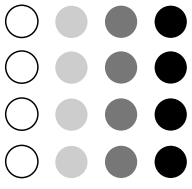


Progress
Review
Groups

Report of the Lung Cancer Progress Review Group

August 2001

NATIONAL® CANCER INSTITUTE

Report of the Lung Cancer Progress Review Group

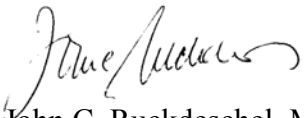
August 2001

From the Leadership

We are pleased to present this Report of the Lung Cancer Progress Review Group (PRG). The PRG enthusiastically accepted its charge to identify scientific priorities and needs and create a national agenda for research on lung cancer, and we believe that this report provides a compelling strategy for progress against this disease.

Rather than propose a long list of recommendations, the PRG has identified five areas of research that will transform the prevention, diagnosis, and treatment of individuals with lung cancer. We believe that these areas truly represent the highest priorities in the field. In addition, we encourage the continued support and refinement of ongoing initiatives that affect lung cancer research and quality of life.

Despite advances in our understanding of the causes, prevention, and treatment of cancer, progress against lung cancer has been slow. We appreciate the NCI's decision to institute a PRG to address this challenging disease, and we look forward to assisting the NCI in implementing the PRG's recommendations and to following their progress.



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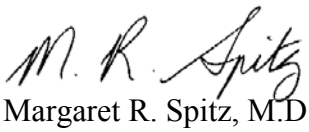

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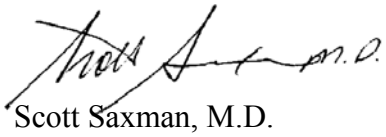

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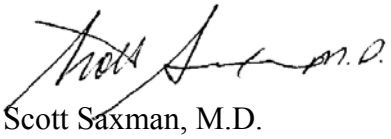

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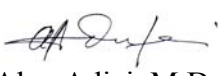

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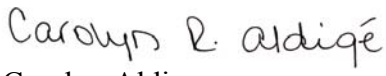

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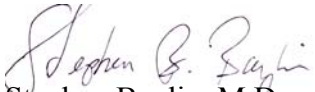

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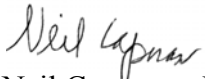

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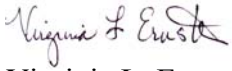

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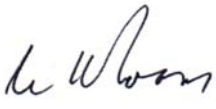

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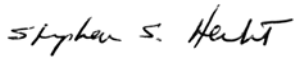

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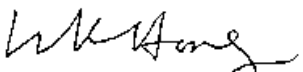

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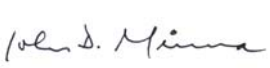

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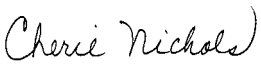

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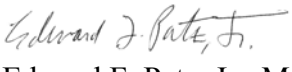

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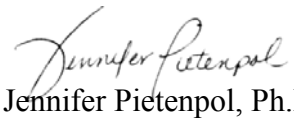

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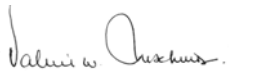

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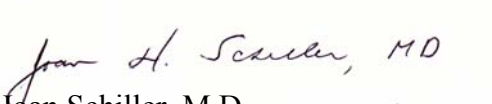

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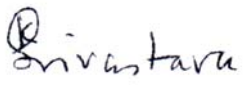

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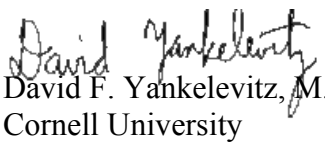

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Acknowledgments

The Report of the Lung Cancer Progress Review Group (PRG) is the product of 10 months of intense work that drew upon the combined skills and efforts of many. The PRG leadership extends special thanks to the following people:

- The researchers, clinicians, and members of the advocacy community who participated in the Lung Cancer Roundtable Meeting in April 2001. The recommendations of the PRG are drawn from their insight and expertise.

- Gerold Bepler, Ethan Dmitrovsky, Craig Earle, Wilbur Franklin, Tom Glynn, Paul Gumerlock, Curtis Harris, Fred Kadlubar, and Thomas Smith, who served as co-chairs for breakout sessions at the Roundtable meeting. Working alongside the PRG members, these individuals were instrumental in planning the breakout sessions and formulating the breakout session reports. We are greatly indebted to them for their tireless efforts.

- Staff at the NCI Office of Science Planning and Assessment, particularly Kate Nagy, Terri Hallquist, Jim Corrigan, and Annabelle Uy, who provided strong guidance, technical support, and adept handling of diverse interests throughout the PRG process.

- Lead writer Barbara Shapiro, who worked closely with us for months to draft and edit this unified report, and the team of expert science writers who worked diligently with us at the Roundtable to produce the early drafts of the report.

- Josette Johnson, Syreeta Tate, Rob Wald, and their colleagues at Palladian Partners, who provided exceptionally efficient logistical support to the PRG.

- Dr. Harold Moses, for his inspiring words to the Roundtable participants.

Finally, we offer our sincerest thanks to the members of the Lung Cancer PRG. This report is a testament to their expertise, insight, and dedication.

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Executive Summary

Executive Summary

Lung cancer is the leading cause of cancer death for both men and women in the United States, killing more people than breast, prostate, colon, and pancreas cancers combined: Fully 85 percent of patients who develop lung cancer die from it. We are still largely ignorant of the molecular events underlying the development of lung cancer and the mechanisms of resistance to drug and radiation therapy; no agent has been found useful in the prevention of lung cancer; and the benefits of lung cancer screening and early detection are mired in controversy. With half of all lung cancers in the United States now diagnosed in former smokers, it is a sobering reality that tobacco control will ameliorate but not, in the foreseeable future, eliminate the problem of lung cancer. Yet we have funded lung cancer research far below the levels that characterize other common malignancies and far out of proportion to its massive public health impact.

In October 2000, the National Cancer Institute (NCI) convened the Lung Cancer Progress Review Group (PRG) to identify high-priority areas of research that have the potential to reduce the great toll of this disease through advances in prevention, diagnosis, and treatment. The PRG's 30 members—expert clinicians, scientists, industry representatives, and consumer advocates—met in January 2001 to select topics for a Roundtable PRG meeting in April 2001. Eight topics were explored in detail in breakout group sessions. The breakout groups produced detailed reports on all eight topics, which are appended to the main PRG report.

The main report of the Lung Cancer PRG highlights the overarching priorities identified by the eight Roundtable breakout groups that transcend their individual agendas. Those recommendations are:

- Foster the creation of scientifically integrated, multi-disciplinary, multi-institutional research consortia (Lung Cancer Consortia; LCC) organized around the problem of lung cancer rather than around specific research disciplines. The support and development of dedicated academic investigators who speak a common language across basic science, translational science, and clinical and population-based studies are key to the success of this initiative. The need for such organizations was articulated by most of the breakout groups, and they are the highest priority of the Lung Cancer PRG.

- Develop and expand new approaches to the biology and treatment of nicotine addiction and mount studies to explore the differential toxicity of various tobacco products, including so-called "safer" or low-tar cigarettes.

- Facilitate and hasten the evaluation of spiral computed tomography scanning as an effective means of detecting lung cancer early, reversing the current stage distribution at presentation, and reducing mortality from lung cancer.

- Elucidate the contributions of injury, inflammation, and infection to the genesis of lung cancer.

- Design, implement, and study "best practices" in lung cancer management.

- Facilitate and encourage training programs that emphasize multi-disciplinary scientific investigation and state-of-the-art clinical care.

The Lung Cancer PRG also made a number of recommendations that could be addressed effectively by ongoing initiatives at NCI, through strengthening of their lung cancer focus. Accordingly, the PRG strongly supports the continuation or, where necessary, the enhancement of programs related to bioinformatics, animal models, molecular profiling, study of special populations, tissue and data repositories, drug development and clinical trials infrastructures, and Centers of Excellence in Communications.

Report of the Lung Cancer Progress Review Group

OVERALL STATE OF THE SCIENCE

Lung cancer presents a series of unique problems related to the virulence of the cancer itself and the response of the medical, scientific, and lay communities to its devastating impact on society. The lung defines our ability to breathe, and the loss of this capacity is one of the most frightening of all medical symptoms. Because it is a disease primarily of older patients who have smoked, lung cancer's negative impact on breathing compounds the concurrent effects of chronic smoking-related obstructive pulmonary disease and coronary artery disease.

Since peaking in 1984, the U.S. age-adjusted lung cancer incidence has decreased by more than 19 percent in men of all ages combined, with decreases since 1970 exceeding 40 percent among men less than age 55 years. Among women, rates continued to increase until recently and are now showing signs of leveling off. These trends largely reflect changes in smoking prevalence, which began to decline first among men and only later among women. Because 85 to 90 percent of lung cancer is attributable to smoking, lung cancer rates will continue to decline only if smoking prevalence declines further.

The scope of the problem, however, remains enormous:

1. Lung cancer is the leading cause of cancer death for both men and women and kills more patients than the next five most common cancers combined. Fully 85 percent of patients who develop lung cancer die from it.

2. In 2001, an estimated 169,500 Americans will be diagnosed with lung cancer. Lung cancer represents 13 percent of all incident cancers annually in the United States and 29 percent of all cancer deaths.

3. Although lung cancer mortality rates began to decline in 1990 for men (about 1.7 percent per year) and the 1-year relative survival rate for lung cancer overall has increased from 34 percent in 1975 to 41 percent in 1996, mortality rates for women continued to increase at least until 1998.

4. Since the 1980s, more women have died from lung cancer than from breast cancer—previously the major cause of cancer deaths in women.

5. Even patients with the earliest surgical stage (T1N0) have disseminated disease between 15 and 30 percent of the time.

6. Although the link to tobacco is the clearest etiologic relationship for a human cancer, the development of lung cancer in persons who have never smoked and in former smokers and the failure of the majority of heavy smokers to develop the disease are poorly understood. The complex inter-relationships among genetic, molecular, and other biologic processes in modulating the carcinogenic response to tobacco smoke need to be further explored.

7. Chemotherapy, surgery, and radiation therapy have had a modest effect on patient outcomes, but these are more often expressed as improvements in "time to progression" or short-term survival than as overall survival. The mechanisms of resistance to drug and radiation therapy are poorly understood.

8. Despite significant progress, the molecular events underlying the development of lung cancer are largely unknown.

9. No chemopreventive agent has been shown to be effective in the prevention of lung cancer, and there is often brisk debate about whether there are any proven means of diagnosing lung cancer early.

If the disease itself were not malignant enough, we as scientists, clinicians, patients, and lay people have made the problem worse:

1. We have allowed a "blame the victim" mentality to permeate our dealings with those who contract the illness through their smoking behaviors, denying them, in the process, much of the social support we routinely provide for patients with other cancer diagnoses. This has hindered the development of effective, broadly based advocacy efforts.

2. We have allowed a pervasive sense of "therapeutic nihilism" to dominate the public and scientific discussion of lung cancer. The small (2 to 4 percent) changes in time to progression and survival that we frequently celebrate for patients with other cancers tend to be dismissed as irrelevant when we observe them in lung cancer trials.

3. Our health care system is poorly organized to deal with lung cancer, leaving surgeons, radiotherapists, medical oncologists, pulmonologists, diagnostic radiologists, and pathologists working in completely separate clinical settings. This has resulted in suboptimal patterns of referral and staging in most communities and many academic centers.

   This "Balkanization" of the health care delivery system for patients with lung cancer results, in large measure, from the nature and content of the discipline-based training programs. For example, the emphasis on cardiac surgery in most cardiothoracic training programs over the past two decades has left us with only a few hundred "general" thoracic surgeons who are skilled in, and committed to, the unique issues surrounding surgery for lung cancer. The concepts of multi-disciplinary care and interdisciplinary respect are given insufficient attention in many, if not most, training programs.

4. We have funded lung cancer research far below the levels that characterize other common malignancies and far out of proportion to its massive public health impact. Support for lung cancer research has been insufficient, given that lung cancer is the leading cause of cancer mortality. There are few non-NCI sources of funding, whether Federal or non-Federal, to buttress NCI spending on lung cancer.

5. There is no question that smoking has had an enormous negative impact on the health of the nation and that reducing tobacco use is one of our highest public health priorities. It is imperative that we enhance our understanding of smoking prevention and treatment, the effects of exposure to tobacco smoke, and tobacco-related carcinogenesis. On the other hand, even if we were to be successful in eradicating smoking today, we would still have decades of lung cancer to treat among former smokers. Therefore, it is also imperative that we continue to explore new treatment strategies and approaches to improve survival in patients who develop lung cancer. We must also continue to

enhance our understanding of the biology of lung cancer so that these findings can be brought to bear on improving our diagnostic, preventive, and therapeutic approaches to lung cancer.

STRUCTURE AND PROCESS OF THE LUNG CANCER PRG

With these compelling issues in mind, the National Cancer Institute (NCI) convened the Lung Cancer Progress Review Group (PRG) in October 2000 to identify high-priority areas of research that could advance progress against lung cancer in the next 5 to 10 years. The PRG was composed of 30 expert clinicians, scientists, industry representatives, and consumer advocates. At a Planning Meeting held in January 2001, the Lung Cancer PRG organized a Roundtable to consider progress and identify research needs. The group selected the key topics to be explored in detail in breakout sessions and identified potential Roundtable participants whose expertise spanned the continuum of research. PRG members also served as co-chairs for the Roundtable breakout sessions.

The Lung Cancer PRG Roundtable met April 16–18, 2001, in Chantilly, Virginia, with approximately 110 participants. The following eight topics were covered in the breakout sessions:

- Biology
- Chemoprevention
- Detection and Diagnosis
- Etiology
- Prognosis and Staging
- Quality of Care
- Therapy
- Tobacco Control

Participants in the Roundtable were selected on the basis of their expertise in the field of lung cancer. Because of the limited number of basic and clinical research programs focused on lung cancer, scientists with molecular biology and signal transduction expertise who were not specifically working in the area of lung cancer were recruited to ensure the broadest possible perspective.

To facilitate in-depth discussion at the Roundtable, participants spent most of the meeting in a single breakout session. However, to focus the starting point for each breakout group, an initial session was held in which clusters of the groups met together to review the science common to their areas and to begin the process of coalescing areas of discussion. The three clusters were:

- Biology, Etiology, Chemoprevention
- Prognosis and Staging, Quality of Care, Therapy
- Detection and Diagnosis, Tobacco Control

In addition, a shorter afternoon breakout session was scheduled with the same breakout topic areas and co-chairs, to allow participants to choose another area of interest. This session was designed to enable cross-fertilization of creative ideas across the group and to assist in identifying cross-cutting themes.

In support of the priority-setting process, NCI provided the Roundtable participants with analyses of its lung cancer research portfolio and extensive information about ongoing NCI initiatives and activities that might address some of the needs of the field.

This report is the result of the PRG's 10-month effort. The main report highlights the overarching themes from the Roundtable breakout groups that transcend individual breakout group agendas and cut across disciplines. Notably, the group made several recommendations related to research

or resource needs that are unique to lung cancer; these are the highest priority recommendations put forward by the PRG. The group also made a number of recommendations that other PRGs have made or that may be addressed by existing NCI initiatives. We strongly support the continuation of these initiatives and the extension of their focus, where necessary, to include lung cancer.

TOP-PRIORITY RECOMMENDATIONS

It is important to note that the following recommendations are all considered major priorities of the Lung Cancer PRG. The order in which they are presented does not represent a priority ranking.

Cross-Disciplinary Lung Cancer Consortia

Recommendation: Foster the creation of scientifically integrated, multi-disciplinary, multi-institutional research consortia organized around the problem of lung cancer rather than around specific research disciplines. The support and development of dedicated academic investigators who speak a common language across basic science, translational science, and clinical and population-based studies are key to the success of this initiative. The need for such organizations was articulated by most of the Roundtable breakout groups, and the formation of these groups is one of the highest priorities of the Lung Cancer PRG.

The Roundtable breakout groups all recognized the growing inability of lung cancer clinicians to participate meaningfully in translational and clinical research, given the fiscal constraints at most major medical centers. Furthermore, each area of research focus at NCI and the American Cancer Society currently has its own study group to advance knowledge within a discipline or to translate it to the clinical setting. The result is that lung cancer clinicians and researchers work in relative isolation and are dissipated across multiple research groups; no "critical mass" of scientific experts working together exists to conduct the large-scale research studies and clinical trials that are currently needed.

The PRG envisions the creation of formal, funded Lung Cancer Consortia (LCC) using the existing Lung Cancer SPORES as core or affiliate members. The membership of the LCC could also include other interested collaborators from NCI initiatives, such as the Director's Challenge, Early Detection Research Network, and Mouse Models of Human Cancer Consortium, as well as other institutions at which the study, treatment, and prevention of lung cancer are a priority. The Lung Cancer SPORES currently collaborate with one another on a variety of basic and translational research initiatives; the LCC would extend this focus to clinical, behavioral, and population-based research. In organization and activity, the LCC would closely resemble the former NCI-sponsored Lung Cancer Study Group (LCSG), which was active from 1977 to 1988 and brought together thoracic surgeons, radiation and medical oncologists, pathologists, radiologists, pulmonologists, and basic scientists, all of whom contributed their expertise to the problem of lung cancer.

Strong and active LCC would offer a number of advantages:

- They would provide a ready-made infrastructure through which large-scale clinical trials, including chemoprevention and screening trials, could be rapidly and efficiently conducted.

- They would facilitate the conduct of interdisciplinary studies, such as those built around the biology/behavior/exposure continuum.

- They would allow ongoing initiatives to be carried out in a more focused and relevant way.

- They would foster collaboration among diverse lung cancer experts, particularly those involved in lung cancer etiology, prevention, and treatment, as well as researchers with an interest in end of life care.

- They would greatly facilitate clinician participation in lung cancer research activities.

- They would promote faster study of preventive and therapeutic approaches unique to lung cancer.

- They would facilitate large-scale epidemiologic investigations and population-based studies of smoking intervention and nicotine addiction. These kinds of studies are not currently in the portfolio of the traditional Cooperative Groups. The current Cooperative Group mechanism separates the relatively small number of lung cancer clinicians and researchers by institution rather than by specific focus on lung cancer.

This concept, as well as interactions among the SPORES, LCC, and NCI, could be further enhanced by organizing meetings, workshops, and consensus conferences that specifically address multi-disciplinary lung cancer research themes.

Tobacco Control

Recommendation: Develop and expand new approaches to the biology and treatment of nicotine addiction and mount studies to explore the differential toxicity of various tobacco and nicotine products, including cigarettes that purport to reduce tobacco toxin exposure (so-called "safe" or low-tar cigarettes).

Recommendation: Continue and systematically evaluate population-based tobacco control efforts currently in progress or planned. Expanding the use of existing guidelines and developing new approaches to both smoking cessation and relapse prevention are of the highest priority. The PRG also encourages the adoption and implementation of these guidelines in lung cancer prevention, screening, and treatment trials.

Consider the following facts:

- 30 percent of all cancer mortality is attributable to tobacco use.

- Cigarette smoking causes chronic lung disease and heart disease. Overall, cigarettes kill more than 430,000 Americans every year.

- When fully implemented, the U.S. Public Health Service guidelines for smoking cessation are effective only 25 percent of the time, with quitting rates increasing with the number of cessation attempts. However, implementation of these guidelines has been limited, and methods for treatment can be improved.

- Smoking prevalence has dropped markedly since the 1964 Surgeon General's report, which is the primary reason that lung cancer mortality rates have begun to decline in the United States. However, an estimated one in four adults in the United States still smoke. Thus, the target group for prevention and detection of smoking-related lung cancer in the United States is 91 million people (44 million former smokers and 47 million current smokers).

- Because of the structural determinants of poverty, smoking and poorer health outcomes are more prevalent in certain racial and ethnic populations. African-American men have the highest incidence and mortality rates from lung cancer.

- Marketing of tobacco products has clearly targeted not only youth but other vulnerable populations. The most effective way to influence the problem of health disparities in the United States is to use population-based tobacco control strategies and protocols to reduce smoking.

The Lung Cancer PRG recognized the scope of the problem and noted several key areas, listed below, in which immediate and intensive research and support is required.

- Harm Reduction. "Harm reduction" is an old concept that is re-emerging with the development and marketing of so-called "safe" cigarettes. Three decades ago, the introduction of "low yield" cigarettes only increased the already significant public health burden due to tobacco use because it permitted smokers to believe they were reducing their risk of illness when no such data existed. Rapid and thorough analysis of the differential toxicity of these products is required, along with research that will examine if "harm reduction" is a viable public health strategy and that will provide a scientific basis for eventual policy decisions.

- Genetics. There is growing research interest in identifying genes and their common variants that may predispose to nicotine addiction. Such biobehavioral research has the potential to target therapies more accurately according to the smoker's genotype and in the context of the social and cultural milieu, and thus to enhance the success rates of cessation interventions.

- Population-Based Programs. Because the tobacco industry's marketing and promotion arm alone outspends the public health efforts of the various states and the Federal Government by an order of magnitude, it is vital to continually review and understand data generated from the large, population-based tobacco control programs currently in progress or planned. Surveillance and evaluation research of population-based tobacco control efforts, such as tobacco price increases, secondhand smoke policies, mass media efforts, and "denormalization" of tobacco use by adults and young people, are critical to offset the ongoing activities of the tobacco industry and create a substantive public health benefit at the population level.

Early Detection

Recommendation: Facilitate and hasten the evaluation of spiral computed tomography (CT) scanning to detect lung cancer at an early stage, reverse the current stage distribution at presentation, and reduce mortality from lung cancer. This will necessitate creation of a comprehensive lung cancer infrastructure that includes sharing of specimens and clinical and epidemiologic data to further our understanding of the pathobiology of the small or early lesions detected by this technology.

Currently, the vast majority of patients present with locally advanced or metastatic disease. Any significant change in the stage distribution at presentation has the possibility of making a profound impact on cancer death rates, given the prevalence of lung cancer. Unfortunately, this area of research has become mired in well-intentioned but ultimately counterproductive

arguments about the merits of the necessity for randomized, controlled trials with overall mortality as the sole endpoint.

Several meetings co-sponsored by NCI and the American Cancer Society have determined that a number of study designs in addition to a mortality endpoint-randomized trial (the gold-standard approach) are important and valid. NCI must continue to take a strong leadership role in facilitating the initiation and completion of a number of trials evaluating spiral CT as a means of detecting lung cancer early and reducing mortality.

Understanding of Lung Carcinogenesis

Recommendation: Elucidate the contributions of injury, inflammation, and infection to the genesis of lung cancer.

Investigators of different disciplines need to work together to outline the specific cellular steps that underlie epithelial development in the airways during embryogenesis and during cell renewal in the normal adult lung. There is a need to study molecular mediators that drive the chronic pulmonary injury process and to develop the best model systems to study these interactions. NCI should bring together investigators from other institutes at NIH to address these emerging issues.

Outcomes

Recommendation: Design, implement, and study "best practices" in lung cancer management.

The extent to which "best practices" (e.g., lobectomy as opposed to pneumonectomy; chemotherapy plus radiation for locally advanced disease) are employed is unclear. The extent to which existing guidelines (e.g., National Comprehensive Cancer Network) are in practice in the community at large is unknown. Expansion of the CanCORS program would allow a common data set on which to validate new measures of quality care and to evaluate novel programs of service delivery.

In the absence of an understanding of whether disparities in lung cancer diagnosis, prevention, and treatment are grounded in physician behaviors, population differences, or health system functioning, it will not be possible to design and implement strategies to correct them.

Training Programs

Recommendation: Facilitate and encourage training programs that emphasize multi-disciplinary science and clinical care.

As noted earlier, discipline-based training programs rarely address true multi-disciplinary science and clinical care. Given the exigencies of discipline-based compensation, it is unlikely that the current training paradigms will change unless funding is specifically directed to address this problem.

Early and mid-career programs for training in lung cancer care and research need to be expanded and innovative designs encouraged through grant and contract mechanisms. As techniques for early detection and prevention are developed, it will be critical to educate primary care physicians, lung-oriented specialists, and other health care professionals.

OTHER KEY RECOMMENDATIONS

The Lung Cancer PRG also made a number of recommendations that could be addressed effectively through ongoing or expanded initiatives at NCI. Accordingly, the PRG strongly supported the continuation or, where necessary, the enhancement of programs related to:

- Bioinformatics, including the Center for Bioinformatics and the National Programs of Excellence in Biomedical Computing.

- Animal Models. There is a need to exploit ongoing initiatives in the development of mouse models to have them mimic the human disease paradigm.

- Molecular Profiling of Tumors, including NCI's Director's Challenge. Existing efforts could be further extended to focus more specifically on lung cancer and to include the study of preneoplastic tissues.

- Special Populations and Population Disparities. We need innovative approaches to study the problem of lung cancer in specific subgroups of the population defined by age, gender, ethnicity, and smoking status, as well as families with multiple affected members and individuals with lung cancer as a second primary cancer.

- Tissue and Data Repositories. Investigators need easy access to high-quality tissue from the normal lung, precursor lesions, and invasive tumors, as well as serum and DNA, that are linked to comprehensive epidemiologic, clinical, and follow-up data. Access to specimens has consistently been identified as a barrier in all PRG reports. These specimens need to be stored according to optimal standard protocols. Collection of biospecimens from cohort as well as screening, chemoprevention, and therapeutic trials has the potential for garnering considerable new information at marginal incremental cost.

- Drug Development and Clinical Trials Infrastructures. There is an urgent need to develop and test new targeted drugs for both the treatment and the prevention of lung cancer. Programs for development and testing of new drugs through NCI's Cancer Therapy Evaluation Program and Division of Cancer Prevention should continue to be supported.

- Centers of Excellence in Communications. These centers could be expanded to include a specific lung cancer focus.

- Tobacco PRG. Although tobacco use is an integral part of the etiology, course, and treatment of lung cancer, the numerous and important issues raised by tobacco use and control transcend the problem of lung cancer and affect many other types of cancer. Therefore, the Lung PRG recommends that NCI convene a separate Tobacco PRG.

CONCLUSION

NCI has had the foresight to create a remarkable scientific infrastructure that offers the promise of true advances against the common epithelial cancers of adults, particularly lung cancer. The Lung PRG salutes and recognizes this progress but strongly cautions NCI that the current dissipation of lung cancer investigators across numerous clinical and research-focused teams is not the optimal approach to attacking this problem. In the same way that the difficulties in translational and clinical science led to the formation of the NABTT (New Approaches to Brain Tumor Treatment) consortium (an NCI-supported group dedicated to study and treatment of central nervous system malignancies), so, too, must the efforts in lung cancer research be realigned.

Ultimately, progress against lung cancer will depend on a concerted, multi-disciplinary

effort. The priorities outlined here provide a framework for such an effort. It is hoped that, by fully addressing these priorities, we will effect a marked improvement in the understanding, prevention, detection, and treatment of lung cancer.

Appendix A: About the National Cancer Institute's Progress Review Groups

Appendix A: About the National Cancer Institute's Progress Review Groups

The National Cancer Institute (NCI) supports basic, clinical, and population-based research to elucidate the biology, etiology, early detection, prevention, and treatment of cancers of various organ sites. These research efforts have produced a substantial base of knowledge that, while providing a wealth of new scientific opportunities that can further advance our knowledge and progress against these diseases, also requires that the Institute determine the best uses for its resources.

To help ensure the wise use of resources, NCI has established Progress Review Groups (PRGs) to assist in assessing the state of knowledge, reviewing the Institute's research portfolio, and identifying scientific priorities and needs for its large, site-specific research programs.

CHARGE TO THE PRGs

Each PRG is charged to:

- Identify and prioritize scientific research opportunities and needs to advance medical progress against the cancer(s) under review.
- Define the scientific resources needed to address these opportunities and needs.
- Compare and contrast these priorities with the current NCI research portfolio.
- Prepare a written report that describes findings and recommendations.
- Discuss a plan of action with NCI leaders to ensure that the priority areas are addressed.

The following section details the process used to execute these charges.

THE PRG PROCESS

PRG members are selected from among prominent members of the scientific, medical, and advocacy communities and from industry to represent the full spectrum of scientific expertise required to make comprehensive recommendations for the NCI's cancer research agenda. The membership is also selected for its ability to take a broad view in identifying and prioritizing scientific needs and opportunities that are critical to advancing the field of cancer research.

The leadership of each PRG finalizes an agenda and process for a PRG Planning Meeting. At the Planning Meeting, participants are identified to take part in a subsequent Roundtable meeting. Topics are identified for Roundtable breakout sessions to which participants will be assigned and for which the PRG members will serve as co-chairs.

A PRG Roundtable brings together in an open forum approximately 100–180 leading members of the relevant cancer research, medical, industry, and advocacy communities to formulate key scientific questions and priorities for the next 5–10 years of research on specific cancers. As part of the process, the NCI provides the PRG Roundtable with an analysis of its portfolio of cancer research in the relevant organ site. This analysis is intended to enable the Roundtable to compare and contrast identified scientific priorities with the research currently being done under the Institute's auspices. Input from the

Roundtable is used by the PRG in delineating and prioritizing recommendations for research, related scientific questions, and resource and infrastructure needs. At its discretion, the PRG may solicit additional input from the research and advocacy communities through workshops, ad hoc groups, or by other means. The PRG also may consider the deliberations of previously convened expert groups that have provided relevant cancer research information.

THE PRG REPORT

After the Roundtable, the PRG's recommendations are documented in a draft report, multiple iterations of which are reviewed by the PRG leadership and PRG members. The final draft report is then submitted for deliberation and acceptance by the NCI Advisory Committee to the Director. After the report is accepted, the PRG meets with the NCI Director to discuss the Institute's response to the report, which is widely disseminated and integrated into the Institute's planning activities. At this meeting, the PRG and the NCI identify the research priorities that ongoing NCI initiatives and projects do not address. Then the PRG and NCI discuss a plan for implementing the highest research priorities of the PRG. This plan becomes a blueprint for tracking and hastening progress against the relevant cancer.

PRG reports on breast cancer, prostate cancer, colorectal cancer, brain tumors, pancreatic cancer, and leukemia, lymphoma, and myeloma, in addition to this PRG report on lung cancer, are available online at http://planning.cancer.gov. Other PRG reports currently in development or planned include reports on gynecologic cancers, kidney and bladder cancer, and stomach and esophageal cancer.

Appendix B: Breakout Reports

Biology

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INTRODUCTION

There is a dire need to make a clinical impact on lung cancer through new strategies for treatment of established disease, earlier treatment intervention, and prevention. Accomplishing these goals is complicated by the fact that there are four major histological types of lung cancer—small cell, squamous cell, large cell, and adenocarcinomas—that may each have unique molecular aspects for precursor lesions and steps in progression. The translational research that will be essential to accomplish the goals for treatment and prevention is, in turn, driven by basic biological research aimed at understanding the cellular and molecular biology attendant to each of the major forms of lung cancer. Although many chromosomal changes have been outlined for progression steps in lung cancer, many of the genes in these regions that uniquely contribute to the origins of each cancer are not known, as they are for tumors such as colon cancer (examples of known genes are p53, p16, and K-ras). This may be largely because, unlike for colon cancer, distinct familial forms of lung cancer are not available to identify germline mutations that provide key information about the origins of the somatic forms of the tumors. Thus, new biological insights must be derived to outline the cellular and molecular pathways for development of lung cancer that will provide the needed markers for risk assessment and early diagnosis and will facilitate the development and evaluation of novel targets for treatment and prevention strategies. Thus, the recommendations from the Biology Working Group of the PRG focus on promoting ways to obtain this critically needed new biological information.

The overall theme of the recommendations is that investigators of different disciplines need to work together to outline the specific cellular steps underlying epithelial development in the airways during embryogenesis and during cell renewal in normal adult lung and chronically injured lung exposed to tobacco. The stem cells involved in these processes need to be clarified and the signal transduction events that program these cells, including signaling to and from non-epithelial components of normal and adult lung, need to be explored and related to steps in lung carcinogenesis. Information on these processes may depend heavily on the study of lower organisms such as *Drosophila* and on derivation of mouse models. In turn, the mouse models can prove to be the key models for the study of lung cancers and testing of new agents to prevent and treat them. The use of genomics and proteomics will be critical for all of this research, as will constant extrapolation of all information to the clinical arena and back to the bench. The recommendations that follow are focused on advancing mechanisms to foster the integrated type of basic research that is clearly necessary to meet the research goals outlined above.

RESEARCH PRIORITIES

General Recommendations

The context for recommendations from this PRG should emphasize opportunities to engage in and foster a highly integrated approach to basic studies of lung cancer. Such integration should involve harnessing the joint expertise of developmental

biologists, cellular and molecular biologists, pulmonologists, clinical scientists, and experts in genomics and proteomics to the lung cancer problem. Intervening steps to prepare for such integrated research projects should include an NCI-supported series of interdisciplinary meetings to foster the concepts and especially the creative use of:

- Animal models: how best to use them in the context of lung cancer, and how to facilitate involvement of the lung cancer research community in making an impact in etiology, prevention, molecular pharmacology, in vivo imaging, etc. This might involve expansion and participation of the lung cancer research community with the current mouse model consortium for the specific needs of lung cancer research.

- Genomics and proteomics: how to use these tools in studies of developmental biology, early progression, etc.

The overall goal of the following priorities is to have a significant impact on understanding of the genesis of the four major histological types of lung cancer and development of new markers for risk assessment, early detection, and targets for prevention and treatment.

1. Define the molecular switches (genetic and epigenetic) of human lung cancer.

A. Identify stem cells involved in the generation of the bronchial epithelium, in renewal of adult normal and neoplastic epithelium, and specific relationships of these cells to the genesis of each of the major types of lung cancer.

B. Determine, at a molecular level, stromal-epithelial cell interactions that guide stem cell programming events and cell fate decision. This work must include efforts to evolve the model systems most useful for these studies.

C. Clarify existing knowledge and develop new knowledge of pathways underlying the development of normal and neoplastic bronchial epithelium. This should include an emphasis on the study of *Drosophila, Caenorhabditis elegans*, and other model organisms for elucidating determinants of cell fate decisions. The work must also emphasize the use of in vitro models using human lung epithelial cells and animal models to outline and validate molecular pathways involved and their participation in the genesis of lung cancer.

D. Creatively use genomics and proteomics for each of the study areas outlined above.

Rationale

In general, lung tumors are not responsive to current therapies, and this fact is complicated by the existence of four major types of cancer arising from a single epithelial cell system. Also, a major translational goal is to develop prevention strategies based on individual risk assessment. The specific molecular steps involved in the genesis of lung cancer, in general and with each of the specific histologies, are not well understood and represent barriers to these translational goals.

2. Elucidate the contributions of injury, inflammation, and infection to the genesis of lung cancer.

A. Develop the best model systems to study these interactions.

B. Identify cells (including epithelial and non-epithelial cells) and molecular

mediators (cytokines, oxygen radicals, products of lipid peroxidation, infectious agents such as viruses, etc.) that drive the chronic pulmonary injury process. This *must* be a collaboration between scientists and clinicians working in the areas of pulmonary biology and cancer biology.

C. Identify the precise epithelial cell renewal events that are participating in the chronic injury response.

D. Determine the contribution of all the above events to the genomic (genetic and epigenetic) changes in the bronchial epithelial cells throughout the stages of development of each of the major forms of lung cancer.

Rationale

Chronic injury, inflammation, and infection may contribute to lung cancer risk and result from cigarette smoking, in addition to the carcinogen exposure inherent to tobacco use. However, relatively little study has focused on the interplay between these parameters in the development of lung cancer.

3. Clarify the biology of gender and ethnic differences in susceptibility to development of lung cancer.

Use genomics and proteomics to study established tumors and early lesions collected from special populations (men and women and different ethnic groups). Inherent to these studies must be a collaborative effort to obtain the appropriate tissue samples required for study.

Investigate potential hormonal determinants of lung cancer susceptibility between men and women.

Determine what model systems may be generated to study these questions. Particularly, for the issue of gender, how does the hormonal milieu influence use of the current animal models to study the genesis of lung cancer and development of new ones?

Rationale

To date, little information has been generated on the differences in susceptibility for lung cancer development between men and women and among different ethnic groups. For example, the occurrence of lung cancer among non-smokers is much higher for Chinese women than Caucasian women. Much might be learned about the biology of lung cancer from studying these different populations from a basic science standpoint.

RESOURCES NEEDED

- The existing NCI initiatives in areas such as the mouse model consortium, the Director's Challenge, tissue banking, and genomics and proteomics must be expanded to meet the specific needs of the research priorities outlined above.

- Support will be required for the suggested meetings to establish concepts underlying the multi-disciplinary research in the suggested priorities.

- The type of research most emphasized in the suggested priorities must be carried out in the setting of grant mechanisms such as interactive R01s and P01s. Consideration should be given to mobilizing a pool of funds to adequately support this research effort. Funding of IDEA awards (high risk, high impact) should be considered for each of the priorities. To foster the required interaction between pulmonologists and cancer biologists, joint funding mechanisms between the National Heart,

Lung, and Blood Institute and NCI should be developed.

BARRIERS

- The biggest barrier to progress toward these research goals would be the failure to perform the investigations in the highly integrated, multi-disciplinary manner articulated in the general recommendations. For example, in terms of technology development, there is a need to juxtapose relevant scientific questions with the new technology.

Chemoprevention

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Writer: *Nancy Volkers*

BACKGROUND

There is a pressing need for effective lung cancer chemoprevention strategies. This section of the PRG report summarizes three research priorities to advance the national lung cancer chemoprevention strategy.

Lung cancer prevention is an attractive approach because the major etiologic agent—tobacco carcinogens—is known. Yet, even if all the national anti-smoking goals are achieved, lung cancer will remain a major clinical problem for decades to come. Previous work has shown that prevention of aerodigestive tract tumors is a promising approach based on the seminal work of Hong and colleagues, demonstrating that 13-*cis*-retinoic acid can treat oral leukoplakia. This work, conducted in the 1980s, was extended by showing that retinoids can prevent second aerodigestive tract tumors in patients with resected head and neck cancers. Similar work by Pastorino and colleagues demonstrated that retinyl palmitate can reduce incidence of second aerodigestive tract cancers in patients with resected stage I non-small cell lung cancer. Yet, independent, randomized placebo-controlled trials using beta-carotene or 13-*cis*-retinoic acid have failed to show clinical preventive benefit in current smokers. Treatment with 13-*cis*-retinoic acid did, however, show a potential benefit in persons who had never smoked.

This work, conducted in large, multi-center clinical trials, underscores the need for identification of subjects who are at high risk for developing lung cancer and are favorable candidates for lung cancer chemoprevention trials. The value of epidemiological observations is therefore obvious, as is the need for more effective chemopreventive (natural or synthetic) agents and appropriate surrogate endpoints that might replace clinical outcome as a measure of efficacy.

At this stage in the field of lung cancer chemoprevention, we do not yet have an example of a successful proof-of-principle trial that identifies effective chemopreventive agents, appropriate target populations, or validated surrogate endpoints. There is a consensus that an extraordinary opportunity exists for targeting lung cancer chemoprevention in the years ahead through the support of the National Cancer Institute. This opportunity derives from the presence of new therapeutic agents that target mechanistic pathways important in chemoprevention. Also, innovative diagnostic imaging approaches such as spiral computed tomography and autofluorescence bronchoscopy, will permit identification of early preneoplastic or neoplastic lesions. Conceivably, these imaging approaches will also highlight new subjects for participation in chemoprevention trials.

However, these prospects exist in tandem with a therapeutic nihilism on the part of physicians and patients. Overcoming this nihilism will require an educational effort.

To exploit the considerable opportunity for advances in lung cancer chemoprevention, three priorities are emphasized for their ability to enhance the national lung cancer chemoprevention effort.

RESEARCH PRIORITIES

1. Develop new lung cancer chemoprevention agents.

Rationale

In addition to earlier encouraging work with retinoids as a paradigmatic approach to prevent lung cancer, newer agents appear quite promising for lung cancer chemoprevention. A comprehensive listing of all candidate lung cancer chemopreventive or therapeutic agents is beyond the scope of this report; however, clearly more candidate chemopreventive agents are available for clinical testing than have previously existed. For this reason, a new paradigm is needed for testing efficacy of new agents in chemoprevention trials.

To date, it is not yet known which pathways are required for the maintenance or progression of preneoplastic lesions. Thus, additional candidate chemoprevention agents that target these carcinogenic pathways are needed. An agent must meet certain criteria, including:

- A relevant mechanism of action.
- Preclinical efficacy in in vitro and animal models.
- A favorable toxicity profile.
- Optimal pharmacokinetics.

To develop new agents, closer collaborations are needed between basic and clinical scientists from academic and pharmaceutical settings. These collaborations should exploit relevant preclinical models and animal models (transgenic, knock-in, and chemical carcinogenesis). Interactions between tobacco carcinogens and candidate chemopreventive agents must be considered, especially because study subjects may continue to smoke; previous studies have demonstrated a negative interaction between certain chemopreventive agents and continuing exposure to tobacco carcinogens. This fact highlights the need to target specific agents to subjects carefully characterized by smoking status (current smokers, former smokers, and recent quitters), by genetic changes evident in the affected epithelium, and by phenotyping.

CHALLENGES AND BARRIERS

Development of chemopreventive agents presents distinct challenges:

- Clinical trials of chemopreventive agents are expensive because of their long timeline and large, disseminated study populations. As a result, chemopreventive agents generally take longer to move from discovery to Food and Drug Administration (FDA) approval than agents under study for treatment.
- There is only modest industry interest and participation in such trials, as well as in development of chemopreventive agents. Concerns relate to patent protection issues, safety in chemoprevention trials for at-risk subjects, and dose-limiting clinical toxicity.
- The existing national infrastructure for such clinical trials is limited.

To expedite the development and validation of new chemopreventive agents, closer collaborations are needed among academia, industry, and community researchers to identify and develop new chemoprevention agents. Surrogate endpoints for chemoprevention clinical trials should be redefined and evaluated by the FDA. Currently, the FDA has been reluctant to adopt surrogate endpoints in place of clinical outcome for chemoprevention trials. The use

of such surrogate endpoints could shorten the time frame for clinical chemoprevention trials, making them less expensive and moving more agents toward approval at a faster rate.

2. Establish a methodology to identify high-risk individuals.

Rationale

Although smoking is an established risk for lung cancer, only a minority of even heavy smokers will develop the disease. If reliable models for individuals at high risk for lung cancer can be developed, validated, and applied, clinical trials can be targeted to those cohorts in which the incidence of lung cancer will be high, limiting the size, scope, and cost of chemoprevention trials.

High-risk profiles exist for heavy smokers, such as a more than 70 pack-year smoking history, older age (more than 50 years old), asbestos exposure, and chronic obstructive pulmonary disease. However, no model that incorporates any biomarkers of risk has yet been developed and validated, and we are still unable to identify those individuals at highest risk for tobacco-induced lung cancer.

Resources exist to develop such methodology, for example:

- Families at high risk for lung cancer, who likely harbor a genetic predisposition, can be studied to identify key genes involved in lung carcinogenesis. Genetic alterations discovered through studying high-risk families can be evaluated in appropriate animal models and validated as causes of lung cancer. These models in turn can be used to assess efficacy of chemopreventive agents.

- Case-control and nested studies within cohorts can be performed to identify host-tobacco-carcinogen interactions and establish surrogate endpoints for lung cancer risk. When interactions have been established, animal models can be used to validate the discovery.

- Imaging technologies can identify preneoplastic and fully transformed lung lesions, which can be used as surrogate endpoints in lung cancer chemoprevention trials.

- Microarray profiles of normal, premalignant and neoplastic pulmonary tissue can be used to establish risk.

- Clues from epidemiologic data (such as exposures to non-steroidal anti-inflammatory drugs and dietary factors) can be exploited.

3. Pursue streamlined, mechanism-based clinical chemoprevention trials.

Rationale

Previous chemoprevention trials have been designed with an empiric approach that is not based on a clear understanding of the biology of lung carcinogenesis and the mechanisms of drug action. It is necessary to develop ways to move agents more rapidly from preclinical settings to phase I and II trials, then validate their safety and efficacy to warrant advancement to phase III confirmatory chemoprevention trials.

Both new and known single agents, as well as combinations, should be studied. It is appreciated that effective chemoprevention trials may require optimal combinations of agents. An advantage of targeted chemoprevention therapy is that a specific carcinogenic pathway is antagonized, limiting toxicity associated with non-selective therapies. Another advantage of

combination therapy is that conceivably, each agent could be administered at low doses, resulting in favorable toxicity profiles.

Proof-of-principle trials (using single agents or combination regimens) afford an opportunity to assess not only whether a biologically plausible pathway is affected by the chemopreventive agent but whether the agent exerts the desired clinical effect. This can be accomplished by monitoring changes in affected epithelium in biopsies obtained before and after administration of the chemopreventive agent.

Such trials should exploit available technologies, including newer ones like microarrays, proteomics, spiral computed tomography, and autofluorescence bronchoscopy. The use of combination regimens and novel delivery approaches, such as aerosolization, should be emphasized.

In addition, the population available for clinical trials should be maximized; patients or subjects who do not meet the criteria for one chemoprevention trial may be eligible for a different one. Less than 5 percent of adult cancer patients enroll in clinical trials. Because chemoprevention trials can involve individuals who have not been diagnosed with cancer, enrollment may be even more difficult. Public education for current, former, and never smokers, perhaps through advocacy organizations and funding of educational announcements appearing in various media, is necessary to make patients and potential trial subjects aware of the purpose, design, and benefit of chemopreventive clinical trials.

Education of physicians is also crucial to reduce the air of therapeutic nihilism and the idea of "blaming the victim." This will not only increase trial accrual but help shift the cultural view of lung cancer as a disease that is somehow "deserved" by smokers who are diagnosed with it.

RESOURCES NEEDED

- A broader national infrastructure is necessary for lung cancer chemoprevention trials. The infrastructure should include multiple centers, greater partnership between academic and industry, and a central repository for biological specimens, epidemiological data, and clinical information.

- Education and training are needed for patients, subjects, and physicians. Funding opportunities could be made available to advocacy groups, which are already important educational resources for affected individuals and their families but often must find funding from industry.

- Increased funding is also needed for mechanism-driven chemoprevention trials, with increased participation by chemoprevention experts in the peer review process.

- There is an extraordinary opportunity in lung cancer chemoprevention. Through focused research priorities and targeted investments, therapeutic nihilism can be overcome and the public health burden of lung cancer can be reduced.

Early Detection and Diagnosis

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Writer: *Bob Petersen*

INTRODUCTION

The potential of new imaging and molecular techniques to significantly improve the detection of localized lung cancer provides an unprecedented opportunity to understand the biology, improve diagnosis, enhance treatment, and reduce mortality. These strategies have just begun to explore the utility of spiral computed tomography (CT), fluorescence bronchoscopy, PET imaging, and proteomic and genomic analysis of tumors and other specimens. These approaches (and in particular the application of spiral CT) have the potential to identify small and early lesions that have not been readily accessible in clinical practice through more conventional detection methods. Molecular profiling may assist in identifying high-risk populations, but spiral CT screening offers a unique opportunity to study early carcinogenesis, and potentially to reduce lung cancer mortality.

However, the clinical and biological significance of these small and early lesions is not well understood. Determining the natural history of small pulmonary nodules and the morphological classification of premalignant sputum and bronchial cells (recognized by proteomic, genomic, and morphologic abnormalities) is essential if these novel strategies are to be effectively used.Although several clinical trials are in progress to evaluate new technologies and study early and small lesions, it is important to create the infrastructure necessary to standardize and share imaging features, clinical and epidemiologic information including smoking and family history, and specimen collection. In addition, as novel functional and molecular imaging technologies evolve, a mechanism for rapid evaluation of these advances in future early detection and screening studies is essential so their usefulness can be fully evaluated. We accordingly make the following recommendations.

RESEARCH PRIORITIES

1. **Provide immediate support for clinical research initiatives covering the natural history, management, and follow-up of early or small lesions to evaluate their impact on lung cancer mortality and to develop optimal diagnostic work-up and treatment options.**

Rationale

Although many of these small and early lesions are now being detected, their true clinical significance remains uncertain. This priority would suggest funding to pursue an improved understanding of this spectrum of lesions by many different disciplines.

2. **Develop a lung cancer infrastructure that includes sharing of specimens and data collected during the screening, evaluation, and follow-up of all individuals with early and/or small lesions.** This process should be initiated by national and international workshops to develop optimal protocols for coordination, communication, and specimen collection and preservation, storage, shipping, and labeling of all such specimens. In addition, common data elements and uniform standards for use in a shared data repository should be developed and implemented in both randomized and cohort studies:

A. Coordinate lung cancer screening activities to link expert groups, including but not limited to biology, imaging, pulmonology, medical and surgical oncology, epidemiology, biostatistics, and pathology as exist within the lung cancer SPORES, the EDRN (Early Detection Research Network), and the cohort and randomized controlled trials, such as the Framingham Heart Study, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, the Lung Screening study (LSS), EPIC (Empowered Patients In Control), ELCAP (Early Lung Cancer Action Project), I-ELCAP, NY-ELCAP, and the Mayo, Moffitt, Munster, and Japanese studies.

B. Create a decentralized infrastructure for collecting, preserving, storing, shipping, labeling, and sharing of these biologic specimens and clinical data.

Rationale

A top priority is development of a comprehensive infrastructure for (a) communication among experts in multiple disciplines and (b) collection of specimens from cohort and randomized controlled trials in which state-of-the-art technologies are applied and clinical data are obtained. The coordination of ideas and the expertise to integrate all specialties in a cohesive manner do not exist. Abnormalities that will be of particular interest include the small or early lesions that are being detected by these technologies. This infrastructure should facilitate rapid dissemination of data and ideas among all specialists interested in lung cancer.

3. **Foster and evaluate promising technologies and tools for lung cancer screening and early detection:**

computer-assisted diagnosis (CAD), volumetric computed tomography (VCT), small animal imaging, virtual bronchoscopy, and tissue sampling. Molecular imaging, and functional imaging (e.g., PET and optical imaging) should be evaluated in the clinical assessment of early and small lesions, and the targets, corresponding probes, and contrast agents of interest for lung cancer should be identified. Phase 3 funding beyond the R21 and R33 mechanisms is recommended for these technologies. In addition to cohort and case-series, randomized controlled trials with lung cancer mortality endpoints should be considered and supported when the usefulness of screening modalities is assessed.

Rationale

Imaging and molecular technologies are developing rapidly but are not necessarily focused on detection of early lung cancer. Expanded funding for new imaging technologies is recommended to ensure that lung cancer research takes maximum advantage of these technologies and to focus development of new technology on the problem of lung cancer. As lung cancer screening by high-throughput chest imaging becomes practical, CAD assistance to the radiologist will be essential for rapid evaluation of large numbers of high-resolution images generated by modern multi-slice CT scanners. In addition, integration of these evolving technologies into current and future studies within the created infrastructure will be important. Although current mechanisms (R21 and R33) may provide short-term developmental support, they are of insufficient duration to bridge the gap between initial development and clinical implementation.

4. **Examine premalignant lung lesions with new technological approaches, including but not limited to proteomics and genomics.**

Rationale

Lung carcinomas are typically late stage and biologically aggressive, which accounts for their poor prognosis. They are believed to represent the endpoint of a series of genetic and phenotypic changes that may precede an invasive tumor by many years. It may be appropriate to target these premalignant changes for early detection and intervention by fully characterizing their molecular characteristics, including evaluation of response to specifically targeted intervention. High-throughput technologies such as genomics and proteomics are becoming widely available, and it will be crucial to apply these technologies to the detection of early lung carcinogenesis and outcome assessment.

5. **Conduct long-term follow-up of individuals diagnosed with malignant and premalignant lesions after screening, to understand the modulation of natural history by targeted therapy.**

Rationale

It will be important to continue funding for participants involved in current screening trials who had a tissue biopsy. The natural history of many of these lesions is not yet well understood; follow-up is essential to optimize future patient management and improved understanding of these small and early lesions.

6. **Conduct long-term follow-up of screened cohorts for clinical outcomes, including but not limited to smoking behavior and cost-effectiveness of screening.**

Rationale

Current screening programs, projects, and activities have identified a spectrum of abnormalities (including genetic profiles for cigarette addiction) with unknown clinical and biologic significance. Long-term follow-up of trial participants will help determine the true clinical significance of abnormalities detected by screening and the ability of emerging technologies to reduce lung cancer mortality.

RESOURCES NEEDED

- Workshops to develop commons standards for interpretation of detection technologies, and the collection and sharing of data and specimens.
- Bioinformatics for database building, web-based data mining, and communication.
- Request for Applications for study of early lesions.
- Funding mechanism to supplement R21 and R33 for technology development.
- Database and funding support of long-term follow-up, including data on lung cancer mortality, of individuals diagnosed with malignant and premalignant lesions after screening.

BARRIERS

- Funding.
- Pre-existing uncoordinated specimen and clinical data collection practices.
- Lack of infrastructure.

Etiology

Co-chairs: *Dr. Neil Caporaso,*
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BACKGROUND

Tobacco is the established central etiologic agent in lung cancer and is the major cause of cancer mortality in the United States. Although more than 85 percent of all lung cancers are attributed to cigarette smoking, only a fraction of long-term smokers (hypothesized to be genetically susceptible) will, in fact, develop lung cancer. The complexity of tobacco smoke and the contributions of non-tobacco modifiers of lung cancer risk lead to challenges for etiological studies and for risk assessment. There is a pressing need to explore factors that contribute to the elevated risk retained by former smokers, even after prolonged smoking cessation. Finally, tobacco use is an addiction that is not easily controllable, and better understanding of the biologic basis of nicotine dependence is a scientific and public health priority.

Currently, we do not have validated-risk assessment models for lung cancer that incorporate biomarkers of susceptibility. The following recommendations are provided to develop such models that will enable us to characterize risk for both smokers and former smokers and will benefit screening and chemoprevention trials, as well as the evaluation of newly developing harm-reduction methods. More broadly, better understanding of etiology on both the molecular and population levels may be key to providing mechanistic insights that can enhance prevention and therapy efforts.

RESEARCH PRIORITIES

1. Explore etiologic factors for lung cancer in special populations.

Rationale

Tobacco research is central to our understanding of lung carcinogenesis and cancer risk. Although knowledge about tobacco carcinogenicity has been obtained from diverse lines of evidence, epidemiological studies in special populations are key to unraveling the interplay of extrinsic exposures and genetic and host factors that result in lung cancer. The study of special populations can address specific questions relating to tobacco risk and modifiers of tobacco risk (e.g., occupational exposures, nutrition, immune deficiencies, diet and nutrition, environmental factors, radiation, prior infection or infectious agents) that can be answered in the context of hypothesis-driven research. Thus, priority should be given to studying those populations, in some instances understudied in the past, that provide special opportunities to better elucidate etiological factors and further our understanding of- tobacco carcinogenesis. Further, the value of these studies is greatly enhanced by collection of biospecimens with the added opportunity to address mechanistic questions. The following groups were identified as providing study opportunities, but the list should not be limited to these:

Former smokers: There are 44 million former smokers in the United States at substantial risk of lung cancer in spite of freeing themselves from nicotine dependence. It is a priority to improve understanding of factors that determine risk in this group. Efforts to better understand

the molecular basis for elevated risk in this group through focused biomarker and genetic studies are needed to design effective interventions.

Minorities: There are behavioral and biological factors that can be elucidated by studying different racial and ethnic groups. For example, African Americans are an understudied ethnic group, with a high risk of lung cancer, and specific socio-cultural factors such as mentholated cigarette use.

Individuals with early lesions: Newer lung cancer screening studies, such as spiral computed tomography, provide an exceptional opportunity to identify individuals with early lesions and to identify biomarkers associated with benign, premalignant and early malignant outcomes.

Nonsmokers: Study of nonsmokers offers the opportunity to improve understanding of carcinogenesis associated with low-level tobacco exposure through environmental tobacco smoke and to identify new etiologic agents and cofactors, such as postulated infectious causes. It is important to better understand the etiologic basis for lung cancer in those apparently free of exposure to tobacco. exposure.

Gender-related risk factors: There are controversies regarding reported differences in smoking-associated lung cancer risk for women and men. There may be behavioral and biological factors that contribute to these differences, but additional studies are needed to determine if such factors exist. Comorbid conditions, such as depression, also should be considered.

Lung cancer subgroups: Accumulating sufficient numbers of patients with unusual histologies (bronchioloalveolar carcinoma), young cases or nonsmokers is difficult for any individual study to accomplish. Efforts should therefore be undertaken to enhance cooperation across cohort or case-control studies of lung cancer subgroups**,** in order to achieve sufficient statistical power to study these and other key groups. Methodological (and sometimes political issues) may prove to be barriers; however, providing incentives through targeted grant supplements, encouraging adoption of common data elements and compatible biospecimen handling protocols should be encouraged. Although such cooperative efforts are challenging, they are a priority that merits continued efforts and incentives.

Occupational cohorts: Occupational cohorts provide key opportunities to understand diverse exposure mechanisms as well as issues critical to workplace safety such as dose-response and threshold issues, to understand how such exposures interact with tobacco, and to evaluate new and evolving environmental hazards. Tumor phenotype studies in these groups provide a key resource in answering mechanistic questions such as whether mutational spectra may serve as valid molecular dosimeters of exposure.

Groups that use harm-reduction strategies: Evaluation of populations that use methods for harm reduction (i.e., cigarette-like devices that reportedly reduce exposures or nicotine replacement therapies as an aid to reduce but not stop smoking) will be critical to understand how the changing nature of cigarettes alters risk. For example, low tar and nicotine cigarettes may result in reduced risk of squamous cell cancer but increased risk of adenocarcinoma. Biomarkers will be important to assess these issues since the public health impact will require time to manifest.

2. **Understand the role of genetic susceptibility in lung cancer.** We support both linkage studies in families to accelerate the identification of high-

penetrance genes and population-based studies of appropriate size and design to study candidate genes.

Rationale

Focused studies on both high- and low-penetrance susceptibility genes are needed. Segregation analysis, family studies, and mechanistic work all support a role for hereditary factors in lung cancer. But in common with other complex diseases, and despite a decade of study, the specific genes accounting for excess risk are incompletely understood. There is a consensus that both family and population-based studies are needed to achieve this understanding. Priority should be given to supporting studies in lung cancer families that have the potential to identify high-penetrance genes. Although it is challenging to identify, characterize, and collect lung cancer families, the potential payoff is great. Resources to support this effort should be a priority, because identifying a high-penetrance gene in lung cancer would be a landmark finding.

Molecular epidemiology investigation of low penetrance genes should be mechanistically focused and should include evaluation of pathways other than carcinogen metabolism, such as those involving DNA repair, cell-cycle control, and apoptosis. To contribute meaningfully to the characterization of such low-penetrance genes, population-based studies must be large (generally enrolling more than 1,000 subjects), take into account ethnicity, include careful exposure assessment, and incorporate appropriate design features and biospecimens. These studies are costly because the scale of the effort implies a substantial infrastructure to support field and laboratory efforts. The scientific payoff is correspondingly great, however, and grant mechanisms to support larger integrated studies should be encouraged. Lung cancer is the paradigm for gene-environment interaction, and unraveling how genes and environment act in concert to promote lung carcinogenesis will have applicability for other cancer sites.

Hypothesis-testing of single and small groups of candidate genes remains important, particularly when mechanistic studies are supportive, but studies that investigate multiple genes relating to specific biological pathways (e.g., the study of DNA repair genes) should be encouraged. Newer methodologies that take advantage of the emerging genetic database will require validation, and the development of new biostatistical methods should be aggressively pursued, since heretofore unknown genes or pathways may be identified. DNA microarrays that incorporate many single nucleotide polymorphisms (SNPs) of unknown function are seen as increasingly relevant. Although they have not yet found application in large population studies, they are likely to be implemented in the near future.

Even with less costly high-throughput genotyping, the study size (thousands) and number of SNP markers (tens of thousands or more) available for the next generation of population studies will require the development of methods to optimize the quantitation and pooling of DNA samples. To conduct these studies that will apply the emerging information from the Human Genome Project, close cooperation among epidemiologists, bioinformatics, and geneticists will be needed.

Where possible, tumor (target) tissue studies should be incorporated into epidemiological studies to investigate the relationship of tumor molecular phenotype to exposure (to address the mutational spectrum of particular exposures), to host genotype (study possible "second hits"), and to clinical variables (specific tumor mutations

that predict histology, prognosis, and response to therapy). Such an integrated study setting, described in the next section, will offer the best opportunities to further validate and apply surrogate markers, such as, for example, DNA repair assays in lymphocytes, that are key to understanding and assessing the impact of exposures and susceptibility on carcinogenic risk.

3. **Study biomarkers in an integrated context.** We place a strong emphasis on development, validation, and application of biomarkers to obtain answers to etiologic questions in the context of comprehensive studies that gather exposure information, clinical data, and tissue. Therefore, we propose the creation of innovative support mechanisms that encourage studies integrated centers that span the continuum of lung cancer and incorporate biomarkers linking behavior and exposure on one side to neoplastic outcomes on the other and that carefully consider the role of genetic susceptibilities at each successive phase of the continuum.

Rationale

There are no well-validated intermediate or susceptibility biomarkers that reliably predict lung cancer. Some may reflect exposure or susceptibility, whereas others may reflect the presence of cancer, but none can sufficiently link the two ends of the spectrum. This is a key requirement for improving risk assessment models. Such models will need to incorporate epidemiological data (including smoking, diet, family history, and other exposures) and multiple biomarkers along pathways that reflect different stages of carcinogenesis.

Recent reports and technology advances suggest progress in many categories of biomarkers including cytogenetic markers (FISH), carcinogen-DNA adducts, tumor mutations (CGH, loss of heterozygosity), proteomics, expression (arrays and specific genes), cytology, and epigenetic markers. Investigations conducted in this type of setting can provide an exceptional opportunity to advance mechanistic understanding, identify subgroups at altered risk, understand the relative contributions of tobacco exposure and host factors to disease, and advance chemoprevention and early detection efforts.

Studies or centers should receive special consideration for funding if they propose such a multidisciplinary approach to development, validation, and use of biomarkers. The Etiology Breakout Group proposed the concept of the BEGIN model, which would incorporate the entities of **B**ehavior, **E**xposure, **G**enetics (Germline), **I**ntermediate Biomarkers, and **N**eoplastic molecular markers (i.e., tumor tissue). (Need to highlight the first letter of each) Such integrated approaches should allow for the most efficient characterization and development of new biomarkers that are needed for risk assessment and chemoprevention approaches. This, in turn, would ensure that biomarker studies are conducted in a setting that promotes multidisciplinary participation, a rich array of study questions that can be addressed, the opportunity to include behavioral issues in studies (e.g., smoking cessation, smoking topography, psychological factors that contribute to smoking persistence), and a highly efficient and cost-effective approach. Questions that are critical to both behavioral and cancer scientists, such as, “What are the genes that contribute to smoking dependency?” may also be efficiently addressed in such study settings.

RESOURCES NEEDED

- NCI's Extraordinary Opportunity in tobacco should be maintained as a means of supporting broad and vigorous scientific and public health efforts focused on the major etiologic factor in lung cancer.

- An ability to combine data across studies is needed. A web site should be created that encourages the use of common data elements relevant to lung cancer and provides technical information on standardization, best practices, and protocols involved in biospecimen collection, processing, and information management.

- Training in genomic, post-genomics (expression and proteomics), and informatics is needed for investigators at all levels to take advantage of interdisciplinary opportunities. Although recently created Transdisciplinary Tobacco Centers have training programs, most are weak in the area of tobacco carcinogenesis.

- Standardized validated questionnaires that assess tobacco exposure accurately at diverse levels should be made available through web-based resources.

BARRIERS

- Previous studies of genetic susceptibility factors have been too small to achieve adequate statistical power. Clinically-based studies that include molecular markers sometimes fail to gather critical exposure data.

- Bioinformatics, biorepository, and data management support are generally needed to support large-scale integrated studies and to promote pooling across studies, sharing of specimens, improved quality control, and other scientific priorities.

- Insufficient data are available to evaluate the ability of purported harm-reduction strategies or products to reduce lung cancer risk.

- Animal models for complex exposures are inadequate for exploration of tobacco carcinogenesis, dose-response relationships, and dose adjustments that mimic harm-reduction strategies.

- Epidemiologic study designs have not fostered the comprehensive evaluation of biomarkers specifically correlating the relationship of surrogate susceptibility markers both with etiologic factors and with tumor phenotype.

Prognosis and Staging

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INTRODUCTION

There are generally recognized deficiencies in the staging of both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Improvements in the staging of lung cancer will form the cornerstone of studies of the biology of the disease, which in turn will allow hypothesis-driven clinical trials and lead to critical advances in therapy. The issues related to staging and prognosis can be broadly considered under the categories of clinical staging and biological/molecular staging.

RESEARCH PRIORITIES

1. **Revise and refine the current clinical staging systems for NSCLC and SCLC—an improvement that will also facilitate evaluation of imaging modalities for lung cancer. This priority requires the development of a linked clinical and pathological database.**

2. **Investigate molecular markers of detection, staging, prognosis, and response to therapy. This priority requires creation of a biospecimen repository linked to the clinical/pathological database and is best achieved through a disease-specific, multi-center, and multi-disciplinary lung cancer group.**

Develop statistical approaches (e.g., algorithms) and present data in a standard format that will make it possible to integrate clinical information and molecular profiling. This priority requires development and support of bioinformatics, statistics, and clinical epidemiologic expertise, as well as relevant infrastructure.

STANDARD CLINICAL AND PATHOLOGICAL STAGING

Rationale

The current staging systems for both NSCLC and SCLC have notable deficiencies because they fail to discriminate several prognostic groups accurately. For NSCLC, the current TNM system, based on primary tumor, regional nodes, and metastasis, may not precisely describe very early (less than 2 cm) tumors, and conversely, may not accurately stratify the more advanced tumor subsets. For SCLC, a significant discrepancy exists between what is usual clinical practice and the American Joint Committee on Cancer (AJCC) recommendations for staging. Most oncologists use a "limited versus extensive" stage classification, whereas the AJCC staging manual indicates that the same TNM-based system used for NSCLC should be applied to SCLC.

Clinical staging is also hampered by variations and inadequacies in pretreatment imaging studies. Few standards exist, and the algorithms for follow-up remain undefined. Investigation in this area is needed.

RESOURCES NEEDED

- Revision of the staging system will require large, multi-center clinical databases with well-characterized patients, long-term clinical follow-up, and careful clinical-pathological correlation. Such databases do not exist. An effort under way by the International

Association for the Study of Lung Cancer (IASLC) is hindered by large international variations in the types and contents of data sets, as well as a lack of funding; therefore, this issue, as well as studies of imaging modalities, would best be addressed by a funded, disease-specific, lung cancer group effort to generate and maintain a clinical database that incorporates standardized nomenclature.

BIOLOGICAL AND MOLECULAR STAGING

Rationale

Improvements in the TNM-based clinical and pathological staging will be unable to describe fully the biology of individual tumors. A staging system that includes molecular profiling of abnormalities will be pivotal to defining prognosis and selecting therapy. Despite much investigation into individual genetic abnormalities in lung cancer during the past decade, comprehensive analysis of genetic abnormalities in relation to clinical and pathological features is still lacking. Molecular profiling is a major objective for which significant resources will be required. This effort may require an intensive study of very well defined, relatively small patient cohorts (100–200 patients), followed by validation across larger cohorts. Genetic studies should include non-smokes as well as smokers.

Beyond contributing to prognosis, important applications of molecular profiling of both smokers and non-smokers include predicting response to therapeutic interventions (chemotherapy, radiation, targeted therapies), detection of occult metastases, and risk stratification for recurrence or the development of second primary tumors. Emerging information suggests that serum markers, including shed tumor DNA and proteins, may be useful in detection, staging, and evaluation of response to therapy. This is an area of novel investigation with great clinical potential.

The wealth of new molecular information and the complexity of the analyses needed to integrate molecular and clinical data, particularly array data, require statistical and bioinformatics research and development of algorithms. Recruitment and training of relevant personnel with multi-disciplinary expertise in these areas (e.g., pathology and bioinformatics) is of paramount importance. The professionals required for this effort should be regarded as participating faculty, not merely as service personnel.

RESOURCES NEEDED

- Critical to this effort will be the previously described prospective clinical database, paired with a biospecimen repository. Such a repository should include snap-frozen tumor and related benign tissues suitable for array analyses; fixed, paraffin-embedded specimens for tissue arrays; serum/plasma, sputum, buccal mucosal cells, urine, and bone marrow. The collection and characterization of such a resource require a close, funded collaboration among pulmonary medicine physicians, thoracic surgeons, pathologists, oncologists, epidemiologists, and molecular biologists. Components of such a resource now exist in various cancer centers and cooperative groups, but a comprehensive and integrated high-quality resource tied to a clinical database does not. A biospecimen repository that can rapidly yield clinical correlation is best developed in a national setting by a multi-disciplinary, lung cancer-specific, multi-center group.

Additionally, bioinformatics and statistical resources are needed in the forms of hardware, software development, and algorithm development. These resources should be developed in both cancer centers and cooperative groups. This effort will also require the establishment of common data elements for clinical, pathological, and molecular data sets.

EDUCATIONAL NEEDS

- The support and development of dedicated academic investigators who speak a common language across all relevant disciplines is key to the success of this effort. At present, the large challenge presented by lung cancer is studied by very small numbers of clinical and laboratory investigators. Formal opportunities for cross-disciplinary education are needed and could be the subject of regular NCI-sponsored training conferences. These should be aimed not only at established investigators and trainees but at the primary physicians who initially care for patients with lung cancer. Of equal importance is the dissemination of new information about prognosis and methods of staging to patients and their caregivers. One way this might be accomplished is through the support of advocacy groups.

BARRIERS

- A significant barrier to creating the biospecimen repository is the increasing regulatory burden on investigators. In recognition of the importance of patient confidentiality and anonymity, this burden could be diminished through a concerted NCI-sponsored effort to standardize and facilitate informed consents and Institutional Review Board review.

- With respect to lung cancer studies, consideration could be given to the fact that most of the molecular alterations under study are somatic rather than germline. Further, in lung cancer—a disease whose biology is poorly understood—exploratory analyses of as-yet uncharacterized or unknown genes should be emphasized. Genetic studies that involve both smokers and non-smokers may reveal genetic predispositions to the disease. Discovery of new genes is critical for advances in lung cancer staging and therapy. Undue regulatory barriers may inhibit this very important approach to the study and treatment of lung cancer.

Quality of Care

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BACKGROUND

Quality of care has been defined by the Institute of Medicine as "the degree to which health services…are consistent with current professional knowledge." In addition, quality care is "…care that incorporates respect for patients' values and preferences" (National Cancer Policy Board).

The quality of care for lung cancer patients was considered in the context of these definitions using the quality triad of structure, process, and outcome. Using this approach, it was possible to identify research opportunities that would address gaps in our current knowledge of the quality of care of lung cancer patients and build on existing research initiatives.

The Quality of Care Working Group considered the structural issues for the quality of lung cancer patient care to be those elements or components of the health system that are required for delivery of services from screening to diagnosis, treatment, supportive care, and palliative care. Although discussion focused on the specific needs of patients receiving treatment and related care, because of the magnitude of the perceived problems, it was also noted that significant structural issues exist in relation to the provision of screening and prevention services and programs.

Health system organizational structures that could affect the quality of care for lung cancer patients include: (a) the type of health care facility (e.g., tertiary care vs. community oncology clinic); (b) the organization of service delivery (e.g., multidisciplinary clinics and tumor boards vs. private solo practice); (c) the availability of human resources and degree of specialization; (d) access to new technologies and equipment; and (e) the availability of, and access to, home health and hospice care. Knowledge of the optimal components and organization of service provision would not only facilitate the spread of current best practices but serve as a platform for the conduct of clinical research and the rapid dissemination of research findings.

The Quality of Care Working Group agreed that it would be extremely useful to know the extent to which best practices for the management of lung cancer are currently adopted and appropriately applied in various settings across the United States. There is research evidence, for example, that curative lobectomy is not used to the optimal extent for minority groups, and there is substantial anecdotal information on the non-uniform use of combined-modality treatment for stage III non-small cell lung cancer (NSCLC) and of systemic chemotherapy in advanced disease. This knowledge base needs to be greatly expanded if current and future treatments are to be disseminated to the benefit of all patients. Studies are required to determine the use of these best practices, including such potentially curative interventions as lobectomy for stages I and II NSCLC and combined-modality chemo-radiotherapy for limited small cell lung cancer (SCLC) and stage III NSCLC. Similarly, information on the use of prophylactic cranial irradiation (PCI) in SCLC and chemotherapy in stage IV

NSCLC would be invaluable in directing efforts to ensure that lung cancer patients are offered the best therapy currently available. In addition, information on the prevalence of inappropriate use of practices, such as the administration of adjuvant chemotherapy or radiotherapy after completely resected NSCLC would be important to shape educational initiatives in order to ensure conservation of scarce resources and the delivery of optimal care.

Additional questions of concern for processes of care include (a) the extent of surveillance for new primary tumors in patients with curatively treated stage I and II NSCLC, (b) the extent to which patients with stage III NSCLC are appropriately assessed (staged) for combined-modality therapy, and (c) whether patients with stage IV NSCLC share in the decision-making for care, receive psychosocial care and informational support appropriate to need, and are offered participation in a clinical trial. For end-of-life care, it would be important to examine the processes of care to ensure optimal control of pain and symptoms, the appropriate use of advanced directives and the involvement of patients and their families in the decision-making for the most appropriate location of dying (e.g. home, hospice, hospital).

The principal outcomes examined in lung cancer clinical trials have been response and survival; patient-related outcomes have been examined much less often. Outcomes of importance to patients include quality of life, complications of therapy, quality of death, economic burden, and satisfaction with care, and these outcomes need to be formally adopted into future clinical research endeavors.

RESEARCH PRIORITIES

1. **Develop, implement, and evaluate models of care delivery to optimize the delivery of best-known clinical practice and to determine the effects of these models on the processes and outcomes of care and on accrual of patients to clinical trials. For example, assess the effect of specialized or multidisciplinary management settings, telemedicine initiatives, informatics support, and integrated supportive and palliative services.**

Rationale

Several studies have found that medical interventions for which good evidence of survival benefit exists are not uniformly adopted (e.g., lobectomy for early-stage NSCLC, prophylactic cranial irradiation for SCLC, and concurrent combined-modality therapy for limited SCLC and stage III NSCLC). There is also evidence of a strong relationship between volume of activity and patient outcomes. Although current initiatives such as CanCORS may start to document the extent of the problem in lung cancer care, further work will be needed to determine why such disparities exist and to develop strategies to correct them. In doing so, it will be important to identify valid measures of the quality of lung cancer care and to evaluate novel programs of service delivery, including approaches such as regional diagnostic assessment units and multidisciplinary consultation, access to allied health professionals for supportive care, access to peer support, and access to hospice care. Research proposals may range from innovative pilot studies to optimize the delivery of such services to a consortium performing cluster randomization to evaluate specific interventions. It will be essential to engage community practices in

these efforts and to evaluate outcomes in relation to patient volumes.

1. **Build on existing NCI programs, to address the special needs of lung cancer patients:**

   A. Earmark funds within the Centers of Excellence in Cancer Communication and related initiatives to study ways to (a) improve communication between doctors and lung cancer patients and their family members; (b) enhance patient and provider knowledge of prevention, screening, and care options; (c) increase shared decision-making around lung cancer therapies and complementary and alternative medicine; and (d) increase participation in clinical trials.

   B. Extend CISNET activities to (a) include the development of a model of lung cancer management to support the evaluation of new technologies and (b) assist design of clinical trials and inform policy decisions.

Rationale

Lung cancer is unique within oncology in many ways:

- It is the most common cause of cancer-related death; for this reason, new screening and treatment technologies can have enormous public health implications.

- The population it affects tends to be older and of lower socioeconomic and educational levels than other malignancies.

- Treatments, particularly for advanced disease, have significant side effects and are often of only modest benefit.

- The stigma that lung cancer is a self-inflicted disease, coupled with a pervasive sense of therapeutic nihilism, conspire to create a medical environment in which many patients with advanced lung cancer are not even offered treatment.

Consequently, it is important to overcome the atmosphere of therapeutic nihilism, to educate care providers and patients, and to identify strategies that facilitate the communication of treatment options that take into account patient preferences for care. It is also important to explore the use of complementary and alternative medicines among lung cancer patients and communication strategies that can heighten awareness of, and participation in, clinical trials.

Because of the great need to make therapeutic progress against this disease, participation of patients in clinical trials must be greatly enhanced. Experience with other diseases provides evidence that patients in clinical trials receive high-quality care. Furthermore, patients with cancer feel that it is an important element of quality of care to have access to trials. It is crucial that patients participating in such trials have adequate decision-making support. For example, decision aids could be developed and assessed in terms of their ability to help patients make decisions with a clear understanding of the goals of the trial and their influence on patient satisfaction with the decision-making process.

Several expensive new technologies are being introduced into lung cancer management, including spiral computed tomography (SCT) for screening and PET scans for staging and assessment of response

to treatment. Because lung cancer is so common, such developments have important economic, public health, human resource, and policy implications. Computerized disease models should be used to evaluate these issues. Moreover, models can be used to optimize the selection of target populations in the design of large prospective trials.

3. **Extend the work currently under way at the NCI Outcomes Branch to develop standard tools for measuring patient-reported outcomes of particular relevance to lung cancer patients, to be incorporated into NCI-sponsored clinical trials:**

   A. Convene a consensus meeting that includes patients to define the specific data elements, their definitions, and methodological approaches necessary to capture these patient-related measures of quality of care: quality of life; assessment of symptoms; physical and psychosocial effects of treatment; patient satisfaction; and economic burden for patients and caregivers.

   B. Convene a separate consensus meeting to define the data on resource use that should be captured alongside clinical trials and define which trials are the best candidates for such economic evaluations. This information can improve understanding of the relative cost-effectiveness of new interventions and assess the economic impacts of their adoption on the health care system.

Rationale

Clinical trials have traditionally focused on response and survival outcomes. Unfortunately, only modest progress has been made in the treatment of lung cancer; consequently, patient-reported outcomes, such as quality of life, cancer-related symptoms, and complications of care, should assume greater importance. For some of these measures, a plethora of instruments already exist; for others, these measurement tools will need to be developed. NCI's Outcomes Branch has convened the Cancer Outcomes Measurement Working Group (COMWG) to evaluate outcome measures for cancer in general. The Quality of Care Working Group proposes that this work be extended to identify a standard set of core measures for inclusion in appropriate lung cancer trials. For some measures, such as quality of life, this will involve choosing the best instruments among many, whereas areas such as patient satisfaction are in need of methodological research, including both quantitative and qualitative techniques and the evaluation of the clinical significance of changes in scores. NCI should provide additional support to clinical trials specifically for the study of these outcomes.

RESOURCES NEEDED

Funds are needed for investigator-initiated pilot studies or randomized trials through existing cooperative groups, NCI's Community Clinical Oncology Program, health maintenance organizations, or new consortia to address issues related to the organization of service delivery to achieve optimal quality of care and maximize clinical research capability:

1. **Building on existing NCI programs:**

   A. Earmark funds in the Cancer Excellence in Cancer Communication program for evaluation of communication issues for lung cancer patients.

B. Provide new funds to CISNET to develop a model of lung cancer disease management.

2. Support the development of standard tools for measuring patient-reported outcomes and economic burden:

A. Fund a consensus meeting of representatives of the lung cancer clinical trials community; the pharmaceutical industry and patients, family members, and survivors to develop data elements and their definitions for inclusion in NCI-sponsored clinical trials.

B. Fund a consensus meeting to determine the resource use data that should be captured alongside clinical trials and the criteria to define the most appropriate trials requiring economic evaluation.

C. Commit NCI funds to apply these tools to measure the patient-related outcomes in future lung cancer clinical trials.

Therapy

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INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality in the United States and in the world. In the United States, the 5-year survival rate remains less than 15 percent. However, major advances in the treatment of lung cancer have occurred in the past decade. For example, a 50–70 percent improvement in the median survival times of patients with locally advanced small cell lung cancer and non-small cell lung cancer has been achieved. Such improvement emphasizes the success of multi-disciplinary lung cancer research.

Advances in lung cancer have not been as well recognized or as widely implemented as would be anticipated, given the common nature and severity of the illness. At the same time, lung cancer offers many great research opportunities:

- This disease has a high incidence and known etiology.
- People at risk are easily identified.
- Tissue is fairly accessible.
- The biotechnology and pharmaceutical industries are interested in studying new agents in this disease.
- The public is acutely aware of the devastating nature of the lung cancer.

Despite these significant opportunities for research, lung cancer receives disproportionately less funding than other cancers. Funding lung cancer research at appropriate levels is especially important when one considers its prevalence and economic impact.

There are several barriers to progress in therapeutic research for lung cancer. These include:

- A lack of funding mechanisms for multi-disciplinary collaborations.
- A lack of lung cancer-specific tumor banks with associated clinical information and ongoing support for tissue acquisition for pathologists and surgeons to collect and process tissue samples.
- Insufficient training and educational opportunities.
- A lack of salary support and academic recognition for clinical investigators.
- Regulatory burdens.
- Limited public understanding of the advances achieved through multi-specialty research and care.
- Lack of adequate support for participation in cooperative group clinical trials.

The rapid rate of discovery of candidate molecular targets for lung cancer therapy and candidate agents has increased the opportunity for benefit from enhanced research support. This progress has created the need for new paradigms of clinical trial design. Additionally, improvements in functional imaging and planning and

delivery of radiation oncology treatment provide an unprecedented opportunity to enhance tumor control while decreasing treatment-related morbidity. Such developments further emphasize the need for coordinated research among many disciplines.

Progress in lung cancer research is evidenced by the activity of the centers with SPORE grants, the success of clinical trial groups that study stages III and IV disease, and the emergence of an active advocacy group, Alliance for Lung Cancer Advocacy, Support, and Education (ALCASE). Progress has been limited, however, in identifying and testing new therapeutic approaches for patients with stages I and II lung cancer, in verifying the clinical utility of molecular predictors of either prognosis or response to treatment, and in being able to rapidly perform phase I and II studies of new targeted therapies with biologic endpoints. Progress will also continue to be limited in the future by the paucity of clinical investigators staying in or entering academic medical oncology in general, and lung cancer research specifically.

A coalition of lung cancer-specific clinical centers of excellence working together, modeled on SPORE lung cancer-specific translational research centers of excellence, would enable clinical opportunities to be addressed. A strong intramural lung cancer center of excellence would synergize with this extramural effort.

RESEARCH PRIORITIES

1. Select, test, and validate new targets in therapeutic clinical trials.

Rationale

The advances in understanding of lung cancer pathogenesis have identified multiple new targets for therapeutic intervention. The number of potential targets and interventions based on these targets exceeds the capacity of clinical trials to accrue the patients needed to address all potential agents. Therefore, a method of selecting and setting priorities for the best targets is necessary. One way to assist this priority-setting process is to identify the most frequent abnormalities in specific lung cancers compared with normal tissues, which requires access to well-characterized specimens from patients with lung cancer of various histologies and stages. These well-characterized specimens with clinical correlations are not available. In addition, there are inadequate ways of funding the acquisition and processing of such biologic specimen repositories, and regulatory burdens inhibit establishment of such repositories.

To use biologic information from tissue samples in clinical trial and clinical management decisions, assays must provide rapid and reproducible results. Because clinical circumstances often allow for only small biopsies of tumor specimens, these assays must be able to be conducted with small amounts of tissue. In addition, clinical trials must test the ability of functional imaging techniques to provide relevant information about antitumor response and targeting success, without the need for invasive procedures.

Adequate attention to all of these issues would require support of thoracic surgeons to obtain the proper specimens, support of pathologists to access and process the specimens appropriately, uniform clinical and pathologic staging, therapy, and follow-up of the patients from whom the tissue was obtained.

2. **Optimize design, conduct, and support of clinical trials:**

   A. Establish a consortium of centers with multi-disciplinary excellence in lung cancer clinical trials.

   B. Develop lung cancer-specific Requests for Applications (RFAs) and Requests for Proposals (RFPs) for study of selected novel therapies in lung cancer.

Rationale

Advances in lung cancer care during the last 10 years have resulted from landmark observations in randomized trials of patients with stage III and stage IV disease. However, advances in biology and technology require new clinical trial paradigms with an emphasis on design and accrual to novel Phase I and II trials, as well as studies of early-stage disease in which the therapies will have the greatest impact on mortality. These novel early-phase and early-stage trials, by definition, will require coordination among centers, each of which must have excellence in multi-disciplinary interactions. Most of these trials will require tissue correlations, functional surrogate endpoints, or both, as discussed in the first recommendation. We recognize that many cancers (e.g., breast, prostate, and ovarian) have multiple specific funding mechanisms, from NIH as well as other Federal and non-Federal organizations. Because few such opportunities are available in lung cancer, the recommendations for RFAs and RFPs are particularly important.

The number of patients accrued to trials in stage I and stage II lung cancer is inadequate. In addition, the number of Phase I and II trials is not sufficient to assess all the new targeted therapies and combinations. This creates the need for new funding mechanisms to support these types of trials. Barriers to clinical trial accrual are listed in the third recommendation.

Solutions to the burdens and costs associated with regulations include the development of standardized informed consent forms, the protocol-specific definitions of standard care and research care, and centralization of Institutional Review Board processes. Uniform and simple ways of complying with regulations in the most cost-effective manner need to be developed centrally.

3. **Support and expand multi-disciplinary interactions in clinical research:**

   A. Support a consortium of centers of excellence that would be able to rapidly design and conduct early-stage and early-phase trials.

   B. Support individual centers that have unique clinical trial concepts and targets.

   C. Compensate principal investigators on all peer-reviewed clinical trials.

Rationale

Early-stage and early-phase trials will require consistent collaborations among specialists with particular expertise in thoracic oncology, including surgeons, radiologists, pulmonologists, medical oncologists, radiation oncologists, pathologists, and laboratory-based scientists. No current funding mechanisms support this type of multi-specialty interaction. We believe that new funding mechanisms should be developed. The first would support a consortium of centers of excellence that could rapidly design and conduct early-stage, early-phase trials. This approach requires a modest infrastructure,

including a competitively designated statistical and informatics center. This consortium could also address other issues, such as a clinical database linked to a specimen biorepository. The second would support individual centers with unique clinical trial concepts and targets through lung cancer-specific RFAs and RFPs.

Only small numbers of academic clinical oncologists are dedicated to lung cancer studies. The reasons include lack of salary support and academic recognition for clinical investigators, lack of multi-disciplinary funding mechanisms, and mounting regulatory burdens and associated costs. Thus, we recommend that the principal investigators on all peer-reviewed clinical trials be compensated for their time and effort by well-defined support that can come from existing center grants or from the new coalition.

The burdens mentioned are coupled with a history of clinical and therapeutic nihilism toward lung cancer in the medical and academic communities. Thus, we recommend RFAs and RFPs for education and communication specific to lung cancer.

RESOURCES NEEDED

Resources that could support current and future efforts in lung cancer include:

1. **International database for staging classification and modifications thereof.** The current lung cancer staging classification was based on data collected through the Lung Cancer Study Group and the M.D. Anderson Cancer Center through the efforts of Dr. Clifton Mountain. This database no longer exists and was flawed by a number of factors, including the fact that patients with stage IIIB or IV disease were not included and old staging and treatment protocols were used. A recent meeting including representatives from International Association for the Study of Lung Cancer, the World Health Organization, the International Union Against Cancer, European Union for Research and Treatment of Cancer, American Joint Commission on Cancer, and others was recently held in London, and all agreed to participate in a new international database. Funding for such a database, however, is problematic. It was agreed that the United States was a logical "home" for such a database, and a competitive funding mechanism was reviewed as highly desirable and efficient.

2. **Support for surgeons and pathologists to collect, prepare, and preserve well-characterized specimens with adequate clinical staging and follow-up for multivariate prognostic studies and for predictive therapy studies.** Adequate collection, processing, distribution, and study of well-characterized specimens was viewed as a critical problem that could be solved by specific funding of data managers to assist surgeons and pathologists in tissue collection and processing and to assist treating oncologists in collecting the clinical information and in follow-up. Funding could flow through groups conducting lung cancer trials, including studies through any or all of the following: cooperative groups, a new Lung Cancer Study Group, and cancer centers. The tissue collection would include paraffin blocks, fresh tissues, and biopsy specimens.

3. **A research consortium for early phase I-II trials and for trials in stages I and II lung cancer, including lesions less than 1 cm.** It was obvious to all participants that a suboptimal number of patients have been enrolled in early-stage trials since the closure of the Lung

Cancer Study Group. It was also clear that input from thoracic surgeons is essential for early-stage trials. The cost of the infrastructure for such a group need not be large, because the statistical portion could, as well as new groups of patients (e.g., with tumors less than 1 cm), available for study. Finally, these trials require multi-specialty excellence in pulmonology, biology, imaging, pathology, thoracic surgery, radiation oncology, and medical oncology. Thereafter, one or two groups consisting of a consortium of centers with multi-specialty experts in early-stage and early-phase trials was thought to be critical.

4. **Support for academic lung cancer physicians-scientists through Cancer Center Support Grant (CCSG) and group mechanisms.** Lung cancer is not seen as an attractive field of research because of the nihilist view of various specialists, the multi-specialty requirements for successful research, the poor outcome of patients, and the stigma of tobacco. Existing political pressures led to creation of multiple avenues for support of investigators in other cancers, including the Department of Defense, private foundations, and NCI. Lung cancer investigators do not have access to these funding mechanisms and receive little encouragement from department chairs. Principal investigators on all peer-reviewed clinical trials need to be compensated for their time and effort in order to have credibility within the academic environment and protected time for their research. Specific support mechanisms are needed. These can be directed through existing CCSG and cooperative group mechanisms.

5. **A strong intramural NCI program in lung cancer.** The previous excellence of the NCI intramural program in lung cancer was viewed as an example of the ways in which intramural and extramural scientists can advance the state of the art. It was noted that the emphasis and excellence of the intramural program had dissipated. The group recommended re-establishing an intramural center of excellence in lung cancer research.

6. **Adequate support for participation in clinical trials.** The regulatory burden on the clinician has increased dramatically over the past five years. The current co-operative group mechanism does not adequately compensate investigators for their regulatory and data management costs of putting an patient on trial. This is a strong dis-incentive for participating in clinical research.

7. **Adequate support for junior investigators.** A young investigator interested in clinical lung cancer research has a formidable uphill task finding protected time to do so, given the clinical and fiscal pressures on most academic departments of medicine. There will be few academic clinical researchers in lung cancer in five to ten years unless resources are found to support them in their early career development. The K24 is an excellent approach to this problem, but requires that investigators already have peer-reviewed support.

BARRIERS

1. **Education and training.** Lung cancer-specific education and training of physicians and other caregivers, the public, and patients and families is needed. There should be RFAs and RFPs for education and training.

2. **Investigator support and recognition.** Clinical lung cancer-specific salary support and academic recognition for

principal investigators is not equivalent to peer-reviewed funding. This could be rectified through the cancer centers, cooperative groups, and a consortium mechanism.

3. **Regulatory issues.** Centralized, simplified processes (including the definition of standard care and research care and a standardized Institutional Review Board) should be endorsed, a standardized consent form should be developed and used, and the costs associated with regulatory burdens should be reimbursed.

Tobacco Control

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BACKGROUND

Nicotine addiction is the single most important challenge facing efforts to reduce lung cancer incidence and mortality in the United States; 30 percent of all cancer mortality is attributable to tobacco use. No other cluster of risk factors, including genetic and biological factors, lifestyle factors, and environmental factors, has as high an association with lung cancer as smoking. Because smoking accounts for almost 90% of all lung cancer cases, and because quitting smoking can reduce (but not eliminate) the elevated relative risk of lung cancer, the greatest impact on deaths from lung cancer in the United States will result from efforts to prevent smoking and from helping smokers to quit. Thus, significant attention and resources should be allocated to interventions to reduce tobacco use and to the evaluation of the effects of those interventions.

Eliminating tobacco use as a risk factor for lung cancer is especially challenging because of tobacco's addictive nature. Although smoking prevalence has dropped 40 percent since the 1964 Surgeon General's report, one in four adults still smokes. Another one in four is a former smoker, who retains an elevated risk for cancer. Furthermore, this is one area where health disparities are most apparent and lethal. The highest prevalence and greatest burden of disease today, and in the future, is borne by those with the least income and education. For example, women with only 9–11 years of education are three times more likely to be current smokers (32.9 percent) than are women with 16 or more years of education (11.2 percent). Furthermore, marketing of tobacco products has clearly targeted not only youth but other vulnerable populations as well. The most effective way to influence the problem of health disparities in the United States is to use targeted population-based tobacco control strategies and protocols to reduce smoking.

Overall, cigarettes kill more than 430,000 Americans each year. We must increase the societal investment and commitment to research that can identify effective tobacco control measures, and ensure the broadest implementation of those measures. At present, the health community is at a distinct fiscal disadvantage. The tobacco industry spends more than $8.2 billion per year promoting its products in the United States alone, 10 times more than all 50 states combined are spending on tobacco prevention and cessation.

Secondhand smoke is the third leading cause of preventable death in the United States, killing an estimated 53,000 non-smokers each year, approximately 3,000 of them from lung cancer. Reviews published in the 1986 Report of the Surgeon General, by the National Research Council in 1986, and by the U.S. Environmental Protection Agency (EPA) in 1992 concluded that exposure to secondhand smoke causes lung cancer. Several large U.S. population-based and smaller hospital-based case-control studies have been published since the EPA review was completed, as has a large multi-center European case-control study. Most of these studies have corroborated the association between at least high levels of exposure to secondhand smoke and lung cancer, although results from single studies have not always been statistically significant.

RESEARCH PRIORITIES

1. **Support research initiatives to understand the biology of and to improve the treatment of nicotine addiction and to examine tobacco harm reduction targeted to those who are unwilling or unable to quit.**

Rationale

The U.S. Public Health Service guideline on smoking cessation provides clear, concise, and evidence-based clinical guidance for clinicians and the general public on what treatment approaches work best. Although significant progress has been made in the success rates from these therapies, there is considerable need for more research on smoking cessation, because the long-term quitting rates at present seldom exceed 25 percent and because real world effectiveness of treatments remains unclear. This challenge highlights the need to develop a greater understanding of the biobehavioral and social processes that are responsible for the trajectories from tobacco experimentation to dependence in order to inform, target, and improve on interventions.

Research on harm-reduction products and approaches should also be given attention. According to the Institute of Medicine report *Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction*, "a product is harm reducing if it lowers total tobacco-related mortality and morbidity even though use of that product may involve continued exposure to tobacco-related toxicants." Given the existing harm-reduction products and the potential for new tobacco and cigarette-like products that are being developed by the tobacco industry, alleged to be "safer" than conventional cigarettes, the development of methods and standards to identify and define the differential toxicity of these products is necessary to protect the public health. Furthermore, the relationship between intermediate biomarkers for exposure to tobacco toxins and disease, and the dose-response relationship between tobacco exposure and these biomarkers, needs to be explored. Of equal importance is the need to address the public health implications of tobacco harm-reduction products and how to communicate to the public the implications of using these products. Three decades ago, the introduction of "low tar" cigarettes only increased the already significant public health burden due to tobacco use because it permitted smokers to believe they were reducing their risk of illness when no such data existed. As new "low-yield products" are introduced by the tobacco industry, an acceleration of research in this area is imperative if we are to avoid further adverse public health consequences.

Examples of necessary research directions follow.

- Improve understanding of the nicotine addiction continuum—from initiation to dependence to cessation to relapse—and the multiple factors and causal pathways that may contribute to the development of nicotine addiction. These factors can range from a greater understanding of the genetic basis of addiction, evaluation of specific receptor targets of nicotine, to changes in the brain resulting from chronic exposure to tobacco. In addition, a greatly expanded effort is needed to explore gene-environment interactions and to better characterize and measure the influence of environmental and genetic factors on the addictive process.

- Improve current pharmacological treatments (e.g., combination medication therapies, non-nicotine products, products that target specific receptor sites, and antagonist therapies); develop novel behavioral treatments that

augment pharmacological treatments or stand alone; and explore patient-treatment matching, which may include a pharmacogenetics approach, and pursue this approach with appropriate attention to privacy and confidentiality issues.

- Develop animal models for understanding the effects of nicotine from the cellular to the behavioral level, including models to test novel medications. Results from animal models should be used to inform human models, and results from human models should be used to drive research with animals.

- Assess harm-reduction approaches, that is, reduced smoking with and without the aid of pharmacological agents and potential reduced-exposure tobacco or cigarette-like products. The recommended areas of research include those specified by the Institute of Medicine report *Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction*: (a) "description of dose-response relationship between smoke and/or constituent exposure and health outcomes in the context of exposure reduction; (b) identification and development of surrogates for disease (e.g. biomarkers that reflect mechanisms of disease and that serve as intermediate indicators of disease and disease risk) (c) the development of appropriate animal models and in vitro assays of the pathogenesis of tobacco-attributable diseases (e.g., cell culture, animal studies, and molecular studies to document specific tobacco toxicants as the most likely causative agents for disease, to better define pathogenic effects of tobacco smoke exposure, to better explain the relationship of disease risk regression and exposure regression, and to validate biomarkers of exposure and biological effect) (d) short-term clinical and epidemiological studies; and (e) long-term epidemiological studies and surveillance." In addition, research on risk perception and risk communication and marketing issues related to these harm-reduction approaches should be pursued to minimize their negative impact on public health.

- Assess the safety of nicotine (e.g., long-term use, use in pregnant women).

2. **Encourage and fund integration of tobacco research into existing and proposed lung cancer prevention, screening and treatment trials.** In addition, smoking cessation advice should be a routine part of any clinical trial involving smokers.

Rationale

Numerous untapped opportunities exist among ongoing intervention trials (e.g., lung cancer screening and chemoprevention) for tobacco-related research to be conducted, integrated, or supplemented. These opportunities—which could range from cessation research to collection of moderator variables to establishment of a longitudinal cohort—can be cost effective, unique, and opportunistic and provide data leading to future NCI studies and initiatives that may help in reducing the burden on society from lung cancer.

Advantages of integrating tobacco-related research, as a formal grant or contract supplement or as an ad hoc initiative, include:

- The opportunity to conduct valuable tobacco research at substantial savings in cost and resources, because much of the initial research cost (e.g., accrual,

staffing) will be borne by the parent grant or contract.

- The opportunity, when integrating with lung cancer genetic studies, to obtain data on tobacco-related gene-environment interaction.

- The opportunity, when integrating with lung screening trials, to conduct studies that can help elucidate the effect of so-called "reduced risk" cigarettes.

- The opportunity to collect and analyze data on the natural history of individual smoking patterns and their role in promoting, delaying, or accelerating lung carcinogenesis.

- The opportunity, when integrating with long-term follow-up trials, to obtain longitudinal tobacco-related data at a fraction of the cost such longitudinal data collection would ordinarily incur, and the opportunity to examine how changes in smoking behavior might modify the effects of treatment and early detection trials.

- The opportunity, when integrating with lung screening or chemoprevention trials, for "teachable moments" and study of the effectiveness of nicotine dependence treatment among participants who smoke.

- The opportunity to "customize" tobacco-specific supplements (e.g., questionnaire items, serum collection) to ongoing trials.

- The opportunity to recruit additional, or "oversample," underrepresented populations.

3. Expand the capacity and resources for NCI population-based tobacco control research, evaluation and surveillance initiatives, including domestic and international data on tobacco control efforts at the societal level, tobacco industry marketing activities, and smoking prevalence trends.

Rationale

Extensive information can be mined and may otherwise be lost—from both ongoing natural experiments with tobacco control programs in the states (e.g., Massachusetts, California, Florida, Oregon, and Arizona) and from future efforts—that can provide invaluable guidance for tobacco control program design, implementation, removal of barriers to implementation, and evaluation of efficacy and effectiveness. Better understanding of these large, population-based tobacco control programs is important, because they have the potential to create a substantive public health benefit at the population level. Population-based approaches, such as tobacco price increases, secondhand smoke policies (e.g., clean indoor air legislation), and further altering norms to decrease the social acceptability of smoking among adults and young people, reach large numbers of smokers compared with efforts that focus solely on individual smokers.

Further, valuable data can be obtained from other activities (e.g., scientifically rigorous assessments of tobacco industry marketing, legal actions, tobacco control program dissemination and adoption) that are not systematically monitored and evaluated by others. These resources would allow for rapid assessments of important research questions and quick-turnaround data collection on an as-needed basis and provide a foundation for future NCI research initiatives.

This is an especially important activity for NCI to undertake, because data collection and analysis proposed here are not

sufficiently supported within NCI or any other organization. If these data do not become available or evaluations of existing or upcoming natural experiments are not conducted, future tobacco control programs will be based on an insufficient database and inadequate data analysis and interpretation. Providing NCI with the ability to collect, analyze, and evaluate these data will go a long way toward making future tobacco control programs as science- and data-based as possible.

Key elements of a population-based evaluation and (community-based) surveillance strategy could include:

- Establishing NCI as a clearinghouse in collaboration with other organizations and agencies—for multiple tobacco-related datasets.

- Building more robust etiological models of such issues as the initiation and maintenance of tobacco use and building the knowledge base about how to deliver more effective treatment methods across a variety of population groups.

- Developing epidemiological field stations capable of the early detection of community, state, and regional trends in tobacco use and tobacco control interventions and evaluating those trends in a timely manner.

- Evaluating natural experiments—either independently or collaboratively—that are likely to become more prevalent as states begin to spend their Master Settlement Agreement (MSA) funds from the tobacco industry.

- Studying the role that key moderator variables (e.g., sex, race, age, genetics, socioeconomic status) may play in tobacco addiction, treatment, and relapse prevention.

- Considering how population disparities and the tobacco industry targeting of vulnerable populations, particularly with regard to socioeconomic status, may drive future tobacco control needs and initiatives.

- Enabling NCI to analyze international datasets specific to lung cancer and generally relevant to tobacco issues (e.g., effect of advertising bans, effectiveness of warning labels, tobacco industry marketing techniques).

- Providing the opportunity to conduct studies of lung cancer and tobacco-related risk assessment and awareness in a variety of settings and with a variety of populations.

- Conducting cost-effectiveness studies, for example, of treatment delivery, specific tobacco control activities, and the effects of dissemination and adoption of initiatives that are scientifically sound and have been proven effective.

RESOURCES NEEDED

Resources that could support current and future efforts in tobacco control include:

- Education and training of a new cadre of tobacco researchers.

- Coordination mechanisms and collaborations and linkages with other NIH institutes, other governmental agencies (e.g., Centers for Disease Control and Prevention, Food and Drug Administration), non-profit organizations (e.g., Robert Wood Johnson Foundation, American Legacy Foundation), and the pharmaceutical industry.

- An increase in the NCI budget devoted to tobacco that more closely reflects the cancer burden caused by tobacco use.

- Expansion of initiatives similar to TTURC (Transdisciplinary Tobacco Use Research Centers, funded by NCI and the National Institute on Drug Abuse) or NCI's SPORE (Specialized Programs of Research Excellence). A transdisciplinary approach involves research that crosses and integrates theories and methods from different disciplines.

- Use of existing expertise and current and future surveillance units to develop standards and standardized measures for surveys and surveillance.

- A Tobacco PRG or second iteration of the Tobacco Research Implementation Group report.

BARRIERS

- Insufficient funds for tobacco control, in proportion to tobacco's contribution to the problem of lung cancer. According to the Tobacco Research Implementation Plan, tobacco-related research projects currently represent around 3.1 percent of the NCI budget.

- Insufficient transdisciplinary communication and collaboration.

- Lack of centers with critical mass of collaborating researchers across disciplines.

- Limited resources to facilitate the development of evaluation standards and standardized measures for tobacco use (including initiation and cessation) and variables such as risk factors, policies, regulations and programs that affect tobacco use.

Appendix C: Lung Cancer Progress Review Group Roster

Lung Cancer Progress Review Group Roster

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