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Special Workshop Report

Cancer Chemoprevention and Cancer Preventive Vaccines—A Call to Action: Leaders of Diverse Stakeholder Groups Present Strategies for Overcoming Multiple Barriers to Meet an Urgent Need

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Abstract

The emerging field of cancer prevention through chemoprevention agents and cancer vaccines offers significant promise for reducing suffering and death from cancer. However, that promise may not be kept unless major barriers to progress are lowered or eliminated. Among the most significant barriers are the relatively small investment from government and industry in research and development of cancer preventive agents; a predominant emphasis of translational cancer research on therapeutic interventions for metastatic or advanced cancer; complexities of prevention trial design; a relatively uncharted Food and Drug Administration (FDA) approval process for preventive agents; insufficient public and patient understanding of the importance and potential for cancer preventive measures, with consequent unpredictable public and patient willingness to take preventive agents; an uncertain reimbursement from payors; and limitations in patent law, liability protection, and data package exclusivity that undermine the opportunity for recouping investment. Viewed individually or collectively, each of these barriers serves as a substantial deterrent to intellectual and financial investment by all sectors of the cancer community. In an effort to ultimately overcome these barriers, a Cancer Prevention Research Summit was assembled June 12–13, 2006 in Bethesda, Maryland, organized by C-Change with support from the AACR. The Summit brought together some 120 leaders from private, public, and not-for-profit entities, including cancer researchers and clinicians; federal health officials; regulatory agency representatives; pharmaceutical, biotech, and food industry leaders; patent attorneys; economists; public and private provider group executives; and advocates. Participants engaged in a detailed process to more carefully define the major barriers, identify potential solutions, and formulate initial priorities and recommendations for action. At the conclusion of this dialogue among experts, the following recommended actions were outlined: define policy solutions to patent, intellectual property, and liability law barriers; create an advisory document about the approval process for cancer chemopreventive agents and vaccines for the FDA; develop new design models for cancer chemopreventive clinical trials; outline the business case for chemopreventive agents and vaccines for federal research agencies, payors and investors; and implement a communications strategy to increase public awareness about the importance of chemoprevention and cancer preventive vaccines. (Cancer Res 2006; 66(24): 11540-9)

Introduction

If cancer is like a weed that runs wild at the expense of others, then it is best to destroy its seeds before they have a chance to take root, grow, and spread. Such is the sentiment of a growing cadre of cancer researchers who fervently believe that attacking precancerous cells before they develop into tumors is a highly promising way to reduce incidence and deaths from this disease.

Part of this sentiment comes from the realization that no strategy for defeating cancer can be complete without a concerted effort in cancer prevention. Health officials already recognize that lifestyle and behavior modifications alone would significantly alter grim cancer statistics. It is estimated that two of every three of the 564,830 cancer deaths expected to occur in the U.S. in 2006 could be prevented through changes in diet, physical activity, and tobacco use (1).

Researchers also are spurred by insights gathered over the past couple of decades into the initiation, growth, and spread of cancer, and how this new knowledge is presenting ways to preemptively eliminate cells that are destined to become cancer. As a result, the field of "cancer chemoprevention"—so named in 1976 by Michael B. Sporn, M.D. (2), Professor in Residence of Pharmacology and Toxicology at the Norris Cotton Cancer Center at Dartmouth Medical School (Lebanon, New Hampshire) is being viewed as a rational and appealing strategy for stemming the tide against this disease. In studies ranging from basic to the clinical, scientists are investigating a growing menu of potential chemopreventive drugs and vaccines, including agents or natural substances that inhibit signal transduction pathways, block the activity of oncogenes, control inflammation, thwart oxidation, and prevent cancer-causing viral or bacterial infection.

The field was placed under the spotlight recently when the FDA approved the use of Gardasil, a vaccine manufactured by Merck, to prevent infection from human papillomaviruses (HPV), a leading cause of virus-associated cervical cancer. In patient studies, the vaccine was 89% effective in preventing infection from the four

Note: C-Change is a 501(c)(3) organization of the top leaders from public, private, and nonprofit organizations, formed to leverage the expertise and resources of the C-Change membership to eliminate cancer as a public health problem at the earliest possible time. The organization convenes multisector leaders in the world of cancer to accelerate and focus the cancer agenda. For more information about C-Change, visit http://www.cchangetogether.org or contact telephone no. 202-765-1600.

For more information about AACR, visit http://www.aacr.org or contact telephone no. 215-440-9300.

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most common strains of sexually transmitted HPV, and 100% effective in preventing precancerous lesions or genital warts. Cervical cancer kills approximately 3,900 women in the U.S. each year and nearly 300,000 worldwide (3).

This major advance not only underscored the potential of chemoprevention but also brought home what is generally conceded as slow progress in this field. At a time when many individuals at high risk for heart disease and stroke are routinely taking statins and baby aspirin to reduce disease risk, and a variety of medications are being prescribed for high blood pressure, similar drugs that could prevent cancer on this scale are still a long way off; in fact, few are even being discovered or developed.

Indeed, many fret over a myriad of real and perceived hurdles that are impeding progress (see Fig. 1). These barriers include a starting point with a relatively slowly evolving body of scientific knowledge and formative infrastructure supporting prevention trial design and implementation; FDA regulations and recent public concerns about safety that make it difficult to approve chemopreventive agents; lack of public understanding about the benefits of cancer prevention strategies; procedures and policies by public and private payors that limit payment for potential chemopreventive agents relative to therapeutic agents; and limitations in patent law that compress the window for investment recovery. As a result, the field has experienced limited investments in discovery and development by the federal government as well as pharmaceutical and biotechnology companies.

To find ways to overcome many of these hurdles, an interdisciplinary and multisector group of approximately 120 participants, including cancer researchers and clinicians; federal health officials; regulatory agency representatives; pharmaceutical, biotech, and food industry leaders; patent attorneys; economists; public and private provider group executives; and advocates met June 12–13, 2006 in Bethesda, Maryland, at a "Cancer Prevention Research Summit," organized by C-Change with support from the AACR.

The Summit was chaired by Ronald B. Herberman, M.D., Director of the University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania, who described the event as "an opportunity to reveal the overall potential of cancer prevention and, in particular, its great potential to impact on the societal and economic burden of cancer."

He added that with the additional focus and attention on chemoprevention agents and vaccines, and the recommended actions for facilitating progress in this field that results from the Summit, we have the opportunity to impact the "current paucity of effective and available preventive agents resulting from a limited investment in discovery and development by the National Cancer Institute (NCI) and [the pharmaceutical industry]."

"The lack of investment stands in contrast to the concerted translation of the rapidly expanding knowledge base about the causes for development and progression of cancer, into the emerging promise of molecularly targeted therapeutics," he continued. "The same knowledge base being applied for discovery and development of cancer treatment agents could be just as well applied to the discovery and development of agents that interfere with molecular events that lead to the development of full-blown cancer."

"Indeed, the boundaries between chemoprevention and targeted chemotherapy are merging, with the realistic expectation that discoveries in both arenas will further accelerate the field for the ultimate benefit of the patient."

To address the most complex and significant barriers to cancer prevention research, Summit participants were divided among four panels. Each panel was led by an expert in the field and was charged with the task of defining the overall barriers in more specific terms and identifying feasible and effective strategies to overcome the identified barriers:

- Scientific and regulatory barriers affecting preventive agent development from early trial design to FDA approval, chaired by Scott M. Lippman, M.D., Chair, Clinical Cancer Prevention, M.D. Anderson Cancer Center, Houston, Texas
- Patient and public perception barriers affecting clinical trial participation and drug compliance, chaired by David S. Alberts, M.D., Director, Arizona Cancer Center, Tucson, Arizona
- Insurance policy and practice barriers affecting reimbursement of prevention agents, chaired by Bruce S. Pyenson, Fellow, Society of Actuaries; Member, American Academy of Actuaries; Principal & Consulting Actuary, Milliman, Inc., New York, New York
- Intellectual property and patent law barriers affecting research and development as well as investment recovery, chaired by Homer L. Pearce, Ph.D., Distinguished Research Fellow (Retired), Eli Lilly and Company, Indianapolis, Indiana.

Assessment of Barriers and Potential Solutions

As a first step in their discussions, each panel was asked to identify major barriers that must be overcome if chemoprevention for cancer is to be accelerated. As a second step in their discussions,

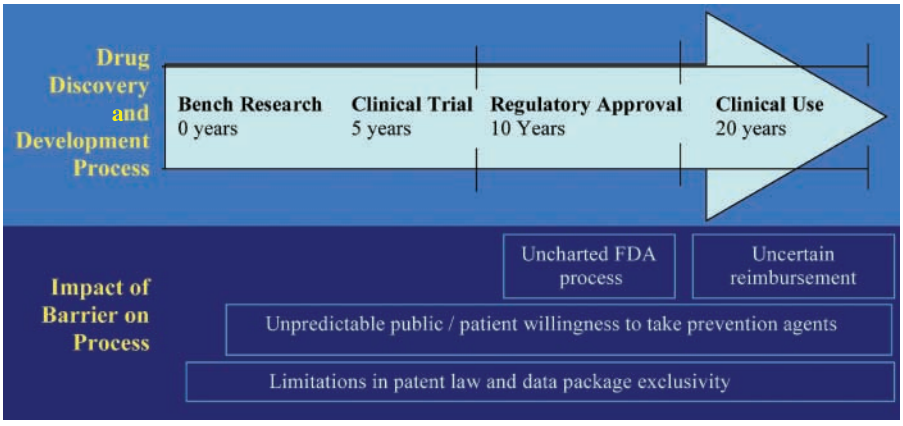

Figure 1. Impact of major barriers on the cancer prevention drug discovery and development process. Net impact: Multiple barriers create a risky environment for the investment of intellectual effort and capital for uncertain return on investment.

each panel was asked to identify potential solutions to the barriers cited in the section above. To summarize the extensive discussions within each topic area, tables are presented in this report that outline the main respective barriers and solutions. Priority recommended actions are summarized at the conclusion of this report.

Scientific and regulatory barriers affecting preventive agent development from early trial design to FDA approval. Turning a normal cell into cancer generally involves a series of biological processes that often takes years, or even decades, from the first event to invasive disease. As commonly outlined, accumulating mutations and loss of cellular control functions cause progressive phenotypic changes from normal histology to early precancer and then cancer [e.g., the progression from intraepithelial neoplasia (IEN) to increasingly severe IEN to superficial cancer to full-fledged tumor growth and then subsequent metastatic spread]. In a 2002 report, an AACR IEN Task Force recommended focusing chemoprevention drug development on IEN because of the close relationship between IEN and invasive epithelial cancer and because reducing IEN burden reduces cancer risk and/or need for interventions. The report suggested that new and accumulating knowledge into the molecular progression of carcinogenesis was providing an opportunity to develop early biomarkers that would signal early cancers (4).

Although several biomarkers have been identified—such as adenomatous polyps for colorectal cancer, prostatic IEN for prostate cancer, oral premalignant lesion for head and neck squamous cell carcinoma, and cervical intraepithelial lesion for cervical cancer, among others—the search for biomarkers that signal precancer and serve as targets for chemopreventive agents has moved slowly.

Because chemopreventive drugs and vaccines would be offered to patients who seem to be otherwise healthy, the need to find biomarkers that provide an early warning signal about potential adverse effects also is critical. Indeed, the recent experience with Vioxx and some other cyclooxygenase-2 inhibitors put the spotlight on the need for biomarkers for possible toxicity that might be associated with long-term use of chemopreventive agents.

Issues such as these offer a glimpse into the complexity of chemoprevention not only for scientists in the field but also for those in the public arena. For instance, the FDA approval process was created to evaluate drugs for treatment purposes, rather than preventive purposes, regardless of whether agents are being recycled from existing therapeutic drugs or new chemicals emerging from the laboratory. Further, limited federal funds directed to the FDA and NCI have not been allocated in a way that supports chemoprevention as a priority. In addition to underfueling the engine for the advancement of knowledge, these funding shortfalls limit the opportunity to attract and retain researchers, eroding the number of young investigators who might enter this emerging field. Indeed, reduced federal funding threatens to decrease the number of scientists wishing to pursue careers in all areas of cancer research. The pharmaceutical industry is also reluctant to invest heavily in chemoprevention for cancer until legal, regulatory, liability, and reimbursement issues are resolved (as stated earlier in this report).

Clinical trials for cancer chemopreventive agents, by their nature, require many years to complete, are costly, and demand the participation of large numbers of patients. However, the public at large, including those who would be asked to participate in clinical trials, has little knowledge or understanding about the field of chemoprevention for cancer, compared with the widespread public understanding about similar efforts to combat heart disease (see Recommended Solutions to Participation in Clinical Research Studies of Cancer Preventive or Risk-Reducing Agents). Today, many otherwise healthy people are taking statins to lower their cholesterol, medication to control blood pressure, and even baby aspirin to reduce clot-forming plaques in their blood vessels. A similar public campaign to underscore the benefits of chemoprevention for cancer is mired in debate, whereas researchers and regulators alike seek to unravel a complicated web of issues surrounding risks and benefits.

Scientific and regulatory barriers to prevention research

Limitations of science and practice
- Complexity of disease(s)
- Discovery and development of new agents (versus recycling of therapeutic drugs)
- Few dedicated tissue banks for precancerous tissue
- Compartmentalization of diseases, scientists, and agencies
- Limited number of cancer prevention trial results, and very few with results indicating strong evidence of success
- FDA approval process geared toward treatment
- Very limited dissemination of evidence for preventive efficacy into clinical practice
- Shrinking pool of young researchers focused on cancer prevention

Suboptimal prevention trial design and implementation
- Limited availability and compliance of trial participants
- High cost of prevention trials (large size, long duration)
- Limited knowledge about and use of biomarkers and surrogate end points (e.g., proteomics, genomics, imaging) for participant selection, and monitoring for efficacy and for toxicity

Lack of public or private commitment or funding to make development of cancer preventive agents a priority
- Relatively low public funding for prevention or clinical development and approval (e.g., within NCI and FDA)
- Little or no private sector investment by pharmaceutical, nutraceutical, or food companies

Limited public knowledge of relative cancer prevention risks and benefits (see Patient and Public Perception Barriers below for additional details)

Recommended solutions to scientific and regulatory barriers affecting preventive agent development from early trial design to FDA approval. The practice of medicine is entering a new era of "personalized" care, during which a person's individual makeup will influence lifestyle choices, including diet and exercise, and potential treatments when disease strikes. The future already has arrived for some types of tumors such as breast cancer, for example. Selective estrogen receptor modulators such as tamoxifen and raloxifene have been shown to reduce the incidence of breast tumors among women considered at increased risk. Identifying individuals at increased risk for specific tumors, based on their genomic profiles, will offer the best chance to maximize benefit versus risk for chemopreventive agents. Not only will utilization of such genomic information for targeted preventive strategies result in fewer individuals with cancer but it will also help to lower the incidence of toxic side effects, which is critical if the field is to flourish.

Clinical trials for chemopreventive agents will require the adoption of standards for preclinical and clinical trials, including

studies needed to accelerate development of early and specific biomarkers for efficacy and toxicity. The recent report of the 2006 AACR Task Force on Cancer Prevention cited several opportunities to develop such biomarkers involving multiple mechanism-based molecular targets identified over the past 3 years, many associated with a wide spectrum of organ sites. Molecular targets listed in the report include chemicals that identify anti-inflammatory/antioxidants, signal epigenetic modulation, and signal transduction modulation (5). Interestingly, many of these biomarkers coincide with potential treatment targets. As a result, prevention studies to determine end points and optimal doses might be integrated with, and nested within, treatment trials already under way.

It is also important to note that chemopreventive agents may be taken by hundreds of thousands of people over many years, or even decades. Under these circumstances, it is reasonable to expect that there will be some uncommon or rare side effects. Tracking untoward or unexpected reactions through a registry would be important from a public health perspective and to get a better understanding of the agent.

Issues about public policy and education continue to be critical if clinical trials for prevention are to be accelerated. As stated elsewhere in this report, understanding of chemoprevention by the public, primary care providers, and oncologists alike is limited and, as a result, those entrusted with public policy have not placed a high priority on research and development for this field. To strengthen resources for research and development, messages need to be created for the public and care providers about the potential role that chemoprevention can play to significantly reduce incidence and death from cancer. Too often, even relatively sophisticated conversations get bogged down in arcane issues of risk versus benefit. At such times, it might be more beneficial to discuss the relative risks posed by the chemopreventive agent versus the risk of dying from cancer.

Recommended solutions to scientific and regulatory barriers to prevention research

Advance science and define standards
- Promote transdisciplinary collaboration
- Develop personal risk/benefit models
- Standardize tissue acquisition and assays

Improve trial design and role of biomarkers, surrogate end points (efficacy and toxicity), link to NCI Early Detection Research Network
- Better trial participant selection (risk markers)
- Novel designs (e.g., nested prevention end points in treatment trials, integrated phase I)
- Better selection of agents to move from phase II to phase III

Seize new opportunities for collaboration
- Partner with food industry
- Tap emerging body of data from Centers for Medicare and Medicaid Services (CMS)/registry data
- Collaborate with FDA on new effort to define processes for evaluating prevention agents for all diseases
- Submit guidance documents to FDA recommending regulatory evaluation techniques for cancer chemoprevention agents and vaccines

Strengthen policy and resources to make cancer prevention research a priority
- Increase public funding to support prevention research as a priority
- Create incentives for industry to collaborate to overcome label protection and study long-term effects, patent issues, and liability concerns (see Intellectual Property and Patent Law Barriers below for additional details)

Improve public listening/communications (see Patient and Public Perception Barriers below for additional details)

Patient and public perception barriers affecting clinical trial participation and drug or vaccine compliance. Clinical trials are studies in humans of new methods of preventing, detecting, or treating diseases, which are based on promising results in the laboratory. These patient studies provide the only way to know if a new drug or diagnostic or preventive agent is safe and effective for use. It is estimated that approximately 10% of American cancer patients need to enroll in clinical studies if continued progress is to be made against cancer (6). However, only 3% to 5% of the 10.1 million U.S. adults with cancer do so today, mostly in treatment trials. This is in sharp contrast to the 60% participation of children with cancer (7).

Enrolling individuals in clinical studies of chemopreventive agents faces additional challenges, including the inconvenience of participation and potential side effects posed to high-risk individuals who are otherwise healthy. Convincing such individuals to enroll in clinical trials will require considerable educational efforts, even among primary care physicians and oncologists. Some believe that most medical oncologists still do not spend enough time with their patients on prevention-related issues, including the benefits of smoking cessation, diet, and exercise; it is also apparent that a high proportion of medical oncologists and primary health care providers are insufficiently knowledgeable about cancer prevention strategies or agents. Even available agents such as tamoxifen, shown to reduce incidence of breast cancer, are not widely prescribed to patients considered at risk. Unless the full spectrum of health care providers is offered sufficient training in cancer prevention, the field will continue to stagnate and the public will be shortchanged.

Indeed, many members of the general public are not even adequately informed about the latest data to detect or prevent cancer, including the value of screening tests that are widely available for breast, prostate, and colon cancer. Fewer members of the public understand the nature of the slow biological progression that results in cancer; however, many purchase billions of dollars in untested remedies they believe will keep them healthy and cancer-free.

Certain populations from low-income, elderly, racial/ethnic, and rural groups represent the smallest percentage of clinical trial participants, even though this population generally bears a disproportionate burden of cancer incidence and death. According to NCI statistics, approximately 88.6% of patients enrolled in publicly funded cancer clinical trials between January 1, 2003 and June 30, 2005 were Caucasian; the remaining 11.4% were represented by African Americans, Native Americans, Asian/Pacific Islanders, and Latinos. Potential barriers to participation of underserved minorities included mistrust of research and the medical system; lack of awareness of clinical trials; lack of invitation to enroll in such trials; cultural barriers; lack of study design eligibility; cost or lack of insurance; language/linguistic differences; low literacy; and practical obstacles, including transportation to and from a trial (8). Without adequate representation of these populations in clinical trials, including those for chemopreventive agents, researchers cannot learn about

the potential differences among ethnic groups and cannot assure generalization of results across different racial/ethnic lines.

Public and patient participation barriers to prevention research

Barriers to participation in cancer prevention clinical trials
- Insufficient policies and resources
  - Inadequate funding for trials
  - Interference in recruitment efforts due to the Health Insurance Portability and Accountability Act
- Inadequate public understanding about the benefits of cancer prevention
  - Lack of knowledge about the health dangers of precancerous conditions and risk-benefit concepts
  - Lack of sufficient research on cancer risk perception and basic decision-making processes
  - Lack of coordination for an effective national cancer prevention communications strategy
- Inadequate clinical trial design
  - Restricted inclusion and exclusion criteria that exclude a large proportion of relevant populations, especially ethnic minorities and elderly
  - Inadequate implementation plan for rapid progress in chemopreventive trials, including insufficient focus on patients with premalignant lesions, and involvement of academic cancer centers in performance of small, proof-of-concept phase II trials
  - Insufficient research on comorbidities that may affect efficacy and safety of chemopreventive agents
  - Insufficient research on outcome variables (validated, intermediate end point biomarkers) to obtain indications of efficacy before longer-term clinical efficacy and toxicity outcomes

Barriers to compliance with use of proven chemopreventive agents
- Misperceptions by at-risk populations about effective cancer prevention strategies
  - Preference for over-the-counter complementary or alternative medicine agents or strategies
  - Excessive fears of adverse effects based on lack of sufficient knowledge about potential benefits versus risks
  - Distrust of big pharmaceutical companies
- Problems with preventive drug agent or vaccine characteristics and with the required regimen
  - Side effects
  - Inconvenience, especially for chronic daily regimens
  - Forgetfulness or distractions
  - Expense, especially if not adequately reimbursed by payors
- Problems with professional practice patterns
  - Extremely slow adoption of chemoprevention in everyday practice
  - Lack of professional education for providers of care for at-risk populations
- Problems with pharmaceutical company or FDA actions
  - Liability and return on investment concerns limit aggressive implementation of effective marketing
  - Lack of adequate postmarketing surveillance to monitor compliance and clinical outcomes

Recommended solutions to participation in clinical research studies of cancer preventive or risk-reducing agents. A coordinated effort to educate the public and relevant health care providers about the value of cancer preventive strategies and the benefits of participating in clinical trials in cancer prevention needs to be implemented.

Such a program should include efforts to educate the public that cancer is a process, involving multiple steps that often take years or decades to evolve. It is generally believed that the vast majority of people in the U.S. have insufficient knowledge about cancer, with many feeling that one day they are healthy, and the next day they have cancer. Many others purchase unproven "alternative medicines," or follow unproven diets, in hopes of staving off cancer. Such misunderstandings need to be corrected at all levels, including school-based education.

Another part of the problem may stem from the word "prevention" as opposed to "treatment." Many members of the public are more oriented toward the word treatment, and may respond more favorably to messages about treating precancers, rather than preventing cancer. Using the term treatment also might be more acceptable to insurance carriers and regulators as well.

Semantics aside, if the general public understood that such interventions worked, whether they were called cancer preventives or treatments, then they might become more enthusiastic about participating in clinical trials. Past experiences should help in conveying such messages. One such example to follow is the Selenium and Vitamin E Cancer Prevention Trial, which enrolled more than 35,000 men to study the efficacy of selenium and vitamin E to prevent prostate cancer (9).

Because primary health care practitioners are on the front line of most Americans' care, this group needs to become sufficiently more knowledgeable and then become more involved with teaching the benefits of cancer prevention. In fact, education about cancer prevention often is not a major part of the medical or nursing school curriculum, a shortcoming that needs to be addressed for oncologists, primary care physicians, and other health care providers. Chemoprevention or preventive vaccines should not be discussed with patients in isolation, but as part of an entire prevention program that includes diet, exercise, and cessation of smoking.

To increase the public's involvement in clinical trials for prevention, the design of these trials needs to change to make them more palatable and convenient for participation. As suggested elsewhere in this report, new outcome variables or biomarkers need to be identified for at-risk populations, to more rapidly obtain needed indicators of safety and efficacy in trials for chemopreventive agents. Such studies also may help participants to become better informed about how long they need to take a chemopreventive agent, whether it is a few months, years, or a lifetime, and for needed chronic administration, how best to remember to take the preventive agents as prescribed. It is also imperative that underserved populations, including minority groups and the elderly, be enrolled in greater numbers in clinical trials for cancer prevention. One possible solution is to focus a study on a minority population.

Because public education and communication are critical for the future of cancer chemoprevention, communications professionals should be enlisted to assist with the planning and implementation of clinical trials. National spokespersons should be identified and recruited as part of this process.

Recommended solutions to public and patient participation barriers to prevention research

General solutions
- Increase the prevention budgets of NCI and Centers for Disease Control and Prevention
- Develop evidence that prevention saves money; evidence should include data that demonstrate the cost due to the lack of access/utilization of preventive services in underserved communities
- Pursue policy changes to include access to care for all: demonstration projects funded by CMS for dissemination of cancer prevention agents; reimbursement for essential preventive services; and reimbursement guidelines consistent with the provision of preventive services

Solutions to barriers to participation in cancer prevention clinical trials
- Increase education, understanding and advocacy at the grass roots level
  - Include training programs for health care professionals, especially those serving minority populations
- Strengthen public-private-industry-corporate partnerships
  - Address partnership issues and collaborative interactions
- Learn from past successes by applying existing evidence about chemoprevention or vaccine strategies for cardiovascular and other diseases
- Develop an implementation plan for successful chemopreventive trials
- Consider new methods in designing chemoprevention trials
  - Involve communications consultants at the start
  - Involve community at the start
  - Ethical guidelines for trials management

Solutions to barriers to compliance with use of proven chemopreventive agents
- Identify new outcome variables to reduce the number of intermediate midpoint studies
- Increase education and training at all levels
- Design population specific chemoprevention trials
- Develop guidelines to pay for compliance with evidence-based prevention guidelines
- Integrate chemoprevention into overall cancer preventive regimen and recommendations for at-risk populations

Insurance policy and practice barriers affecting reimbursement of prevention agents. In 2004, total national health care expenditures continued to increase faster than the rest of the economy—at thrice the inflation rate. Total spending was $1.9 trillion, or $6,280 per person, representing approximately 16% of the gross national product (GNP; ref. 10). Under current projections, total spending may possibly reach $4 trillion in 2015, or 20% of the GNP (11). For many reasons, including international competitiveness, this is unsustainable.

Given this economic burden, frequently called a "crisis," any attempts to add new covered benefits will face resistance. To put it simply, insurance carriers and payors (i.e., Medicare, Medicaid, or private/commercial companies) want to pay less, not more. Coverage for cancer prevention likely will need to meet a higher standard for reimbursement than cancer therapeutic agents, which are already covered. Because of questionable coverage, some investors may feel that a stronger business case exists for research into therapeutic agents, although this hypothesis has not been verified.

Medicare is the largest medical insurance company in the world and private carriers often follow Medicare's coverage decisions. Signed into law in 1965, Medicare is a social insurance program designed to provide all older adults with affordable comprehensive health care coverage. However, the enabling act does not allow Medicare to pay for prevention, aside for a few exceptions later defined by Congress. These include preventive interventions such as vaccines for influenza and pneumococcus, and early detection services such as PSA tests, mammography, fecal blood testing, and colonoscopies (12).

Medicaid was also signed into law in 1965. Each state administers its own Medicaid program whereas the federal CMS monitors state programs and establishes minimum requirements for service delivery, quality, funding, and eligibility standards. Medicaid policies for eligibility, services, and payment vary considerably, even among states of similar size and geographic proximity (13). Whereas each state has discretion in some areas, CMS does set minimum standards, which suggests an approach for Medicaid coverage of chemoprevention.

Private insurance is regulated by the 50 states and assorted U.S. territories, so mandates requiring chemoprevention coverage could require action by each individual state. The National Association of Insurance Commissioners does offer one avenue for collective action. Larger employers are almost always self-insured and regulated by the federal Employee Retirement Income Security Act rules, not the states, which adds yet another complexity to a legislative solution.

Reimbursement barriers to prevention coverage

High costs
- Existing budget pressure on all payors makes discussions for expanding coverage difficult, despite the potential downstream benefits
- Potentially significant drug/product and counseling treatment costs

Limitation in practice
- Payors do not make coverage or medical necessity decisions using evidence-based medicine (science) across all existing medical spending, so chemoprevention bears a higher burden of evidence

Limitations to science
- Evidence of success from prevention clinical trials is limited

Limitations in policy
- Prevention does not exist as a benefit category for Medicare, other than for exceptions provided by Congress
- Medicaid and insurance rules vary among the 50 states and the U.S. territories

Recommended solutions to insurance policy and practice barriers affecting reimbursement of prevention agents. Given the current health care cost burden, prevention strategies will likely need to meet a higher standard than therapeutic agents for reimbursement. The panel recommends that the cancer prevention community adopt evidence-based medicine as its standard for

communicating value. Evidence-based medicine means applying the best evidence to the best practices, not only for what should be covered but also for what should not be covered. Today, reimbursement decisions often are not backed up by this high standard; many decisions, in fact, are contradicted by the evidence. Payors will not automatically pay for chemoprevention that has a poor evidence base. Hence, the need to use the language of value and evidence-based medicine.

An agency needs to be identified for evidence-based decisions. One such organization might be the Agency for Health Research and Quality, the lead federal agency charged with improving the quality, safety, efficiency, and effectiveness of health care for all Americans (14).

As a suggested path to covering chemoprevention, the community should help payors understand and compare the value of cancer prevention to that of third and fourth-line treatments for advanced cancer, which offer little potential for significantly increased survival. To assist with this effort, advocacy groups should be enlisted who could best communicate to payors, regulators, and the general public about how chemopreventive agents can lower the nation's health care bill and are a better value than other kinds of treatments that are routinely covered.

Recommended solutions to reimbursement barriers to prevention research

Select an arbiter for evidence-based medicine
Recommend reduced coverage for interventions without supporting evidence; recommend additional coverage for interventions with supporting evidence
Communicate evidence-based medicine paradigm and value paradigm to all stakeholders
Develop value paradigm challenge to the cancer community
Realize that cancer prevention agents will need to show better societal value than other major areas of spending
Pursue regulatory reform about reimbursement for effective cancer prevention agents by Medicare
Establish consistent rules among states for Medicaid and insurance reimbursement for cancer chemoprevention

Intellectual property, patent law, and liability barriers affecting research and development and investment recovery. To encourage investment in the research and development of new discoveries and medical innovations, society has set up a system of laws that grants exclusive marketing rights for a drug or device over a limited time period. Once that window of opportunity lapses, others may enter the market and sell generic versions of the original.

For drugs designed to treat cancer, the process requires an enormous investment in time and financial resources before final approval is given for marketing. Often, trials end in failure, with no significant recovery of investment. Failures, in many cases, stem from inadequate accrual or subject compliance, and inadequate time for conclusive results in a long-term study. The development of chemopreventive drugs or preventive vaccines requires even more time to produce the evidence needed for FDA approval. As a result, current regulations governing the time period for marketing exclusivity are not adequate to encourage investment in this field.

Two types of regulations have been devised to protect intellectual property: patents and data package exclusivity.

- **Patents**—As defined by a trade agreement known as TRIPS (Trade-Related Aspects of Intellectual Property Rights), a period of 20 years from the filing date is granted for patents in all fields of technology. After the patent expires, third parties (e.g., generic companies) may enter the market. The clock begins ticking when a novel invention is first disclosed either in a publication, the beginning of a clinical trial, or submission of a drug application to the FDA. Patents cannot be filed after the first public disclosure. For most treatment trials, drugs can take a decade or longer of preclinical and clinical testing before final approval is received from the FDA, frequently taking up much of the drug patent life. To bring a prevention product to market, approvals could take as many as 5 years longer. Thus, there is currently little incentive for a company to invest new resources for additional time-consuming studies to evaluate the safety and efficacy of the drug for a secondary purpose, such as the prevention of cancer.
- **Data package exclusivity**—These rules allow the innovator a defined period of marketing exclusivity to protect the clinical trial data produced by the innovator and submitted to the regulator to show the product is safe and effective. These data are generated during the course of the clinical trial and are not the actual "invention" of the product. Generally, the period of patent exclusivity runs parallel to the patent term; however, unlike patents, this protection begins at the time of marketing approval. In the U.S., the period of data package exclusivity is 5 years for new chemical entities and only 3 years for new uses—an inadequate time period for a company to reap a return on investment.

Intellectual property issues become even more complex when one considers the real possibility that effective cancer prevention may require a combination of drugs. Consider the difficulty of bringing a single drug forward, and then consider the risk/benefit equations and the ability to recoup investment on multiple drug combinations. Currently, there are few approvals for single cancer-preventive drugs or vaccines, and so there is little established basis for determining add-on benefits of second agents. In addition, if more than one company is involved, there are likely to be different bases for determining efficacy and safety that will need reconciliation for development of intellectual property for cancer preventive strategies.

Clearly, using a combination of preventive agents is a real possibility that needs to be addressed, which becomes even more problematic when one reflects on the onerous burden already shouldered by the U.S. Patent and Trademark Office (PTO). In 2004, the U.S. PTO received 384,000 new patent applications (ref. 15; some more than 1 million pages in length), with a backlog of more than 1 million patent applications. On average, technology applications are pending for 8 years, longer than the lifetime of the technologies. Yet, there are between 4,000 and 5,000 patent examiners in the U.S. today, who need to rule on an eclectic mix of discoveries, ranging from what are called "bicycle patents" to more sophisticated inventions involving chemistry and biology.

Pharmaceutical industry officials also are worried about new legislative initiatives designed to liberalize patent laws and they are concerned about court decisions in recent years, which have virtually all gone against the innovator. Through aggressive litigation challenging patent and data exclusivity, some generic manufacturers realize huge returns on small research investments.

The recent trend of the courts is not to uphold the traditional injunction against infringement, which is used to restrain potential competitors from infringing on existing patents in which health or safety of the consumer is at issue. These decisions are setting precedence for future verdicts in patent cases that will likely have a negative impact on the field.

Perhaps the biggest hurdle faced by those in the industry is the court of public opinion. The public generally believes that patent laws exist solely to help the pharmaceutical industry make more money on their products at the expense of the consumer. As a result, it is often perceived that the price for drugs is excessive, forcing some patients without insurance coverage or with fewer financial resources to go without needed medication. Although pharmaceutical companies and consumers are heavily involved in patent reform for the benefit of both the companies and the consumers, marketing and public relations strategies designed by pharmaceutical manufacturers seldom promote understanding of the value of intellectual property protection.

Yet another major barrier is the considerable concern of companies about their current major liability to compensate for unforeseen adverse effects induced by chemopreventive drugs or preventive vaccines. The real prospect for major and very costly litigation from individuals adversely affected by cancer prevention approaches puts a major pall over the willingness of the pharmaceutical or biotechnology industry to invest in the development and testing of cancer preventive agents.

Intellectual property, patent law, and liability barriers to prevention research

Inadequate period of time to recoup investment
- Lack of effective patent term
- Inadequate period of data exclusivity

Uncertainty of future patent law
- Court action moving in wrong direction
- Presumption of validity that comes with patent has been lost

Different intellectual property risk models for new prevention drugs and existing drugs with previous therapeutic indications

Lack of public understanding of the value of patent protection

Limiting government reimbursement policies that undermine value of patent

Insurance policies

Operational limitation of the U.S. PTO

Difficulty in assessing patent rights and terms when treating with multiple or combination drugs from one or multiple manufacturers

Extensive liability of companies for adverse effects from preventive agents

Recommended solutions to intellectual property, patent law, and liability barriers affecting research and development and investment recovery. The Drug Price Competition and Patent Term Restoration Act, also known as the HatchWaxman Act, was passed by Congress in 1984. Its goal was to establish a delicate balance between the competing interests of brand name drug companies and generic drug companies, with the public as the ultimate beneficiary (16).

As stated earlier, protection of intellectual property rights is of limited duration: 20 years from the filing date for patents, and 5 years for marketing exclusivity. If chemoprevention for cancer is to be jump-started, then the clock needs to be reset to allow more time for companies to recoup the enormous investment to develop these agents for the market. As stated in a recent update from the 2006 AACR Task Force on Cancer Prevention (5), consideration should be given to the following changes in U.S. patent law to give a fixed predictable time frame for protection: starting the clock at the time of patent issuance rather than when the patent was filed; extending the patent life for chemopreventive uses; or making the U.S. period for data exclusivity conform with that of Europe, which is 10 years for new chemical entities, and an option of an additional year for new uses (17). Another concept worthy of discussion is the notion of transferable patent rights, in which patent term credits could be transferred from one new agent (i.e. bioterrorism) to another (i.e. cancer prevention drugs).

Efforts should also be made to support reforms in the U.S. PTO, including the quality of the patent examination process, so that the patent that emerges can withstand legal scrutiny from the courts and be in harmony with global patent law. Congress has recognized the need to bolster the U.S. PTO and has increased funding. Expansion of the PTO over the next 5 years is expected to double the number of examiners; however, no business plan for restructuring is in place. Recommendations have included, for example, outsourcing patent search, establishing working relationships with other offices worldwide (so that applications would only get one review), requiring more information from applicants, and granting patents after less review (but also with less enforceability).

As a condition for success, policy makers and the general public need to be better informed about the importance of intellectual property laws and the benefits of patents for the public good. As part of that dialogue, the public should be educated about the key role that prevention can play in reducing incidence and death from

Recommended solutions to intellectual property, patent law, and liability barriers to prevention research

Promote increased public awareness that patents play a key role in prevention R&D
- Improved accuracy of media coverage of intellectual property issues
- License some patents for social responsibility

Predictable patent protection
- HatchWaxman reform
- Patent law reform
- Predictable product exclusivity period
- Amicus briefs in court cases to explain the importance of maintaining patent protections

Change the way business is done at the U.S. PTO
- Harmonization of global patent law
- Improve quality of patent examination
- Support for ongoing reform efforts at the U.S. PTO and its need for increased resources

Promote transferable patent rights
- For example, technology developed for bioterrorism or other fields should be allowed to be more easily transferred for medicine, including chemoprevention

Promote tax incentives to companies developing cancer preventive agents

cancer. Providing workshops and forums about such issues for the media may help bridge this gap in understanding. Groups representing advocates, professional organizations, public health organizations, and schools should be enlisted to help with this effort.

To allay the liability concerns of companies developing or testing agents for cancer prevention, there will be a need to convince Congress of the importance of cancer preventive interventions and of the potential major benefits, as well as risks, so that legislation might be developed to limit the liability of companies for adverse effects that occur from such interventions.

Action Plan

After review of the many recommendations stemming from the Cancer Prevention Research Summit and subsequent discussions with the Panel Chairs, the following five immediate actions have been recommended for pursuit by C-Change and collaborating organizations. In addition to issue-specific actions, each panel identified several concepts that, if more widely understood and accepted by key audiences, would help advance their specific concerns. Through the collaborative development of a strategic communication initiative, key messages will be captured and disseminated to audiences to promote an increased investment in cancer chemopreventive and vaccine research.

A summary of recommended action items is found below. The action items reflect issues unique to each Summit panel and will be pursued by working groups of topic-specific experts. A detailed work plan for each action item follows the summary.

Summary of cancer prevention research action items

Goal	*Immediate Action*
Change patent, intellectual property, and liability laws and processes to remove deterrents to investment in cancer chemoprevention and vaccine research and development	Define detailed, specific solutions to patent and intellectual property law and liability barriers
Strengthen the FDA process for evaluating cancer chemopreventive agents and preventive vaccines	Recommend changes to FDA approval process for cancer chemopreventive agents and preventive vaccines
Accelerate the accumulation of evidence for efficacy and safety by improving cancer prevention clinical trial design	Recommend design models for cancer chemoprevention clinical trials
Plan for reimbursement for cancer chemopreventive agents and vaccines	Make the business case for chemopreventive agents and preventive vaccines
Increase the understanding of the importance of cancer prevention and chemopreventive research by key stakeholders and constituent groups	Develop a communication plan for the speaker's kit and companion documents for each of the key stakeholder groups

Work Plans

Action I: Define solutions to patent, intellectual property, and liability law barriers. The goal of this action step is to change patent and intellectual property laws and processes removing deterrents to investment in cancer chemoprevention and preventive vaccine research and development. Target audiences include legislators, the pharmaceutical industry, researchers, advocates, and the U.S. Commerce Department. The work product will be a patent and intellectual property law assessment and guidance document. C-Change will commission a scholarly assessment of current barriers to cancer chemoprevention and preventive vaccine development related to patent and intellectual property law. The assessment will include feasible solutions to current barriers and highlight the next steps toward accomplishing this goal.

Action II: Recommend changes to FDA approval process for cancer chemopreventive agents and vaccines. The goal of this action step is to strengthen the FDA process for evaluating cancer chemopreventive agents and vaccines. Its target audiences would include the FDA, legislators, pharmaceutical industry, researchers, advocates, and the NCI. The work product will be a regulatory guidance document. In response to a request from the FDA, a multisector workgroup of scientists will develop a guidance document outlining key considerations for evaluating cancer chemopreventive drugs and vaccines, defining the role of biomarkers and surrogate end points, and adapting agency processes.

Action III: Recommend study design models for cancer chemoprevention and cancer preventive clinical trials. The goal of this action step will be to accelerate drug discovery by improving cancer prevention clinical trial design. The target audiences will include researchers, the pharmaceutical industry, the FDA, and the NCI. The work product will be a cancer prevention trials guidance document. A multisector workgroup of scientists will develop a guidance document for optimal cancer chemoprevention trial design, including discussion of the role of biomarkers in participant selection, surrogate end points for efficacy and toxicity, and other strategies to control trial size, duration, and cost.

Action IV: Make the business case for chemopreventive agents and vaccines. The goal of this action step is to improve public and private investment in cancer preventive interventions and to improve reimbursement for cancer chemopreventive agents and vaccine. The target audiences include payors, employers, the NCI and other federal agencies, the pharmaceutical industry, cancer prevention researchers, and legislators. The work product will be a cancer chemoprevention investment and reimbursement guidance document. A multisector workgroup will establish the framework for demonstrating the comparative value of chemoprevention, when such evidence becomes available. The document will include definitions; the scientific case for increased investment in cancer preventive interventions; recommendations for reducing non-evidence-based practice through examples of current use and coverage; and illustrations of underused, evidence-based chemopreventive agents.

Action V: Develop a communication plan for the speaker's kit and companion documents. The goal of this overarching step is to increase the knowledge and understanding of cancer prevention and chemopreventive research among key stakeholders and constituent groups. The target audiences will include the following: payors, employers, the pharmaceutical industry, cancer prevention researchers, legislators, the FDA, the NCI, advocates,

the U.S. Commerce Department, policy makers, hematologists/oncologists, the CMS, primary care physicians, and other relevant health care providers. The work product will consist of a communication plan and a speaker's kit. The communication plan will be devised with the guidance of communications professionals. The plan will define target audiences, adapt the content accordingly, and likely include a variety of communication tactics such as electronic and print media, press conferences, Hill briefings, and other speaking engagements.

The strategic communications initiative will promote an increased investment in cancer chemopreventive and vaccine research by the following methods:

- Increasing the understanding of cancer prevention and of cancer chemoprevention and preventive cancer vaccines
- Illustrating the effectiveness of evidence-based medicine and the inappropriateness of non-evidence-based practices
- Explaining the role of patent and intellectual property law in promoting innovation as well as current limitations that inhibit cancer prevention agent and vaccine development
- Encouraging scientific advances in clinical trial design and biomarker development.

The speaker's kit will allow leaders to convey a set of consistent messages about the value of, and need for, chemopreventive agents and vaccines. The presentation content will include key message points about intellectual property and patent law; insurance coverage and reimbursement; chemoprevention trials; and understanding primary and secondary cancer prevention. Several scholarly documents will be developed as companion pieces to the speaker's kit. Each document will summarize the current state of cancer chemoprevention from legal, regulatory, scientific, and financial perspectives. The papers will provide strategic recommendations to advance policies and practices aimed at increasing the research and use of cancer preventive agents and vaccines.

In summary, the extensive planning for, and discussions at the recent C-Change Summit on Cancer Prevention Research represents the beginning of an important process to address the current barriers to effective cancer prevention research, so that the development, clinical validation, and dissemination of cancer chemopreventive agents and cancer preventive vaccines can be substantially facilitated and made available to all Americans at risk for developing cancer. The recommended solutions and aggressive action steps to implement these solutions offer real hope that, in the near future, the incidence and progression of cancer can be substantially and progressively reduced.

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