it worthy of coverage
4. Agree upon how advocates can support payer efforts to displace ineffective or wasteful spending to make room for chemoprevention in the health economy

Payers include insurance companies and HMOs, state Medicaid programs, Medicare, and self-insured employers and similar organizations.

This manuscript was developed by a multi-sector panel of volunteers including C-Change members and other thought leaders. C-Change would like to acknowledge and thank the following individuals for their contributions to this collaborative effort.

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### **About C-Change**

C-Change is a not-for-profit organization whose mission is to eliminate cancer as a public health problem, at the earliest possible time, by leveraging the expertise and resources of our members. C-Change is the *only* organization that assembles cancer leaders from the three sectors – private, public, and not-for-profit – from across the cancer continuum – prevention, early detection, treatment, and quality of life.

Former President George Bush and former First Lady Barbara Bush are Co-chairs of C-Change and Senator Dianne Feinstein serves as Vice Chair of C-Change, a 501(c)(3). C-Change is comprised of approximately 130 of the Nation's key cancer leaders who share the vision of a future where cancer is prevented, detected early, and cured or is managed successfully as a chronic illness.

One of the underlying principles of C-Change is to serve as both a forum and a catalyst for identifying issues and major challenges facing the cancer community, and for initiating collaborative actions to complement the efforts of individual C-Change Members. C-Change invests in the resolution of problems that cannot be solved by one organization or one sector alone.

For more information about the Cancer Chemoprevention Initiative, please contact C-Change at 202-756.1600 or visit [www.c-changetogether.org](http://www.c-changetogether.org)

## II. Executive Summary

Disease prevention is well-established in medical practice and has emerged as a charged topic due to potentially competing economic, political, and personal issues (1). Although common sense says it is better to prevent disease than treat it, approved preventive agents have generally had to meet more stringent scientific criteria than treatment agents(2). The current healthcare system provides limited incentives for physicians or patients to engage in disease prevention efforts. Rather, the healthcare system is focused primarily on reacting to and paying for illness.

The promise of cancer chemoprevention has been prominently discussed elsewhere (3). Because very few healthcare decisions are made without consideration for payment decisions, reimbursement policies for cancer chemoprevention are important investment criteria for drug researchers and developers, prescribing criteria for practitioners, and ultimately, treatment options for patients. Given today's healthcare cost crisis, promising health interventions will need to compete for dollars with existing uses of financial resources. This paper provides guidance to researchers, advocates, and payers regarding the importance of reimbursement decisions related to chemopreventive agents:

- Today's healthcare system faces enormous financial pressures and is undergoing rapid change driven by advances in technology, consumer pressure, and other economic realities. This new environment calls for new approaches to paying for value-added innovation.
- With a careful reflection on existing reimbursement structures and policies, cancer chemopreventive agents can be integrated into these existing systems.
- Cardiac disease prevention is one example of how a huge public health burden has been reduced through the use of preventive drug therapies, providing useful analogies for cancer.
- The concept of value in healthcare is not new, but today's emphasis on cost and evidence-based medicine will give strong competitive advantages to high-value interventions. This paper presents various approaches to determining value, but emphasizes that the concept of a value-based decision, rather than either a non-evidence-based decision or a cost-based decision is probably more important than a particular metric or formula chosen to calculate value.

Since no one organization can resolve these complex challenges, cooperation will be required to seize the opportunity afforded by chemopreventive therapies. The uncertainty of reimbursement can be addressed through the collaboration of the science, cancer care, payer, and advocate communities to: define the true value of treatment and replace non-evidence based treatment options with evidence-based prevention and treatment options. By confronting these difficult issues, more efficacious and affordable treatments will be made available to address cancer as a public health problem.

### III. Making Room for Innovation: Environmental Background

Many demands are being placed on the healthcare system: increase quality care, cover the uninsured, and manage out-of-control costs. How can emerging chemoprevention services secure stable reimbursement streams in this seemingly conflicting context?

Within the US healthcare system, healthcare treatment and service choices abound, but not all treatments and services are equally efficacious or appropriate for all individuals. Chemopreventive agents are currently being researched to target specific cancers in specific individuals. Advances in chemoprevention are an ideal contrast to the billions of dollars we spend in services which are too often ineffective, inefficient, wasteful, or harmful.

Historically, analysis of clinical efficacy by researchers and analysis of product cost and/or value by insurers and policymakers have been completely independent activities. This section concludes with a call for a dialogue among researchers, payers, and policymakers to define principles of coverage and reimbursement for chemopreventive agents. *That dialogue is needed now, when product development is in its early stages.*

#### Challenges with the Traditional Approach

Cancer chemoprevention does not fit well into the traditional insurance coverage framework for several reasons. This chapter focuses on obstacles to reimbursement that emerge from the existing characteristics of medical coverage decisions.

Standard pharmaceuticals and biotechnology products obtain reimbursement for a prescription agent by gaining FDA approval and then seeking availability through private or government payers. Payers and pharmaceutical companies negotiate prices through a largely unregulated process that considers the prices and characteristics of competing products or treatments and potential demand.

Due to rising healthcare costs, payers are especially reluctant to expand coverage to new categories of services or products. Cancer chemoprevention is prevention, and reimbursement is often focused on treating conditions or illness. For example, although physical exercise is essential for health, medical benefits do not pay for gym memberships. A similar challenge arises when convincing payers and policymakers to reimburse for cancer chemopreventive agents. A closer look at different decision-making methods highlights the challenges faced by chemopreventive agents. Two contrasting approaches to secure reimbursement include:

- Traditional: Chemoprevention agents compete for payment in an already crowded healthcare market where the existing services are generating considerable spending.
- Value-based: Chemoprevention products seek to secure reimbursement by demonstrating superior value compared to existing spending and possibly winning favored status relative to other, existing categories of spending.

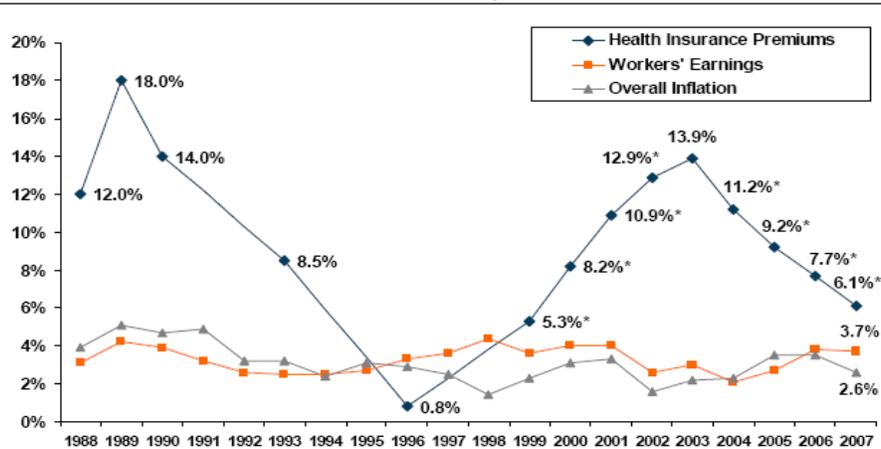
## **The Changing Economics of Payers**

A large percentage of public and private monies are spent on healthcare. Because this spending is high and increasing, enormous pressure exists from all government and private payers to restrain spending. Funding for cancer prevention agents will require solid evidence of relative clinical effectiveness for avoiding disease and relative cost-effectiveness for spending on prevention in lieu of disease. Advocates and vendors have often claimed the ability to control costs through better preventive care, but evidence of success is weak. Healthcare spending continues to grow much faster than the economy while researchers accumulate mountains of evidence of wasted resources and poor quality. *Spending for cancer chemoprevention is best secured by more elegantly illustrating its value and by advocating for reallocation of current healthcare spending on less efficacious treatments to effective chemoprevention.*

## **Cost and the Healthcare Payer Environment**

Perhaps the most important fact regarding US healthcare is that 16% of Gross Domestic Product is spent on healthcare. Nearly half of this allocation comes from government expenditures. This percentage is much higher than any other industrialized country. This economic situation becomes even more precarious as wages become more depressed and medical benefit costs continue to increase (Figure1).

Employers pay for the majority of healthcare costs for working age Americans and their dependents. In order to pay for increasing healthcare costs, many employers have reduced benefits (by increasing patient cost-sharing) or have required higher employee contributions. Both of these changes, in effect, reduce average net wages. The growing interest in consumer driven healthcare with its higher deductibles is prompted, in part, by its potential to reduce cost. As employers struggle to afford healthcare benefits, the number of uninsured workers grows. The large number of uninsured persons is to a large extent an affordability issue, as a shrinking number of employers are offering health benefits.

**Exhibit 1: Increases in Health Insurance Premiums Compared to Other Indicators, 1988-2007**

\*Estimate is statistically different from estimate for the previous year shown ( $p < .05$ ). No statistical tests are conducted for years prior to 1999.

Note: Data on premium increases reflect the cost of health insurance premiums for a family of four. The average premium increase is weighted by covered workers.

Source: Kaiser/HRET Survey of Employer-Sponsored Health Benefits, 1999-2007; KPMG Survey of Employer-Sponsored Health Benefits, 1993, 1998; The Health Insurance Association of America (HIAA), 1988, 1989, 1990; Bureau of Labor Statistics, Consumer Price Index, U.S. City Average of Annual Inflation (April to April), 1988-2007; Bureau of Labor Statistics, Seasonally Adjusted Data from the Current Employment Statistics Survey, 1988-2007 (April to April).



### Figure 1: Health Insurance Costs Are Growing Faster than Wages and Inflation

The Centers for Medicare and Medicaid Services (CMS) has the largest budget of any government program (\$545.5 billion in 2006) (4,5), and has repeatedly tried belt tightening by restricting payments to physicians, hospitals, suppliers, home care agencies, and others. Similarly, many states have attempted to control their Medicaid spending through managed care and fee restrictions, although growing long-term care needs have proved difficult to address.

*In this context, any expansion of coverage to new treatment categories is viewed skeptically. Payers are seeking to spend less in the short-term or at least to hold healthcare costs stables, not spend more.*

### Waste: An Opportunity to Improve Quality and Cost

When quality of care is compromised, avoidable expenditures can be incurred by the healthcare system. Quality flaws have become prominent, with medical errors causing an estimated 100,000 deaths annually(6), and avoidable, hospital acquired infections affecting over 4% of hospital patients. Another example of poor quality leading to additional cost and suboptimal outcome is the cumulative effect of poor medication adherence. Compliance with life-saving medications is poor in patients taking agents for hypertension, diabetes, and hypercholesterolemia. Sub-therapeutic medication levels allow for disease progression and increase adverse event risk, accelerating care costs. Some of these quality challenges are relatively recent (the emergence of Methicillin Resistant Staphylococcus Aureus(7)), or represent suboptimal clinical management (reaching statin therapy goals (8)), but many issues have probably been unmeasured or under-recognized for decades (hospital acquired infections and medical errors). By addressing these opportunities to improve or preserve quality, unnecessary expenditures can be avoided.

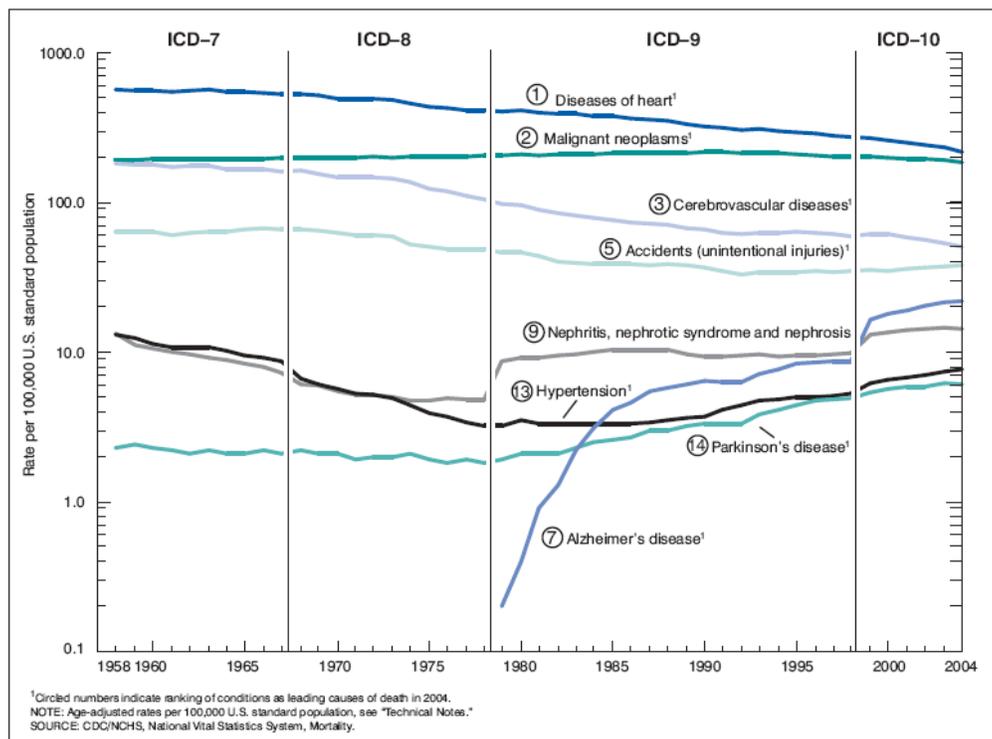
Inefficiency, regional variability, and waste in the system are staggering. For example, spending on chronic disease in the last two years of life between 2001-2005 varied significantly between states after adjusting for age, sex, race, and primary chronic disease diagnosis. For example, in New Jersey, total Medicare spending per person in the last two years of life for patients with at least one chronic disease condition was \$59,379 or 32% below the national average. Conversely, spending in North Dakota was \$32,523 per person or 30% below the national average (9). The costs associated with medical errors are similarly staggering, with hospital acquired infections alone are estimated to cost \$6.7 billion for 2002 (10).

The above examples provide a range of opportunities for reducing health care costs and simultaneously improving quality, safety, and outcome. While each of these improvements requires notable changes in practice behaviors and existing coverage norms, the potential yield from leadership commitments in these areas would be significant. *Tackling these inefficiencies would allow for shifts in spending to innovative and value-added treatments.*

### Fixing the Cancer Lag

Figure 2 shows the age-adjusted mortality rates for leading causes of death since the late 1950s and illustrates that while heart disease mortality has declined dramatically, cancer mortality rates remain unchanged. (The logarithmic scale of the vertical axis means changes appear much less dramatic than they are.) Cancer chemopreventive agents will provide an opportunity for significant decreases in age adjusted mortality related to cancer with the potential to mimic the progress that has been made in heart disease mortality rates.

**Figure 2: Improvements in Cancer Mortality Are Lagging Other Diseases**



From National Vital Statistics Reports, Vol 55, No 17, August 21, 2007, updated Oct 10, 2007 (Table 5 in original). This shows age-adjusted death rates on a logarithmic scale.

Payers spend billions of dollars treating cancer. Individuals at risk for or living with cancer also spend additional billions of dollars per year on proven and, unfortunately, unproven treatments and over-the-counter prevention products. Given the size of the population at risk for and living with cancer, a relatively small reduction in per-person expenditures would result in a significant savings.

To demonstrate the power of prevention, we examined heart disease as an instructive model. While behavior change is always mentioned as a key ingredient in cardiovascular health, pharmaceutical treatment is the basic instrument driving the decline in adverse cardiovascular events such as heart attacks or strokes. Key drugs include cholesterol reducing agents (statins, etc.), blood pressure medicines (diuretics, calcium channel blockers, ACE inhibitors, ARBs, etc.), and anti-coagulants (aspirin or others). Several pharmaceutical 'blockbusters,' brands with annual sales of well over \$1 billion are in these categories, while aspirin is, of course, available over the counter. Additional spending can be attributed to laboratory tests, diagnostics, and physician visits associated in the prevention of heart attacks and strokes.

*While potential spending on future chemoprevention agents is, of course, unknown, spending on cardio-preventive agents to reduce adverse cardiovascular events provides a real-world analogy to potential spending on chemopreventive agents to reduce adverse cancer events.*

#### **IV. To Cover or Not To Cover: Reimbursement Decisions and Mechanisms**

Deciding what to pay for – and what not to pay for – is a basic responsibility of any payer in any kind of health system, whether private, welfare state, socialized, single payer, or mixed. Socialized medicine systems may explicitly ration care and not provide certain services. Private systems use contractual terms with policyholders and with healthcare providers to restrict payments through both the scope of covered benefits and utilization controls. Resources to pay for care are simply more limited than the potential demand for the available choices. Structures to control costs and reimbursements are a basic part of any contemporary healthcare system.

In general, Medicare does not pay for preventative services. The law provides that CMS can pay only for medical services that are reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. As with any rule, however, exceptions exist. CMS has been instructed by Congress to pay for certain preventive services, like prostate screening, mammography, certain vaccines and diabetes screening. Unfortunately, no mandate exists for the federal government to pay for other important cancer preventive services. *Since Medicaid programs and private plans often follow Medicare's lead, Medicare policy is important. By demonstrating the value of prevention and the fact that it can be implemented in a budget neutral manner, this trend can be reversed.*

An historical dispute over cancer care coverage provides a particularly poignant reminder of the financial and policy decisions that emerge as science evolves. The saga of lawsuits to force insurer coverage for bone-marrow transplants for breast cancer patients stands as a bitter reminder of the value of evidence-based medicine standards (11). In the late 1980s, some oncologists believed that high-dose chemotherapy combined with bone marrow transplantation

would offer a cure for advanced breast cancer. Insurers refused payment because the treatment was experimental. Lawsuits forced coverage and damage payments, emotionally charged articles about victims appeared in the media, and several state legislatures mandated coverage. By the late 1990s, researchers demonstrated that the treatment was not effective, after more than 30,000 women were subjected to harmful and useless treatment.

As long as cancer research continues, payers will continue to face difficult decisions regarding cancer treatments. Potential concerns include payment for costly imaging studies that may or may not affect a patient's course of treatment and expensive third-line chemotherapy used as an ad-hoc experiment outside established protocols or clinical trials. *Given these historical and current patterns, payer sensitivity over cancer chemoprevention is likely to be high.*

### **Legacy and inertia of services covered by insurance programs**

Changes to healthcare benefits are often slow. Medicare and Medicaid were designed in the 1960s. Medicare's benefit structure had no significant changes until Medicare Part D, which was implemented in 2006.

Health benefits subject to collective bargaining are especially resistant to change, due to the fact that changes (often reductions in benefits) are often seen as concessions by labor to management. Consequently, some collectively bargained benefits may continue to have co-pays set in the 1970s or earlier (even \$0 co-pays), but, by the standards of 2007, low annual or lifetime limits, such as \$50,000.

Benefit programs are typically modified in modest ways, and, usually to accommodate inflation, the changes are often increases in cost-sharing, increases in employee contributions, and restrictions in which providers will receive preferred treatment and lower patient cost sharing. Expansions in coverage are generally modest and often reflect legislative rules, such as coverage for infertility treatment or mental health parity. In today's economic environment, reductions in benefits are commonplace, as reduced benefits cost less to employers, Medicaid, or Medicare. Increases in cost-sharing (such as increasing office visit co-pays from \$10 to \$20) are more common than eliminating particular benefits (such as eliminating coverage for chiropractic care).

### **Examples of Coverage Limits**

To limit expenses, health benefit programs typically restrict coverage by using medical necessity criteria. This means that coverage is not assured until the provider demonstrates that the patient requires the service or item based upon medical criteria. Furthermore, treating disease typically does not include items of convenience for the patient, but things that are medical necessary. Almost all insurers exclude payment for experimental treatment (although many will pay for some expenses associated with patients in formal clinical trials). Historically, payers have used the following considerations for excluding particular services from coverage: (12)

1. Services not medically necessary to treat a condition or for prevention
2. Experimental services
3. Cosmetic surgery, except for reconstructive reasons

#### 4. Services for which payment is not required

Without strong scientific evidence for effectiveness on well-defined populations, payer exclusions for cancer chemoprevention would be justified under the first or second points. Cancer chemopreventive therapies with strong scientific proof of effectiveness would fall outside these exclusion criteria – in other words, would have a basis for coverage.

Larger payers including Medicare evaluate new technology through a medical technology (“med-tech”) assessment process. This process includes evaluating the scientific literature regarding the advantages, disadvantages, side effects, and other characteristics of proposed treatment. Approval may include requirements that the patient and provider meet certain conditions. *However, currently, cost-effectiveness is rarely used as a determining criterion* (13).

The political process has also created “mandates” that require payer coverage for particular services. States regulate insurance policies, so required coverage varies by state. Some states use a comprehensive evaluation process (14), while others have created mandates apparently without seeking scientific support. The content of self-insured programs, which most large employers operate, is not regulated by the states.

Health insurance benefits are designed to satisfy perceived customer needs. That includes providing services that may have weak supporting evidence but are popular with purchasers or, in the case of employee benefit programs, popular with employees.

In the past, coverage for prevention was limited. Payers recognized that almost everything could be thought of as contributing to health – housing, food, vacations, etc. Prevention that addresses particular medical conditions, such as vaccinations, are generally covered through commercial health benefits programs. However, an act of Congress was required to change the Medicare statutes to cover certain vaccines (15). Coverage for diagnostic procedures seems easier, with Medicare covering colonoscopies, mammograms, prostate tests, and bone density tests.

*Identifying a precursor condition to an adverse clinical event seems to change the perception of prevention into active treatment.* For example, the recognition that hypertension and hyperlipidemia are diseases that lead to increased risk of cardiovascular events (heart attacks and strokes), was followed by coverage for blood pressure medicines and lipid-lowering agents.

#### **Evidence-Based Medicine as the Paradigm for Payment**

Due to the fact that the healthcare system operates largely in a fee for service environment, a natural economic incentive prevails for medical providers to promote the use of more services, which has the potential to increase utilization and cost without improving quality (16). As has been widely documented, much medical spending is either ineffective or actually harmful (17).

Medical management practices by payers can apply to many kinds of medical services. As a matter of cost and quality control, payers often use a process known as medical necessity determinations to identify particular patients who do not meet indications for needing a particular service (18). Medical necessity determinations are intended to prevent inappropriate utilization of services which can increase utilization and cost without improving quality (19). Narrowly speaking, medical necessity determinations do not affect the benefit design but influence

utilization of covered benefits for individuals. To oversimplify, although an MRI may be a covered service, an insurer will not pay for the MRI unless it is reasonably needed for the patient's diagnosis or treatment.

Currently, standard practice for payers entails making medical necessity determinations relying on evidence-based guidelines (20) or treatment protocols and indicating such in contracts with network providers.

## **V. Coverage Analogies for Cancer Chemoprevention**

While coverage is common for a variety of preventive agents for other conditions, coverage for chemopreventive agents presents some unique challenges and opportunities with regard to existing benefit structures. The purpose of this section is to examine these analogies to learn lessons relevant to coverage for chemopreventive agents.

In order to appropriately consider the potential parallels, several differences between chemopreventive and other existing preventive agents must be noted:

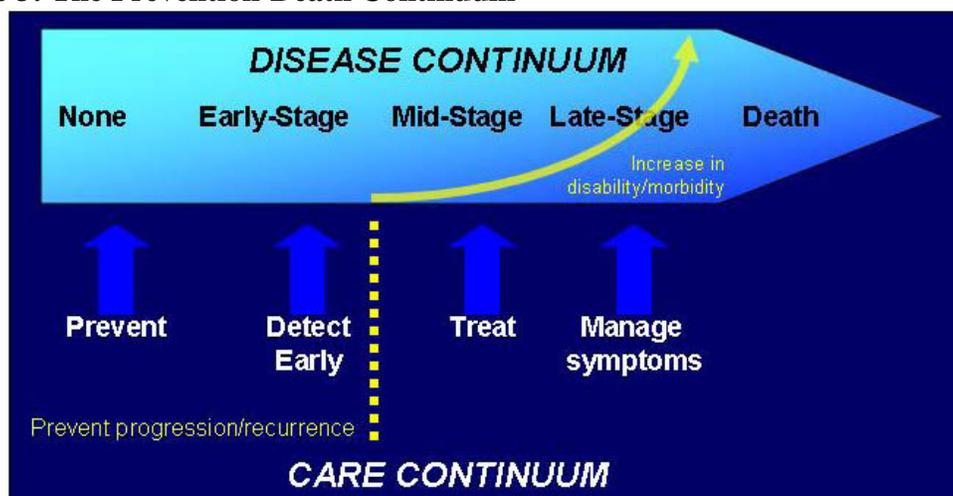
1. New classes of drugs will be subject to scrutiny.
2. "Pre-cancer" as a disease to be treated is not a well-established concept. By contrast, hypertension and hyperlipidemia are recognized as conditions that increase the risk of cardiovascular events such as heart attack and stroke.
3. Newly developed agents might be expensive (although new, preventive uses for older agents may be less expensive).
4. Proof for formulary inclusion process will likely be based on new science, such as using biomarkers for determining indications, and this new science may delay both FDA and formulary approval.

*Because indications for taking chemopreventive agents are likely to be determined by biomarker measures involving, for example, new laboratory blood tests, insurers will not be able to examine historical claims data to readily estimate the population of beneficiaries whom could benefit from the therapy. However, payers can examine the costs incurred by caring for the population who developed that particular cancer for which the agent is intended, model the cost of new treatment options, and consider the potential for cost reduction in preventing the disease rather than treating the disease.*

### **Prevention: An Overview**

Most serious diseases span a prevention-death continuum, creating many opportunities to intervene in the disease process to influence which of several possible endpoints will occur (e.g., mild illness, serious illness, death). Although not always feasible, prevention is often the ideal form of intervention. Effective disease prevention, compared to the treatment of symptomatic disease, reduces pain and suffering, and in some cases, may avert healthcare costs.

Many diseases can be effectively prevented through lifestyle changes (for example, changes in diet or exercise), medication, or surgery (Figure 3 and Table 1).

**Figure 3: The Prevention-Death Continuum**

For the purpose of discussion, preventive interventions have been classified below into one or more of 3 levels. By avoiding the terms “primary prevention” or “secondary prevention,” debate over these meanings that differ across diseases or conditions is avoided.

**Table 1: Preventive Interventions**

Level	Conceptual Definition	Examples
1	Traditional public health measures	<ul style="list-style-type: none"> <li>▪ Not smoking</li> <li>▪ Routine vaccinations</li> <li>▪ Washing hands</li> <li>▪ Exercise</li> <li>▪ Healthy diet, weigh control</li> </ul>
2	Diagnosed risk for developing disease	<ul style="list-style-type: none"> <li>▪ Treating hypertension among people without apparent cardiovascular disease</li> <li>▪ Treating pre-cancers or people with genetic predisposition, but who do not have cancer</li> </ul>
3	Diagnosed sub-clinical disease or disease	<ul style="list-style-type: none"> <li>▪ Aggressively lowering cholesterol or blood pressure in a person who has had a heart attack</li> <li>▪ Preventing or delaying reoccurrence of cancer after treatment e.g. long-term Tamoxifen therapy</li> </ul>

## Therapeutic Analogies that are Now Covered

Preventive interventions pertaining to cardiovascular disease, heart disease, and strokes provide illustrative examples of coverage by commercial insurers. These analogies are helpful in understanding the relevance to gaining insurance coverage for chemopreventive agents in the future.

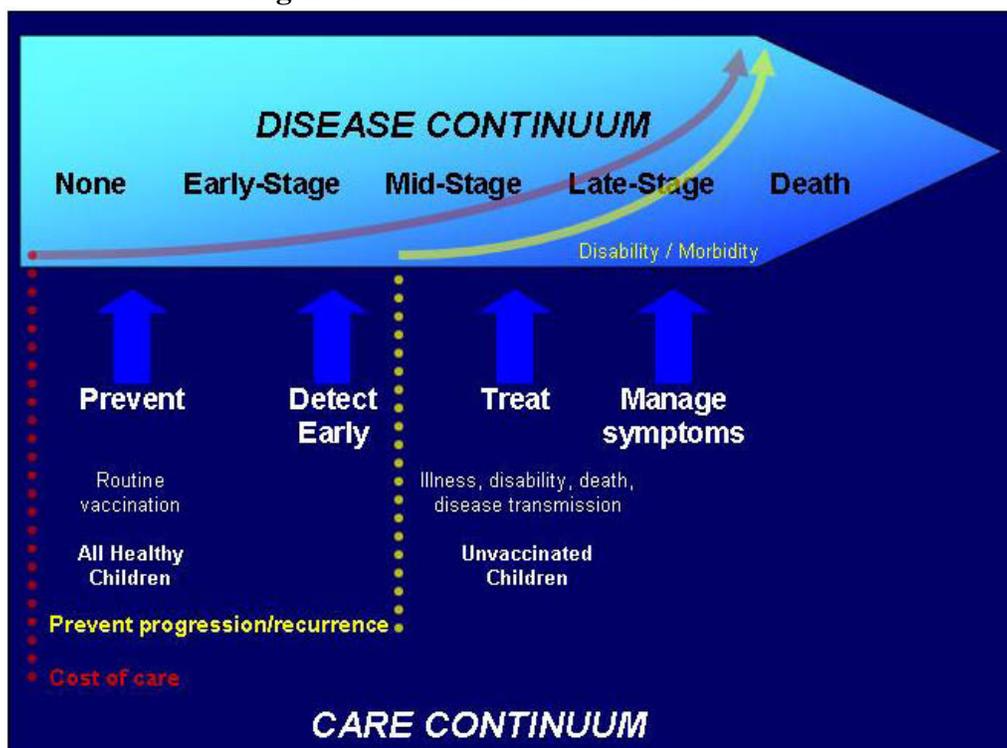
## Common Preventive Agents: Case-Studies

### Vaccines

Classical vaccines *prevent* individuals from developing specific infectious diseases such as measles, polio, and influenza. Vaccination also protects communities from disease outbreaks by reducing the number of individuals in a given area who are susceptible to communicable diseases (21,22).

Nearly all comprehensive commercial health benefit plans provide coverage for immunizations. Vaccine programs reduce disease outbreaks and healthcare costs associated with vaccine-preventable diseases (22). Routine childhood vaccination saves nearly \$10 billion in direct medical costs and \$43 billion in societal costs for every birth cohort (all children born in one year) by preventing at least 13.6 million cases of disease and 33,000 deaths (23). Certain vaccines lead to a substantial and immediate reduction in medical spending. For example, in 1995, a vaccine to protect children against varicella (chickenpox) was introduced. The widespread use of this vaccine reduced varicella-related healthcare costs by 75% between 1994 (when costs totaled \$85 million) and 2002 (when costs totaled \$22.1 million) (23).

**Figure 4: Vaccine-Preventable Disease**



### *Cardiovascular Disease*

The American Heart Association estimates that more than 70 million women and men in the United States have some form of cardiovascular disease and 927,000 die of the disease every year (24). Heart disease and stroke, the major forms of cardiovascular disease, account for nearly 38% of all reported deaths in the United States (24).

The association between hypertension (HTN), hyperlipidemia, and cardiovascular disease events (e.g., heart attacks and strokes) was established by the Framingham Study. Reducing lipids and blood pressure to normal levels has been proven to reduce cardiovascular events. In fact, several large studies have found that patients who take cholesterol-lowering drugs for 5 to 7 years can decrease their risk of heart disease by about 30% (25). Similarly, clinical trials have shown that antihypertensive medications can reduce the mean incidence of stroke (by 35% to 40%), heart attack (by 20% to 25%), and heart failure (by up to 50%) (26, 27, 28).

Because hypertension and hyperlipidemia are diseases in themselves, blood pressure and lipid medicines are considered both preventive medications *and* treatments. Furthermore, hypertension and hyperlipidemia treatments are also used to prevent subsequent cardiovascular events in people who have already had cardiovascular events. Devices such as pacemakers and stents can also be considered preventive because they have been proven to prevent cardiovascular disease events (e.g., heart attacks). However, because these devices do not actually *prevent* disease, they are level 3 prevention interventions: they reduce the amount of morbidity or disability caused by an existing disease.

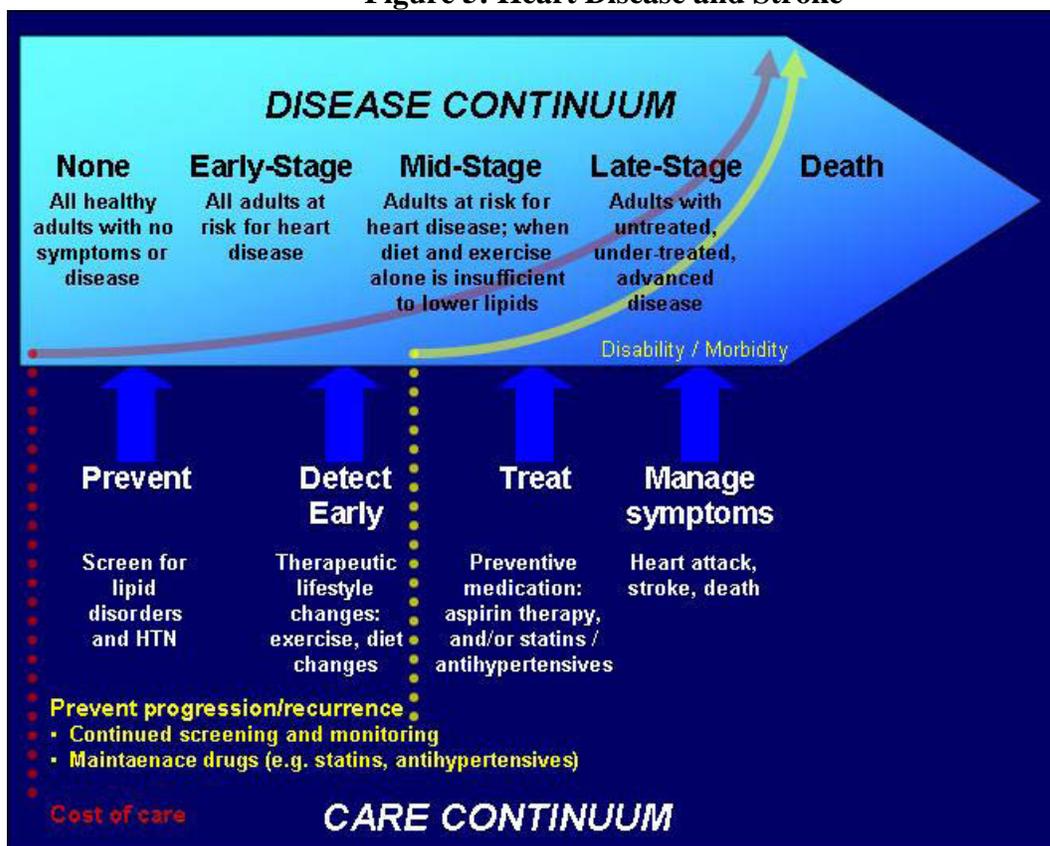
Typically, health benefit plans provide coverage for the level 2 and level 3 prevention and treatment of heart disease and stroke. Covered preventive interventions include statins and antihypertensive medications; devices; and preventive surgeries, such as valve replacements.

Hypertension screening is low cost on an individual level. Interestingly, no study has evaluated the cost-effectiveness of population-wide screening for hypertension. Nevertheless, as a result of its low cost and favorable efficacy and safety profile, treatment of hypertension is highly cost-effective, ranging from \$10,000/QALY - \$27,000/QALY for persons with diastolic blood pressures of 110mm Hg and higher (26). In fact, controlling blood pressure with medications is one of the most cost-effective methods of reducing premature cardiovascular morbidity and mortality(29,30) Antihypertensive medications have also been proven to increase life expectancy (31).

In 2002, the National Cholesterol Education Program (NCEP) panel analyzed the costs and benefits of lipid-lowering drugs and found that, based on current retail prices, low-density lipoprotein-lowering drug therapy is *highly cost-effective* for persons with established coronary heart disease (including a prior coronary heart disease event); *cost-effective* for the “primary” prevention of coronary heart disease in persons with a coronary heart disease risk equivalent (the person does not have coronary heart disease but does have an absolute 10-year risk of developing major coronary events, such as myocardial infarction and coronary death, equal to that of persons with coronary heart disease), and those at high risk for coronary heart disease; and *acceptable* for

the primary prevention of coronary heart disease in persons whose 10-year risk of “hard coronary heart disease” (heart attack and death from coronary heart disease) is between 10% and 20% (31).

**Figure 5: Heart Disease and Stroke**



**Table 2: Common Preventive Agents**

Disease/Conditions Prevented	Type of Prevention	Intervention	Cost-Effectiveness
<b>Vaccine-Preventable Disease (e.g., influenza, measles)</b>			
	Level 1	Vaccination	All cost-effective, many cost-saving
<b>Cardiovascular Disease</b>			
<b>Heart Attack</b>	Levels 2 & 3	Aspirin therapy	Cost-saving
<b>Atherosclerosis, Arteriosclerosis, Coronary Heart Disease</b>	Levels 2 & 3	Therapeutic lifestyle changes; lipid lowering medications	Cost-effective
<b>Stroke, Heart Attack, Coronary Heart Disease</b>	Levels 2 & 3	Therapeutic lifestyle changes; antihypertensive medications	Cost-effective

### Chemoprevention: How and Why it Works

Chemopreventive agents are medications that prevent cancer by limiting the initiation, promotion, and/or progression of carcinogenesis. They may work by inactivating carcinogens in the body, inducing enzymes, or providing needed antioxidants. Chemopreventive agents can also inhibit tumor growth by acting as suppressors or stimulating apoptosis (cell death) (32).

Chemopreventive agents can be Level 1, 2, or 3: some agents prevent the onset of disease (e.g., the HPV vaccine *prevents* cervical cancer), others may prevent the disease in high-risk people (e.g., tamoxifen) or the recurrence of disease (e.g., tamoxifen).

**Table 3 : Chemopreventive Agents**

Disease/Conditions Prevented	Type of Prevention	Intervention	Cost-Effectiveness
<b>Cancer</b>			
<b>Breast Cancer</b>	Level 2 (when used to prevent cancer in high-risk women); Level 3 (when used to prevent recurrence)	Tamoxifen	Cost-effective
<b>Cervical Cancer</b>	Level 1	HPV vaccine	Cost-effective
<b>Potential Others</b>	?	?	?

### Chemopreventive Agents: Case-Studies

#### *Breast Cancer*

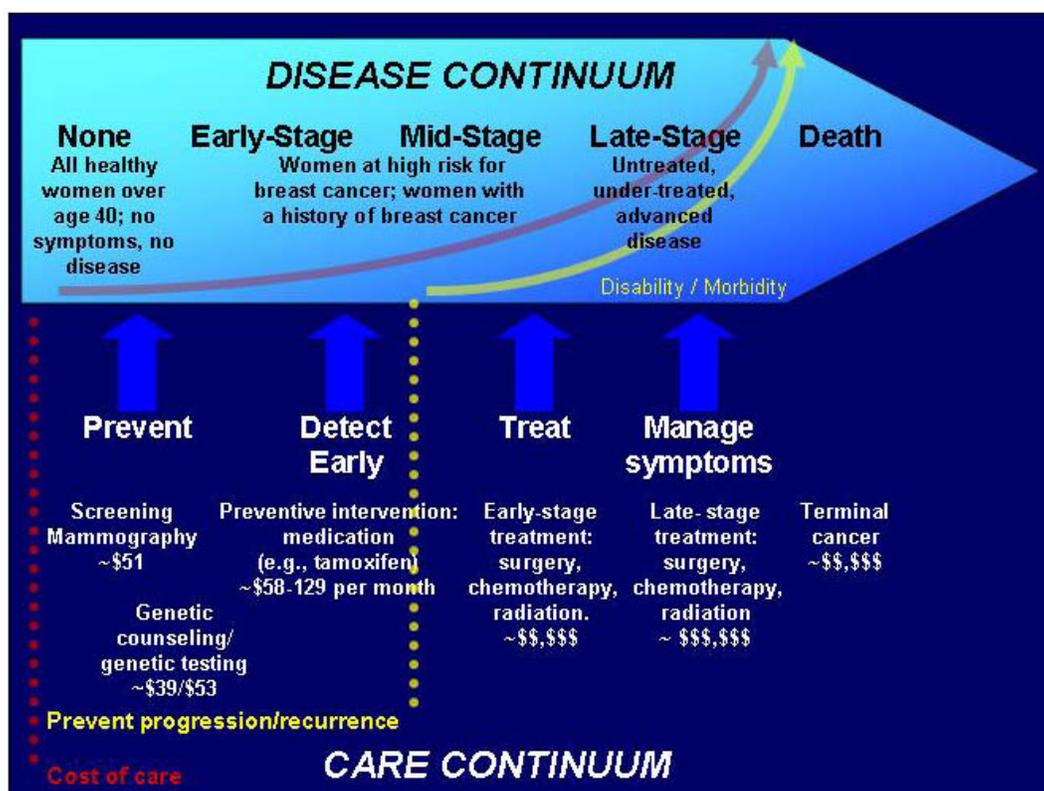
Tamoxifen is the targeted hormonal therapy studied and prescribed the longest for breast cancers testing positive for estrogen receptors. Tamoxifen can be used to treat breast cancer; it can also be used to prevent recurrence. As a treatment for breast cancer, tamoxifen slows or stops the growth of cancer cells. As a preventive or adjuvant therapy, tamoxifen helps to prevent the original breast cancer from returning and also helps to prevent new cancers from developing in the other breast.

The Early Breast Cancer Trialists' Cooperative Group has been conducting scheduled worldwide meta-analyses from randomized trials for the treatment of early breast cancer since 1985(33). The 2000 meta-analysis demonstrated that among women with estrogen-positive breast cancer (the most common form) 5 years of tamoxifen therapy, irrespective of the use of chemotherapy and of patient age, reduced the annual recurrence rate by half and breast cancer mortality by a third (34). Most of the effect on recurrence was during the 5 year treatment phase of tamoxifen. However, the protective effect of tamoxifen against mortality persisted at the 15 year analysis, and the cumulative reduction in mortality at 15 years was twice that at 5 years.

Recently, another targeted therapy, trastuzumab, has emerged as an adjuvant therapy for specific breast cancers that over-expressing HER2/neu and as a preventive intervention. Two NCI sponsored trials, NSABP 31 and NCCTG 9831(35) and an international multicenter trial(36) studied the preventive properties of trastuzumab. When given after primary therapy, trastuzumab reduced the rate of recurrence, particularly distant recurrence, by approximately 50%.

Tamoxifen is a moderately cost-effective intervention for women aged 35 to 50 years who are at significant risk for breast cancer based on family or personal history (37). Among women who begin taking the medication at age 35, the approximate cost of tamoxifen therapy is \$46,619 per life-year saved (38). For women over the age of 50, chemopreventive therapy costs more than \$50,000 per life-year saved (39).

**Figure 6: Breast Cancer Prevention**



Cost Estimate Source: Thomson Medstat. Marketscan, 2004.

### Comparison Statement

*Lessons from cardiovascular and vaccine-preventable diseases can be applied to cancer, specifically preventive oncology. Like vaccines, chemopreventive agents can be given to a disease-free individual to prevent him/her from developing a specific disease in the future. Like statins and antihypertensive medications, chemopreventive agents can also lower a patient's risk of a negative outcome (e.g, disease, death). Finally, like a pacemaker or aspirin therapy, chemopreventive agents can prevent the recurrence of a negative event (heart attack or cancer, respectively).*

### **Cost and Cost-Effectiveness of Preventive Interventions**

*For any disease, the economic value of a preventive intervention is largely a function of the effectiveness of the intervention, its cost, patient compliance, and the impact of side effects both on the cost and long-term outcomes. A health intervention is considered “cost-effective” when the intervention provides a health benefit (e.g., improved quality of life) at an acceptable cost. In the United States, there is no generally agreed upon cost-effectiveness ceiling; however, it is commonly said that interventions that cost more than \$50,000 or \$100,000 per quality-adjusted life year are not cost-effective (40).*

As stated above, vaccines are generally cost-effective and some are even cost-saving. Antihypertensive medications and lipid-lowering drugs are also cost-effective in most populations. Tamoxifen, a chemopreventive agent that prevents breast cancer and breast cancer recurrence, is moderately cost-effective for high-risk women aged 35-50.

Several other chemopreventive agents are likely to become available in the next decade. The cost-effectiveness of these future interventions is unclear. *By supplementing clinical trial design with additional financial data, researchers would be able to complement their clinical efficacy and safety outcomes with utilization or economic data or outcomes. As a result, payers could more easily and fully consider the value of these new agents.*

### **Coverage Challenges**

*As noted in the sections above, insurance coverage is common for interventions (medications, devices, surgeries, immunizations) that can prevent cardiovascular events, vaccine-preventable diseases, and many other conditions. Chemopreventive agents are similar in many respects to other types of preventive agents; however, except for level 3 interventions, they are less likely to be covered in health benefit plans. This coverage differential is a result of several factors. First, chemopreventive agents are new. New interventions, specifically new drug classes, are subject to scrutiny due to safety, cost, and resource allocation concerns. Second, chemopreventive agents may be more expensive than other current preventive agents. Third, the practice of healthcare purchasers paying to prevent a disease that may or may not occur in the future, other than vaccines for infectious diseases, is innovative and not yet universal. Despite these challenges, chemopreventive agents show great promise. New agents will prolong life, reduce suffering, and shift healthcare dollars from treatment to prevention. Most patients and payers would, if given effective choices, agree that paying to *prevent* cancer is preferable to paying to *treat* cancer.*

## VI. Primer: Methods for Valuing Healthcare

National leaders have repeatedly identified the US healthcare system's high cost, poor quality, and lack of insurance coverage as a crisis (41). These observations raise significant concerns over the real value of our healthcare system. Agreement is nearly unanimous that evidence-based medicine is part of the solution.

Chemoprevention agents will likely face the same evidence-based jury as other kinds of care. Because of political inertia and the difficulty of quickly changing existing medical practice patterns (42), new medical services and products are likely to face scrutiny before existing ones. Services and products that demonstrate better value, whether new or existing, should more likely receive coverage by payers, but inertia is a barrier to such coverage change. The concept of value in healthcare is not new, but today's emphasis on cost and evidence-based medicine gives strong competitive advantages to high-value interventions.

Converting evidence-based medicine into value is difficult, partly because the definition of value differs across individuals and organizations and sectors. Numerous, evolving methods exist to measure healthcare value, several of which are described in Figure 7. *The concept of a value-based decision, rather than just a cost-based decision is probably more important than a particular metric or formula chosen to calculate value. Advocates and payers would be well served by considering value measures to compare cancer chemoprevention to other kinds of treatment for which we currently or could potentially provide insurance coverage.*

### Value and Spending

Healthcare spending reflects millions of decisions by payers, providers, and consumers. Value varies with organizations' or individuals' interests. For example:

1. An employer may consider the direct employee benefit costs such as medical expenses, life insurance, and disability income, as well as potential health affects on worker productivity, retention, or union relations.
2. A hospital may consider whether a particular service will increase its revenue or decrease its supply or labor costs.
3. An individual may view value from the standpoint of convenience, comfort, longevity, or social role.
4. A political entity may decide on value by considering an issue's popularity or the persuasiveness of lobbyists.

Because both medical care and the broader economy are changing so rapidly, trying to quantify value that a particular medical intervention brings will always be a moving target.

The health cost crisis means that comparative value no longer means just comparing two different therapies for a particular disease state. It can mean comparing spending on chemoprevention for patients at risk for breast cancer to spending on an entirely different condition, for example, physical therapy visits for a patient with advanced Alzheimer's disease.

A number of variables can be considered when comparing the value of various choices in healthcare including:

- Scope: Does the intervention or condition affect few people or many?
- Severity: Is the condition devastating or merely an inconvenience?
- Practicality: Is it possible or practical for the healthcare system to deliver the intervention within existing or feasible skill-sets or infrastructure?
- Timeframe: How long will the therapy continue? How long will the effects last?
- Hard or soft costs: What are the direct medical costs? What are the indirect costs such as effects on productivity (absenteeism and presenteeism) or attendance?
- Cost “elasticity”: Are these cost implications susceptible to the influence of regulatory changes, consumer demand, competition, or collective purchasing power?

*These variables will have greater or less value and/or significance when considering the recipient of the value - employer, patient, family, provider, supplier, government, and society.*

### **Measures of Value in Healthcare**

Common notions of healthcare value measures are described in Figure 7. The intent of this figure is to illustrate concepts and differences rather than provide authoritative definitions. Each measure has its strengths and weaknesses as well as different relevance to various stakeholders. Again, the general concept of value is being highlighted, not any particular method or formula (43).

### Methods for Determining Value

The concept of value is a building block in determining comparative cost-effectiveness. The following statement is taken from a Health Care Financing and Organization newsletter.

“Comparative effectiveness and cost-effectiveness may not generate cost-savings. If a prevalent, cost-effective technology or service is used by a large number of people, the financial impact may be greater than a less cost-effective technology. These strategies, however, may assist policymakers with redirecting resources from less effective to more effective medical technologies, which may improve value and control healthcare spending (13).”

- **Value = Combination of High Quality and Low Price**

This formulation appears in a brochure on healthcare transparency by the US Department of Health and Human Services Secretary, Michael Leavitt (44). “Every American should have access to a full range of information about the quality and cost of their healthcare options.” While this formula does not lend itself to quantification, it is the conceptual basis for many of the attempts to quantify value. This concept is sometimes presented as the slightly more mathematical,  $\text{Value} = \text{Quality} / \text{Cost}$ .

- **Value = Price**
- **Value = Cost**

The idea that value is equal to the price of a service or the cost of a service is rarely explicitly stated. The “contribution” of healthcare to the Gross Domestic Product (currently at 16%) is tabulated as the sum of healthcare spending, which is valued at the actual prices paid. The “value = price” concept is often criticized by advocates and provides as part of arguments that reimbursement is inadequate and should increase.

- **Life years gained**

This measure is simply a measure of the extension of life through some intervention. This does not take into account the quality of life during the extra lifetime.

- **Quality Adjusted Life Years (QALY)**

Quality Adjusted Life Years attempt to capture both the quantity and quality of life produced by a particular healthcare intervention. One QALY equals a year of perfect health, which is the product of 1 year and a quality of life of 1.0. Living a year with less than perfect health is less than 1.0 QALY, because it is the product of 1 year and a quality of life of less than 1.0. Death has a quality of 0, and some health states could be considered to have quality of life worse than death and have negative scores (45). The subjective nature of determining quality of life scores is a weakness of this method. Another complexity arises when considering quality of life scores relative to age - a scoring system that is appropriate for seniors may not be appropriate for children.

(continued)

**Methods for Determining Value**

○ **Disability Adjusted Life Years (DALYs)**

Disability-Adjusted Live-Years is a measure of both the years lost life from premature death and the years lost to disability (46). While longer QALYs represent success, longer DALYs represent a gap. As with QALYs, DALYs rely on subjective quality values of different disabilities that may be open to criticism.

○ **Cost-Effectiveness**

Cost-effectiveness involves comparing the costs and outcomes of different interventions. Return-on-Investment (see below) is a simple measure of cost-effectiveness.

Cost-effectiveness comparisons in healthcare often use cost utility ratios. Cost-utility ratios based on QALYs are the additional costs required to generate one QALY. For example, if a \$100,000 intervention adds 2 QALYs to an individual, the cost-utility ratio is \$50,000 per QALY. One way to compare the value of different interventions is to consider interventions that are low cost per QALY as superior to those that are higher cost per QALY (47, 13).

○ **Return on Investment (ROI)**

Return on Investment is a simple ratio of the cost of an intervention to the cost or cost-savings generated by the intervention. This method is popular among vendors of disease management services (48) and other vendors to payers. ROI is not widely used in financial markets or investment decision-making because it does not allow for easy scale comparisons (size of the population affected, aggregate spending, etc.), does not include considerations of the time value of money or inflation, and does not consider risk or the return on alternative investments.

○ **Actuarial value**

Actuarial value typically produces dollar estimates of value to evaluate benefit programs such as Medicare, Medicaid, employer-sponsored programs, or other insurance type programs. The evaluation may consider payer cost, beneficiary cost, or both. Typically, this method uses models that include service-level utilization and unit cost along with cost-sharing and administrative costs. Time horizons can be short- or long-term. Multi-year projections consider the time value of money along with inflation. The following table is an example of output from an actuarial value approach:

Potential Trade-Offs to Pay for Increased Screening (49)

<b>Health Benefit Decision</b>	<b>Typical Range of Cost or Savings (estimated 2006 PMPM)*</b>
Cost of coverage for chiropractic services	\$1.35 to \$4.00
Increase generic utilization by 10%	\$2.65 to \$3.05
Reduce inpatient days/1,000 by 20 days thru improved medical management	\$3.60 to \$8.00

\*The ranges reflect differences in national average reimbursement. Actual costs may vary depending on reimbursement, utilization, benefit limits and cost sharing

## VII. Call for Collaboration and Action

As noted in the Foreword, the field of cancer chemoprevention faces numerous barriers to unleashing its potential, namely uncertain reimbursement for new agents; limitations in current patent law and intellectual property (IP) protection; emerging science and an uncharted clinical trial design and drug approval processes. C-Change has engaged numerous experts and leaders to address these complex and interrelated issues by contemplating and proposing solutions for action. In all cases, the solutions to each of these complex and interrelated issues will require cooperation. No one organization or sector can resolve these barriers. With regard to the uncertainty of reimbursement, C-Change recommends the following action and calls upon the collaborative spirit of key leaders to move forward:

- Scientists developing chemopreventive agents should complement their clinical trial findings regarding agent safety and efficacy with data regarding treatment costs. With additional data, payers and other entities could more easily consider the value of treatment with chemopreventive agents that may (or may not) appear costly per dose and lengthy in treatment, but could be cost-effective in comparison to cancer treatment.
- Payers considering insurance benefit coverage for chemopreventive agents should consider avoided cancer treatment costs as part of their value assessment. Without a longer-term vision of cancer costs, the healthcare system will become increasingly unaffordable. Investing more in cost-effective prevention will pay off in lower treatment costs in the future.
- The cancer community should advocate for the inclusion of evidence-based cancer prevention and treatment interventions and the exclusion of interventions not supported by evidence in payment decisions.
- The advocacy community should promote inclusion of evidence-based treatments and exclusion of treatments not supported by evidence in payment decisions for all diseases to ensure the best health quality, value and outcomes for the Nation.
- The advocacy, payer, and healthcare communities should collaborate on decisions to eliminate wasteful spending on treatments and practices not supported or contraindicated by evidence.

With more complex and personalized emerging science come more complex decisions. If the Nation desires more effective treatments, leaders must make difficult choices to create room for new options by moving beyond the limitations of historical decision-making processes. The healthcare economy can not be sustained and health goals will not be met if the traditional course of reimbursement decisions is maintained. Most importantly, the promise of chemopreventive agents will be lost if we do not find a way to support their innovation and delivery.

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