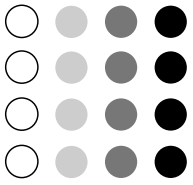

Charting the Course:
Priorities for Breast Cancer Research

Report of the Breast Cancer Progress Review Group

August 1998

NATIONAL® CANCER INSTITUTE

From the Chairpersons:

More than one year ago, the Breast Cancer Progress Review Group (BC-PRG), comprised of basic and clinical researchers from academia, industry, and government, and representatives of the patient advocacy community, accepted the charge of the National Cancer Institute (NCI) to develop a national plan for the next decade of breast cancer research. In carrying out this charge, the BC-PRG assessed the status of basic, translational, and clinical breast cancer research, employing the broad expertise of its members, input from the scientific community, and a comprehensive report on the NCI's breast cancer research portfolio. Based on this assessment, the PRG identified and prioritized the scientific research opportunities and needs that must be addressed to continue and accelerate progress in treating breast cancer, and ultimately, to prevent this disease. The BC-PRG's recommendations related to these identified opportunities and needs, provide, we believe, a blueprint for addressing the crucial questions that must be answered to eliminate the threat of breast cancer.

Therefore, on behalf of the Breast Cancer Progress Review Group, we are pleased to submit the attached report to the Advisory Committee to the Director of the NCI. It is our hope that these recommendations, reflecting the extensive and diligent work of the members, will prove to be valuable in our shared quest to further reduce the toll of human suffering and death due to breast cancer.

We look forward to discussing our findings with you and the leadership of the National Cancer Institute.

Respectfully,

Nancy Davidson, M.D.
Co-Chairperson
Breast Cancer Progress Review Group

Harold Moses, M.D.
Co-Chairperson
Breast Cancer Progress Review Group

We the undersigned members of the Breast Cancer Progress Review Group concur with the enclosed report

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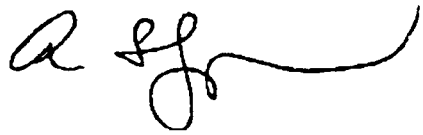

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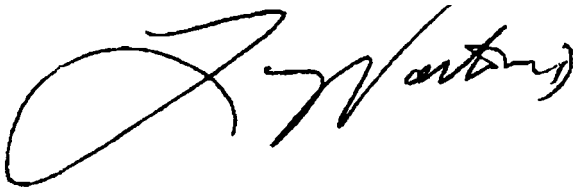

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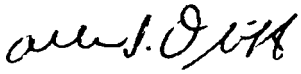

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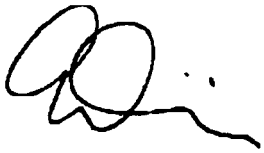

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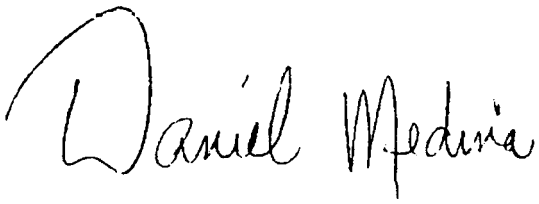

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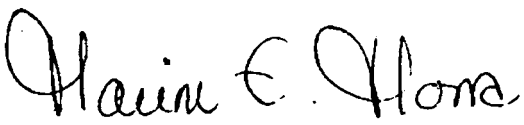

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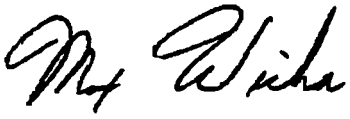

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Acknowledgements

The work of the Breast Cancer Progress Review Group (BC-PRG) that led to this report involved nearly a year's worth of deliberations, meetings, and conference calls. Dr. Jeff Abrams served as the Executive Director of the BC-PRG and the NCI Task Force. His expertise and experience in the field of breast cancer research, along with his adeptness in working with the diverse interests of both groups, made him indispensable to the process.

Coordination of this major effort was assured by the dedicated staff of NCI's Office of Science Planning and Assessment (OSPA) in the Office of Science Policy. Leading the OSPA team was Anna Levy, whose managerial skills and broad-based scientific understanding helped the Group to overcome the many obstacles posed by multi-disciplinary collaboration. She was ably assisted by Susan Rossi, Jason Nichols, Grace Ault, Marilyn Duncan, and Annabelle Uy. Cherie Nichols, the Assistant Director of OSPA, merits special thanks for contributing her organizational skills and experience to this new NCI endeavor.

An essential part of the PRG's charge was dependent on a review of the current status of NCI's breast cancer research. The PRG wishes to thank all of the members of NCI's Breast Cancer Task Force who contributed to the portfolio review, "The Breast Cancer Research Portfolio of the NCI - A Survey of Research and Resources, 1997."

Finally, Suzanne Reuben of Progressive Health Systems deserves special recognition as the PRG science writer. Suzanne's talents helped the PRG co-chairs meld a unified report from a multiple-authored series of scientific reviews and recommendations.

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Executive Summary

Executive Summary

Breast cancer continues to rob women of their health, their productivity, and their very lives. It robs families of mothers, grandmothers, sisters, aunts, wives, and partners. In 1998 alone, an estimated 178,700 women will be diagnosed with invasive breast cancer, and more than 43,000 women will be lost to this disease. Breast cancer strikes women of all ages, races, ethnicities, socioeconomic strata, and geographic locales; however, older women, African Americans, the poor, and others with limited health care access are disproportionately affected. Male breast cancer, because of its rarity (an estimated 1,600 new cases in 1998), is most often treated according to the lessons learned from studying the disease in women.

Over the past two decades, intensive research sponsored by the National Cancer Institute (NCI) into all aspects of breast cancer has led to many important discoveries--we understand more than ever before how a healthy breast cell becomes cancerous, how breast cancer spreads, why some tumors are more aggressive than others, and why some women suffer more severely and are more likely to die of their disease. We are having increasing success in translating these discoveries into therapies that extend cancer-free survival and improve the quality of life for those continuing to live with the disease. Likewise, our discoveries are leading to more refined technologies for detecting and diagnosing breast cancer, better supportive care and improved outcomes for patients during and after treatment, and finally, we are getting closer to identifying effective strategies for preventing the disease altogether.
Though these advances have been significant and provide hope for the future, we still have far to go to remove the threat of breast cancer from women's lives. To help chart the next crucial steps toward this ultimate goal, the Advisory Committee to the Director of the NCI requested that a multidisciplinary Breast Cancer Progress Review Group (BC-PRG) analyze the NCI's current breast cancer research portfolio and develop recommendations for achieving the next decade of progress.

The BC-PRG believes that by applying and expanding our foundation of knowledge, and with ample measures of teamwork, technology, and tenacity, major progress against breast cancer can and will be made in the next five to ten years. At this gateway to the next era in breast cancer research, the BC-PRG has identified 13 critical areas of equal priority spanning the continuum of breast cancer research and care in which greater emphasis is now imperative. These are presented below not in priority order, but in a manner that addresses issues from the bench to the bedside:

1. ***Our limited understanding of the biology and developmental genetics of the normal mammary gland is a barrier to progress.*** Much of our biological research in breast cancer has focused on understanding the initiation and development of the disease. This research has been fruitful, but it is now clear that a more complete understanding of the normal mammary gland at each stage of development--from infancy through adulthood--will be a critical underpinning of continued advances in

detecting, preventing, and treating breast cancer. This focus represents a major shift in breast biology research and requires increased support for these studies and the materials needed to conduct them.

2. ***Better model systems for human premalignant breast disease and breast cancer are needed.*** Appropriate animal models and models of human mammary cell and organ culture are urgently needed to accelerate progress in breast cancer research. We need these models to conduct experimental human genetics, to identify biological markers that indicate if preventive and therapeutic agents are working, and to test potential new agents for prevention and treatment. The models that currently exist are not sufficiently varied and do not reliably predict human experience. In addition to transgenic and knock-out mouse models, breast cancer research across the spectrum of investigation requires organ culture systems, cell strains, and cell lines from normal, premalignant, and cancerous human breast tissues.

3. ***Our current knowledge of the genetics and biology of precancerous lesions and their progression to invasive, metastatic cancers is incomplete.*** We need a fuller understanding of gene mutations and gene expression in breast epithelial cells through all stages of cancer development and progression, including metastasis. These genetic changes and gene expression differences must then be correlated with known cellular, tissue, and clinical characteristics. With this knowledge, we can identify target molecules to be used as agents of prevention, detection, and therapy. This work will require access to carefully collected and catalogued human breast tissues.

4. ***Key biomarkers and surrogate endpoints for epidemiologic studies and prevention and therapy trials need to be identified.*** Current and future advances in basic biology and genetics should be used to identify and validate markers that detect breast cancer far earlier than is currently possible. It is hoped that such markers also could serve as indicators of risk and surrogates for actual cancer development. The markers could be used to develop and test prevention and therapeutic strategies, and significantly expedite the lengthy clinical trials process. Among the important activities in this research will be to achieve a consensus on criteria for accepting specific biomarkers as study endpoints, resolving issues relating to technology transfer, and finding ways to develop and improve access to extensive biorepositories.

5. ***Pivotal research cannot be conducted without the appropriate tools and technologies.*** Funding is seriously deficient for developing and disseminating new technologies and for purchasing expensive equipment

for breast cancer prevention, diagnosis, and treatment research. Though costly, these tools are now indispensable to progress in breast cancer research and strategies must be implemented to increase access to them. Shared resource and technology transfer mechanisms should be fully explored to make these tools more accessible and affordable, and NCI should take the lead in standardizing and disseminating key technologies, software, and information sources.

6. ***The capacity for developing new treatment approaches at academic health centers is being underutilized.*** Advances in the cellular and molecular biology of breast cancer have identified more promising targets for drug development and other treatment approaches than can be exploited by current mechanisms. The academic health centers have ample intellectual resources to pursue this important work, but require resources for drug screening, genomics, and chemistry infrastructure. It is critical that the NCI lead the effort to forge academic/industry/NCI partnerships for drug development. Effective collaboration between these parties with their unique and complementary strengths could greatly facilitate development of new drugs for breast cancer prevention and treatment.

7. ***Existing mechanisms must be modified to facilitate translational, prevention, and therapy clinical trials.*** It is imperative that we develop faster mechanisms for designing and conducting innovative clinical and translational trials at single academic health centers or consortia of academic health centers. Moreover, since the majority of breast cancer patients are treated in the community, the cooperative groups must be more strongly supported and should strive for enhanced minority participation in clinical trials. Translational research must also receive heightened emphasis in the cooperative groups if major progress is to take place. Finally, reimbursement of the health care costs of clinical trials by insurers (e.g., health maintenance organizations, Medicare, and other payers) is essential to the success of this entire effort. Although research grants should cover the research costs, it is legitimate and in the interest of society to require that clinical care costs be borne by health insurers for patients on approved clinical trials.

8. ***Breast cancer basic and clinical research and communications efforts need to embrace patient and survivor needs and concerns.*** Breast cancer research efforts of all types should reflect the values of those most directly affected by the disease--high risk or recently diagnosed patients, long-term survivors, and their families. Effective and understandable education and communication about risk, detection, and treatment must take into account the differing motivations, concerns, and characteristics of diverse groups

of women, including those typically underserved. Interventions are needed to improve quality of life across the full continuum from risk assessment to treatment at the end of life. The expertise and collaboration of patient advocates representing our ethnic diversity must continue to be sought in developing research priorities and in designing and implementing programs.

9. ***We do not adequately understand biobehavioral mechanisms and decision-making relevant to cancer prevention, detection, and treatment.*** There is little understanding of the processes and mechanisms underlying behavior related to diverse cancer issues from genetic testing to prevention, screening utilization, treatment, and preferences for palliative care when disease is advanced. In addition, decision-making about all aspects of cancer prevention and care is highly complex and is influenced by myriad demographic, cognitive, personality, and cultural differences among people, and by the help they receive in making cancer-related decisions. We also do not know how people use both traditional and new media to process information and make decisions. A focused program of research is needed in basic behavioral change, decision-making, and communicating research findings and their health implications to the individual.

10. ***Strategies must be implemented to attract new investigators to breast cancer research and to provide the multidisciplinary training required to translate laboratory discoveries into better breast cancer prevention and care.*** Increasingly, new investigators whose talents are needed to achieve the next generation of progress against breast cancer are choosing careers in industry or private practice over academia because they do not perceive the likelihood of a viable career in academic breast cancer research. This situation grows more dire with each passing year. We believe incentives for academic researchers are needed if both academia and private industry are to make optimal contributions to progress against breast cancer. It is also critical that multidisciplinary training take place so that individuals can participate effectively in multi-investigator collaborations that bring basic research discoveries to the bedside.

11. ***Breast cancer research is increasingly becoming a multidisciplinary endeavor that requires better communication among investigators***. To promote communication across the breast cancer research continuum, a breast cancer task force should be established with representation from all of the major disciplines and with oversight and fiscal resources to address critical areas of breast cancer research not covered by other mechanisms. Tools are needed to improve the sharing of resources, databases, and other

information. Informatics development for all types of research will be essential throughout the next decade. There is an overarching need to expand NCI's communications outreach to address the diverse needs for disseminating cancer research results discussed in all areas of this report.

12. ***Current review and funding mechanisms do not encourage innovation or accommodate longitudinal studies and other special research needs.*** The existing peer-reviewed, investigator-initiated research project grant mechanism has served us very well over the years and should be continued and enhanced such that funding is available for at least 40 percent of high quality applications. Other options are needed, however, to support important research not currently well served by existing mechanisms. Seed money should be provided for innovative, higher risk ideas, and peer review of these "idea" grants should be through a mechanism other than the current NIH Center for Scientific Review and NCI Division of Extramural Activities study sections. Special study sections, non-governmental review and funding groups, contract mechanisms, and targeted funding all offer possible approaches to fostering innovation and meeting specialized research needs. There is a critical need for more reasonable review and funding of multidisciplinary grant applications, and for longer term funding for tissue resource development, longitudinal epidemiologic studies, and prevention and therapeutic trials.

13. ***Current approaches to informed consent and confidentiality protection are a major barrier to breast cancer research.*** The need to protect the rights and confidentiality of breast cancer patients and those at risk is recognized fully; however, current consent procedures are so cumbersome that they impede crucial research on the disease and may discourage participation by clinicians and patients. Ways to streamline and standardize the informed consent process for clinical trials and strategies to simplify protocol review, such as empowering regional or national Institutional Review Boards, must be addressed. Methods to encourage women of all races and ethnicities to donate tissues for research purposes while simultaneously protecting them from harm must be developed.

In addition to intensive discussions on how best to address breast cancer issues that cross-cut the research and care continuum, the BC-PRG worked in eight subgroups representing the major disciplines engaged in breast cancer research. These subgroups identified, distilled, and prioritized in concert with the full BC-PRG, the most important key scientific questions and research opportunities for the next five to ten years specific to each discipline. While all of the scientific questions and opportunities identified are important emphases for the next decade of breast cancer research, those judged to be of the most immediate or central importance are highlighted below.

Biology: Most of the research to date in breast cancer biology has focused on changes in the basic biologic processes that enable breast cancer to grow, particularly the role of hormones, gene alterations, and biochemical communication within and between cells. This research has been extraordinarily valuable, however, at this time *we need to refocus breast cancer biology research to expand our knowledge in three key areas:(1) normal breast development, (2) the earliest breast lesions leading to invasive cancer, and (3) how breast cancer spreads throughout the body.* This represents a major shift in emphasis in this realm of research and will require resources for necessary training, the development of animal models, access to human tissues and essential compounds, technology development and access, and collaboration between diverse disciplines and between industry, academia, and government.

Etiology: Although a substantial number of factors have been associated with breast cancer development, most breast cancer cases cannot be attributed to any of the known risk factors. To devise effective methods for preventing breast cancer, we must understand which factors--alone or in combination--raise the risk of triggering a tumor, and which factors protect against the disease. Goals for the next decade of etiologic research are to: (1) *identify and validate the risk factors that can be modified to reduce breast cancer risk,* and (2) *achieve a better understanding of how various genetic and environmental factors interact to affect the risk of breast cancer.* To reach these goals, we need model systems that better mimic human breast disease; greater collaboration among investigators from diverse disciplines; new technologies for "high throughput" testing of DNA, RNA, and proteins; targeted funding for innovative, high risk studies; and clinical trials to assess the effects of environmental and other variables.

Genetics: We know that all breast cancer is genetic, although only a small fraction of cases result from inherited genetic predisposition. Most breast cancers are due to non-inherited gene alterations that occur in breast epithelial cells; many of these remain undiscovered. Major goals for genetics research in the next decade will be to: (1) *identify all of the genetic alterations that occur at each stage of normal breast development and progression of breast epithelial cancers*, (2) *identify targets of therapeutic intervention based on genes that go awry,* and (3) *create an informed and experienced workforce to provide medical and genetic counseling and clinical care for women with inherited predisposition to breast cancer.* Achieving these goals will require that new technologies such as arrayed DNA and expression libraries be made more available to public sector investigators. Similarly, human tissues and cell lines must be made more available so that gene and gene expression profiles can be generated. Transgenic mouse models are critically needed to accelerate progress in breast cancer genetics research.

Prevention: Prevention strategies aim to delay or prevent the initiation, promotion, and progression of breast tumors in women. Crucial steps over the next decade toward achieving this central goal will be to: (1) *develop better animal and human models of precancerous breast biology* so that targets for preventive interventions can be identified, and (2) *develop and validate biologic indicators (surrogate endpoint biomarkers) that can replace the development or lack of development of cancer as a measure of a preventive intervention's success.* The current

research structure does not provide for the unique needs of research in this area. Strategies must be implemented so that indispensable long-term biomarker studies can be conducted, and precancerous models can be developed. A multidisciplinary Prevention Research Working Group should be created to work with the NCI and members of the scientific community to prioritize drug development and guide preclinical and early clinical trials design.

Early Detection, Diagnosis, and Prognosis: The ultimate goal of detection, diagnosis, and prognosis research is to develop noninvasive methods for detecting and characterizing precancerous and cancerous breast lesions with certainty when they are small and more easily treatable. Among the most important areas for investigation in the next five to ten years will be: (1) *determining the potential of the newer imaging technologies to detect and diagnose breast disease better than physical examination and conventional mammography,* and (2) *developing new serum and tissue-related methods to diagnose clinically significant breast disease and predict clinical outcome better than is possible with conventional tissue examination and currently available biomarker tests.* Progress in these areas will require a wide range of translational studies, and will depend in part on the results of basic biologic studies and the use of basic biologic tools including animal models. Investments must be made in new technology development and technology upgrades for the aging academic research infrastructure.

Treatment: Continued breast cancer treatment research is needed to achieve longer disease-free survival, longer overall survival and genuine cure, less toxic treatments with fewer side effects including second cancers, better quality of life for patients during and following treatment, and improved access to the highest quality treatment for all women. Among the most important avenues of investigation for the next decade will be: (1) *developing innovative approaches to breast cancer treatment in the laboratory and through pilot clinical trials*, and (2) *testing the most promising therapies in large clinical trials* focused on better survival, lower toxicity, reduced breast cancer incidence, and ease of delivery. Treatment research progress will be aided substantially by fostering multidisciplinary, multi-investigator translational studies; establishing a study section with funding authority for clinical investigation; achieving better coordination among the cooperative groups, cancer centers, and Specialized Programs of Research Excellence (SPOREs); and ensuring that routine care costs of patients in clinical trials are reimbursed. To encourage private industry to permit academic research using proprietary compounds, reasonable ways must be found to protect corporate investment in their development.

Control: A major focus of cancer control is finding the best ways to apply current knowledge about cancer to diverse populations as a means of reducing the national cancer burden. In the next decade, two of the most important areas of cancer control research will be to: (1) *gain a better understanding of the fundamental mechanisms underlying basic behavioral change,* and (2) *identify how psychosocial factors influence disease-related outcomes such as disease response and survival*. Actions needed to facilitate this research include creating a unit focused on basic behavioral and social research within NCI's Division of Cancer Control and Population Sciences, attracting investigators to this area by stimulating graduate and postgraduate training in basic