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GUEST EDITORIAL

Early Detection Cancer Research Network

Given the limited success and substantial toxicity associated with most forms of cancer treatment, preventive intervention is now playing a growing role in cancer research. Increasingly, institutional and individual priorities reflect this shift in the research paradigm, away from treatment-focused efforts and toward prevention-directed strategies. One consequence of this trend is consideration of how an understanding of the molecular machinery of cancer can be used for more accurate detection and diagnosis. However, with this new focus has come the realization that molecular-based detection strategies require the expertise of multidisciplinary research groups. Stakeholders include cancer biologists, epidemiologists, technology developers, statisticians, computer scientists, chemists, and clinicians. Bringing these groups together to address this challenging task will expedite the discovery and clinical applications of molecular signatures in earlier cancer detection and cancer risk assessment. In practical terms, molecular signatures or biomarkers are defined as *cellular, biochemical, molecular, or genetic alterations by which a normal or an abnormal biological process can be recognized or monitored.* Biomarkers are measurable in tissues, cells, or fluids.

Since no single institution or individual has the resources or expertise to galvanize the infrastructure needed to fully use our knowledge of the molecular genetics and biology of cancer, the National Cancer Institute has now stepped up to this challenge in the form of the Early Detection Research Network (EDRN). The goal of this multi-year, multi-institutional program is the earlier molecular detection and risk assessment of human cancer. The EDRN infrastructure is built on multi-institutional expertise and resources, and has been identified as an extraordinary opportunity for investment by the National Cancer Institute (http://www.nci.nih.gov). The EDRN will link centers of expertise in tumor biology, diagnostic technologies, and clinical trial methodologies in academia, industry, and government.

The conceptualization of the EDRN began two years ago in response to recommendations from the Cancer Prevention Program Review Group, appointed by the Director of the National Cancer Institute, to accelerate research in molecular early detection. Investigators participating in this review group agreed that methodologies to detect early cancer and assess the risk of cancer were not moving rapidly enough beyond the laboratory setting. Several practical hurdles were noted. The systematic application of biomarkers for earlier cancer detection, or even risk assessment, is fragmented and not well coordinated. While studies on genetic and molecular biomarkers of cancer have been supported by the NCI through its traditional funding mechanisms for years and have advanced our understanding of molecular pathogenesis, research emphasis on the continuum of preclinical tumor development and the early evaluation of new techniques and their clinical application has been lacking. In many studies, investigators do not fully explore the biological implications of their findings or systematically test the clinical application of the molecular markers discovered. This barrier has resulted, in part, from the lack of a stable connection between basic laboratory research and the opportunity for rapid clinical evaluation and validation. Other factors contributing to the lack of systematic evaluation and the development of useful biomarkers include the unavailability of high-quality matched human tissue specimens from normal, suspicious, pre-neoplastic and multistage neoplastic lesions, and the lack ancillary demographic and follow-up clinical data. Consequently, the results of many existing studies are fragmented and cannot be generalized to the population as a whole, and sometimes even the population of inference cannot be defined.

The Early Detection Research Network (http://edrn.nci.nih.gov) is based on the premise that the "vertical" integration of discovery, evaluation, and validation will expedite the discovery and clinical application of biomarkers when these phases are carried out in a systematic and concerted way. With this in mind, the Network has three main components: Biomarkers Developmental Laboratories, Biomarkers Validation Laboratories, and Clinical/Epidemiology Centers. The Biomarkers Developmental Laboratories will have responsibility for the development and characterization of new biomarkers or the refinement of existing biomarkers. The Biomarkers Validation Laboratories will serve as a Network resource for clinical and laboratory validation of biomarkers, including technology development, standardization of assay methods and their refinement. The Clinical/Epidemiology Centers will conduct clinical and epidemiological research on the application of biomarkers. Statistical, logistics, and informatics support will be provided through an auxiliary Data Management and Coordinating Center (DMCC). The DMCC will also develop the theoretical and statistical approaches to the problem of simultaneous pattern analysis with multiple markers. A Steering Committee composed of the Principal Investigators in the Network and appropriate Na-

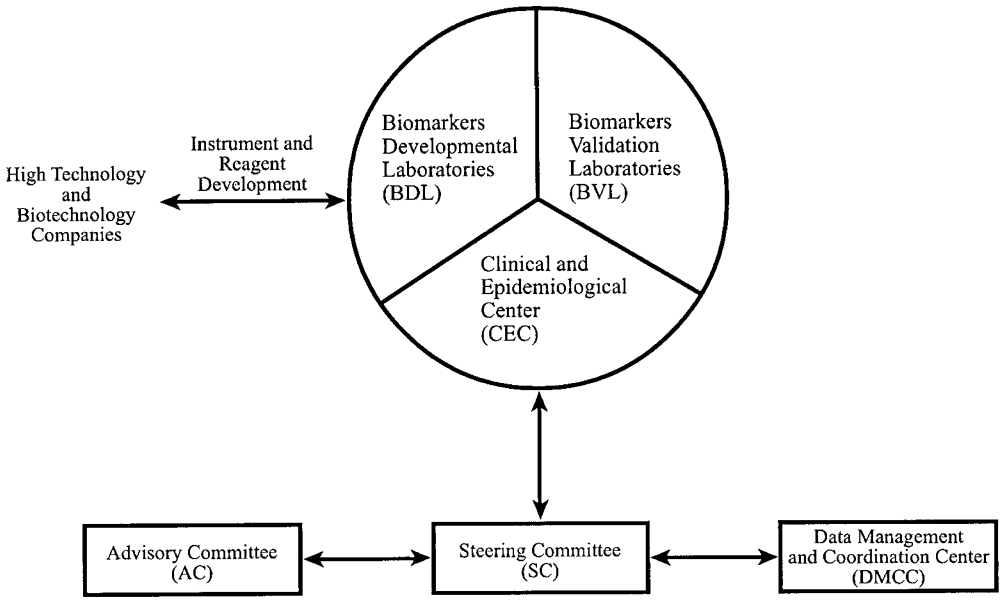

Figure 1.
Organization of the Early Detection Research Network.

tional Cancer Institute staff will coordinate the work of the consortium (Fig. 1).

With the creation of EDRN, a multicenter network is formed with resources for translational research that include laboratory sciences, clinical sciences, public health, biostatistics, informatics, and computer sciences. Its specific goals include the following:

1. The development and testing of promising biomarkers or technologies in institutions having the scientific and clinical expertise needed to obtain preliminary information that will guide further testing.
2. The timely and early phase evaluation of promising, analytically proven biomarkers or technologies. Evaluation will include measures of diagnostic predictive value, sensitivity, specificity, and whenever possible, medical benefits, risk, and harms, such as predictors of clinical outcome or surrogate endpoints for early detection and for prevention intervention clinical trials.
3. The timely development of biomarkers and elucidation of expression patterns, sometimes of multiple markers simultaneously, that will form the basis for larger, more definitive, validation studies of cancer detection and screening.
4. Collaboration among academic and industrial leaders in molecular biology, molecular genetics, clinical oncology, statistics, computer science, public health, etc., for the development of high-throughput, sensitive assay methods for early detection biomarkers.
5. Early phase clinical/epidemiological studies to evaluate the predictive value of biomarkers, eg, cross-sectional retrospective evaluations.
6. Encouragement of collaboration and rapid dissemination of information among awardees to ensure progress and avoid fragmentation of effort.

The success of this effort depends largely on exploring the relationship between earlier detection and reduction in mortality and morbidity. Data show that detection and treatment of premalignant or early lesions (eg, by mammography and Pap screening) can reduce mortality. Although clinically proven, both technologies have problems with sensitivity, specificity, and predictive value. Therefore, it seems reasonable to explore the application of novel molecular-based technologies for earlier, more specific detection and risk assessment, leading possibly to the institution of chemoprevention before the invasive cancer develops. These are the overarching goals of the EDRN.

"With the creation of the Early Detection Research Network, we are entering a new era of translational research, where the journey from the laboratory to the clinic is a coordinated, collaborative effort," said NCI Director Richard Klausner, M.D. "Ultimately, the Network will benefit patients by the rapid creation of better tests to find cancer and the discovery of points in time at which to intervene to prevent the disease." The National Cancer Institute (NCI) has awarded nearly $18 million a year in grants for 5 years to create 18 Biomarkers Developmental Laboratories, 8 Clinical and Epidemiologic Centers, 2 Biomarkers Validation Laboratories, and 1 Data Management and Coordinating Center. The National Institute of Standards and Technology and the Centers of Disease Control and Prevention have also joined the consortium. Projects involving the collaborative efforts of investigators outside the EDRN are encouraged. Associate Membership, as this cooperation is called, can be sought through an established Network investigator who would sponsor the interested investigators.

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