

National Cancer Institute



Division of Cancer Prevention

**The Early Detection Research Network
(EDRN)**

Strategic Plan

**U.S. DEPARTMENT
OF HEALTH AND
HUMAN SERVICES**

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EXECUTIVE SUMMARY

Developing a collaborative network is a challenging, if not a daunting task. Identifying biomarkers involves a rigorous process that begins with discovery and leads to development, validation, and finally application in the clinic. The success of this process requires a complex, dedicated infrastructure that facilitates coordination and collaboration among a variety of institutions and academic- and industry-based scientists and clinicians. EDRN has fulfilled these expectations by establishing a process for biomarker development using a multidisciplinary and multi-institutional approach. This infrastructure, combined with the development of a highly interactive database and informatics system through EDRN's collaboration with the Jet Propulsion Laboratory (JPL), serves as a model for the conduct of translational research and is well-aligned with the goals and objectives of the National Cancer Institute (NCI) and the larger National Institutes of Health (NIH) community.

The EDRN has progressed well in the past 13 years by developing the best possible ways to utilize the available resources. However, it will need substantially enhanced infrastructure support to successfully meet its goals during the next 5-year funding cycle, especially if the number of proposed biomarkers and collaborations continue to increase at the rate they have since the program's inception. Increasing expectations of the role of validated biomarkers in early detection have driven the field for an accelerated flow of biomarkers through the various phases of development. EDRN has developed appropriate incentives that facilitate quicker "hand-offs" of biomarkers through the various phases of development minimizing any unnecessary/excessive time delays. The EDRN supports milestone-driven research and provides incentives for projects that meet goals regarding moving biomarkers from the discovery phase to the validation phase of development. In addition to having an aim dedicated to rigorous evaluation and validation of biomarkers, EDRN had the foresight to collaborate with NASA's JPL to build a leading edge, national, bioinformatics network for the capture, management, distribution and analysis of cancer research data and also develop a database that will pay dividends for other NCI programs and facilitate monitoring of project progress.

Planning for translational research opportunities for patients and their physicians regarding biomarkers developed by EDRN must occur during the initial planning for biomarker development. EDRN is accomplishing this goal by involving stakeholders, i.e., basic scientists, clinical scientists, clinicians, statisticians, information scientists, public health professionals, patient advocates, and clinical testing laboratories that are Clinical Laboratory Improvement Amendments (CLIA) approved in formulating strategic goals for EDRN for the next 10 years. The goals developed from ongoing discussions with EDRN and non-EDRN investigators, workshops and task force convened by the EDRN and professional societies such as the AACR, EDRN program evaluation committee, and members of the Network Consulting Team (NCT) who have been evaluating EDRN over the past 13 years. The report outlines and elaborates on organ-specific research priorities in building resources and addressing clinical questions in the most efficient and timely manner. EDRN's strategic goals for the future include the use of latest technologies (e.g., omics-based) and systems biology approaches to develop new serum- and tissue-based biomarkers for early detection and diagnosis in order to identify clinically significant diseases and predict clinical outcomes, with or without conventional tissue examination.

Some organ-specific goals are described below:

- For breast cancer, mammography remains the mainstay of screening. However, the technology is beset by low sensitivity and specificity, thereby yielding a high number of false-positive cases. EDRN strategic goals include whether biomarkers can: 1) further improve the interpretation of conventional mammography; 2) stratify benign disease into high and low risk for progression; 3) be used as contrast agents to improve the performance of any imaging modality. The plan includes the use of Breast Cancer Reference Sets that will contain serum, plasma, DNA, RNA, and buffy coat from normal healthy women, women with benign disease, ductal carcinoma *in situ* (DCIS), and

invasive breast cancer to test biomarkers addressing the clinical needs described in the preceding paragraph.

- In case of lung cancer, EDRN has already pursued a variety of lung cancer markers that were not able to distinguish non-diseased high risk smokers from lung cancer patients, although they clearly differentiated smokers from non-smokers. These findings highlight how smoking induces profound molecular alterations in the epithelial linings of the lungs setting them on a path towards neoplasia. EDRN strategic goals include: 1) develop tests for early detection of lung cancer that can achieve a performance above the overriding risk factor that smoking presents; 2) develop markers that can be used in conjunction with CT imaging (which has high sensitivity, but also high false-positive rate) to determine which patients may need further work up for diagnosis of lung cancer.
- Prostate-specific antigen (PSA) tests result in detection of a large number of false-positive prostate cancers, leading to large number of unnecessary biopsies and repeat biopsies – a phenomenon known as “overdiagnosis”. Consequently, there is an urgent need for predictive markers for early detection of aggressive prostate cancer, which could be distinguished from the less aggressive non-lethal forms of prostate cancer. EDRN discovered tumor markers like TMPRSS2-ETS fusion transcripts (TMPRSS2-ERG, TMPRSS2-ETV1, TMPRSS2-ETV4), which are frequently detected (~50%) in prostate cancers. Interestingly, other recently EDRN discovered markers, such as a mutant SPOP and overexpressed SPINK1 are detected in TMPRSS2-ETS fusion-negative prostate cancers. Some of these markers were recently validated and others are going through further verification as biomarkers for early detection and early detection of aggressive cancers. There is a need for biomarkers to minimize false positives, reduce unnecessary repeat biopsies, differentiate between aggressive and non-aggressive forms of prostate cancer, and estimate risk. EDRN strategic goals include: 1) development of markers based on recent advances in cancer biology (e.g., markers associated with prostate cancer stem cells; markers associated with reactive stroma adjacent to a tumor focus) and application of an integrative approach to biomarker development for early and aggressive forms of prostate cancer; 2) development of biomarkers for prostate cancer risk assessment, based on recent results of whole genome association studies, and provide guidelines for integration of risk markers into clinical practice; 3) improve the performance of existing markers (e.g., PSA by evaluating its molecular forms, such as [-2]proPSA and by combining them with tumor specific markers such as PCA3 and TMPRSS2-ERG).

In this document we have described EDRN’s short and long-term goals. While the biomarkers for population-level early detection and screening remains part of the long-term goals, the improvement of current detection and diagnostic modalities are achievable short-term goals. Translation of biomarker discovery into cancer early detection and diagnostics requires a broad spectrum of disciplinary expertise. Collaborative projects among the EDRN investigators facilitate biomarker research and its translation into clinical application in an efficient manner. Equally important, EDRN collaborations have a long-standing relationship with industry and private sectors, which are changing their business model to support biomarker discovery for early detection and diagnostics. EDRN will continue to develop such strong partnerships.

EDRN is also developing strategic alliances with non-profit foundations, such as the Canary Foundation and the Lustgarten Foundation, Federal agencies, such as the National Institute of Standards and Technology (NIST) and the Food and Drug Administration (FDA); and professional organizations, such as American Society of Clinical Oncology (ASCO) to develop a transparent process for creating well-defined consensus standards and guidelines for biomarker development, validation and qualification to reduce the uncertainty in adoption of biomarkers for clinical use. In the future, the EDRN proposes to work with Centers for Medicare and Medicaid Services (CMS) to review new biomarkers and to reach consensus on coverage and pricing.

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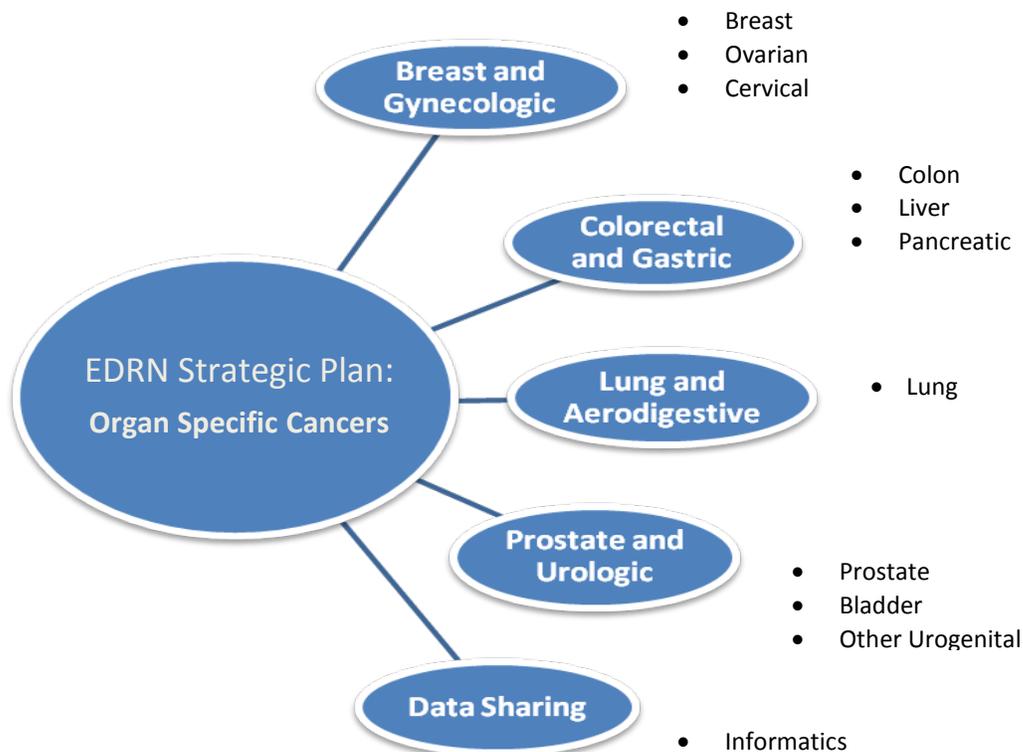
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EDRN OBJECTIVES

The overarching goal of the National Cancer Institute's (NCI's) Early Detection Research Network (EDRN) is to conduct translational research by discovering cancer biomarkers and translating such biomarkers into clinical applications through:

- Strategic and systematic evidence-based discovery;
- Development and validation of biomarkers to detect cancer early and assess risk;
- Coordination of biomarker research in extramural community and with other NCI prevention and treatment programs developing strategies to reduce cancer morbidity and mortality.

The EDRN fulfills its objectives by way of its leadership and by providing an infrastructure and environment that fosters translational research by encouraging collaborations among basic scientists, population-based scientists, and physician scientists with expertise in clinical applications. These multidisciplinary investigators facilitate the integration of knowledge into evidence-based cancer biomarker research. The EDRN strategically focuses on cancers where there is a high potential for influencing cancer morbidity and mortality identified through previous scientific knowledge base. In this regard, the EDRN focuses its activities on major epithelial cancers and a subgroup of cancers within these organ systems. To further support this approach, the EDRN has established collaborative working groups for each of these organ systems, whose membership emphasizes multidisciplinary expertise as follows:



EDRN objectives include:

- Continue to discover, develop, evaluate and validate promising biomarkers and or technologies necessary for identification of cancer risk, early detection and early diagnosis, and prognosis of cancer and prognosis of cancer risk;
- Combine tumor biomarkers with imaging to reduce the false positive rate of imaging and to improve the detection of significant cancers.
- Develop and validate biomarkers to improve the detection of cancer progression for patients on active surveillance.
- Develop assays and evaluate advanced technologies for accelerating biomarker discovery and translation into the clinical area. This would include measures of diagnostic or predictive accuracy, sensitivity, specificity and, whenever possible, medical impact/benefits;
- Develop and implement diagnostics assays in support of the EDRN objectives by using multiple biomarkers, gene expression patterns, protein and pre- and post-translational changes, including epigenetic changes in genes;
- Facilitate the development of high-throughput, sensitive assay methods to identify and implement cancer biomarkers that are useful in assessing cancer risk, detecting early stage cancers, diagnosis and prognosis;
- Support collaboration among academic and industrial leaders, who have clinical areas of interest in molecular biology/molecular genetics, clinical oncology, computer science, public health or other related areas;
- Conduct clinical/epidemiological studies (e.g., cross-sectional, prospective, retrospective, etc.) in order to evaluate the predictive value of biomarkers;
- Continue to expand the informatics infrastructure to facilitate pre-competitive data sharing on biomarker discovery, development, and validation; and
- Serve as a core resource so that NCI and the cancer community at large can leverage the well-developed EDRN infrastructure and expertise in order to facilitate translational cancer research and cancer therapeutic trials.

In addition to its role of biomarker discovery and biomarker discovery translation into clinical applications in a broad range of epithelial cancers, the EDRN represents a core resource that can support and accelerate external critical advances in cancer research and its translation into clinical cancer care. The EDRN acts as a core resource for NCI and the greater cancer community through its ongoing strategies for productive interaction among basic and clinical scientists, ongoing strategies for the network's expertise in epidemiology, clinical diagnostics, biostatistics and informatics, and its well-annotated biorepository for certain tumor sites. This role, as a core resource, positions the EDRN as a strong partner with other cancer programs, including clinical trials, cooperative groups, Specialized Programs of Research Excellence (SPOREs), and other NCI and community-designated cancer centers.

EDRN STRATEGIC GOALS

The EDRN supports the development, validation and clinical application of biological biomarkers that can provide reliable detection, diagnostic and prognostic information on cancer, and where the biomarkers can also serve as surrogate markers for assessing the response to chemoprevention and treatment. Areas of particular interest include molecular assays to replace tissue-based assays with biological fluids-based assays, improvement of body-imaging techniques, and development of a knowledge base for improving evidence-based screening of cancer. With the help of new technologies, candidate biomarkers are being identified. However, the translation of these new biomarkers is lagging due to the lack of reproducibility of biomarker assays and the need for improved study design in the discovery process. EDRN has begun addressing these issues by developing quality specimens, robust study designs, standard operating procedures and collaborations among technology developers.

Types of biomarkers of particular relevance to the EDRN's strategic goals include genetic, genomic, epigenetic, gene expression, microRNA, proteomic, glycomic, metabolomic, and other as yet uncharacterized novel categories of biomarkers. Genetic and genomic biomarkers include single-locus/gene, multiple-locus/gene, and genome-wide assays of gene copy number (including amplification or deletion), mutation, sequence variations/polymorphisms, linkage disequilibrium, chromosomal and sub-chromosomal translocations and other alterations or associations. Epigenomic biomarkers include DNA methylation, several types of histone modifications, and other changes to DNA that do not alter the DNA backbone. Expression biomarkers include, but are not limited to, messenger RNA and microRNA (additional species of small RNA, such as piwi RNA, and the large number of poorly characterized or as-yet completely uncharacterized noncoding RNAs also of potential interest). Proteomic biomarkers include not only the amino acid sequences of proteins or peptide fragments but also post-translational modifications of those proteins, including, but not limited to, phosphorylation, sulfation, myristoylation, farnesylation, glycosylation and many others. Glycomic markers include all measures of the sugar side chains found on many proteins, and these markers can also be detected by many different means. EDRN's short-term and long-term strategic goals are described below.

SHORT-TERM GOALS

- Work to augment the ability of commonly used screening tests to detect major epithelial cancers, such as colon, breast, cervical, and prostate cancers. Also, facilitate the co-development of diagnostic tests for prevention or therapeutic interventions (theranostics).
- Employ cost-effectiveness measuring tools to evaluate biomarker discovery, development and validation, and to collaborate with the NCI's Cancer Intervention and Surveillance Modeling Network (CISNET) on integrating cost-effectiveness models in the discovery and development processes.
- Create well-defined consensus standards and guidelines for biomarker development, validation and qualification using the Translational Research Working Group (TRWG)-developed Device Pathway to reduce uncertainty in discovery and development of biomarkers.

LONG-TERM GOALS

- Develop new serum- and tissue-related methods for early detection and diagnosis in order to identify clinically significant diseases and predictions of clinical outcomes, with or without conventional tissue examination, by utilizing currently available biomarker tests.
- Expand collaborative efforts and shared resources to improve the capacity to conduct biomarker development and validation trials.
- Many detectable lesions and cancers are asymptomatic and not life threatening. However, current inability to discern which lesions will lead to clinically significant morbidity and death vs. benign or slow-growing cancers leads to excessive testing, a phenomenon known as overdiagnosis. About 25% of breast cancers detected on mammograms and about 60% of prostate cancers detected with PSA tests could represent overdiagnosis. There are ongoing debates regarding how to recognize and manage overdiagnosis. One proposed strategy is the development of disease-specific biomarkers that can distinguish aggressive from non-aggressive cancers. It is possible that new insights from genomics from The Cancer Genome Atlas (TCGA) and novel molecular approaches will ultimately allow us to more accurately predict tumor behavior at the tissue, cellular or molecular level.
- Progress in early cancer detection and image-based diagnosis has been hampered by the lack of understanding regarding the natural history of the disease. Innovations in molecular biology, genomics, proteomics and immunology may provide insights. EDRN is considering the following questions:
 - Why do some preneoplastic lesions progress rapidly and require intervention?
 - Therapeutic intervention is often triggered by assessment of a static picture of disease (histologic snapshot of observables assumed to be representative of the whole tumor), rather than knowledge of the inherently dynamic nature of the underlying disease. Current assessments are thus incomplete. What could be done to advance knowledge of cancer progression? Can information derived from the integration of imaging and molecular diagnostics further this understanding?
 - What types of molecular properties confer aggressiveness to some preneoplastic lesions? What could be done to study such behaviors to avoid overdiagnosis and overtreatment?
 - What could be done to define and characterize preneoplastic lesions in order to improve current standards in histology and cytology?
- EDRN's future direction aims to develop strategies for studying the natural history of cancer to aid in developing better tools for determining which cancers are clinically important. Integrate the genetic, cell signaling and biochemical pathways with biomarker discovery efforts to have a broader applicability across different tumor types. Determine the potential of novel network- and pathway-based markers to detect and diagnose cancer. Pathway biomarkers would allow a systems biology approach to diagnosis, prevention and therapeutic strategies.

RESOURCES AND TECHNOLOGY

- Establish a biomarker database to capture and share methods and pre-competitive data on the validation and qualification of biomarkers.
- Standardized methods for tissue procurement and banking that are not only indispensable for current studies but also for emerging technologies which require validation. EDRN has begun collecting selected specimens that are well characterized, with comprehensive clinical, demographic, and epidemiologic information included. EDRN will continue assembling prospectively collected specimen reference sets for each organ site to facilitate pre-validation and validation of biomarkers. EDRN is already collecting sample reference sets, a set of well characterized controls and cases, for rapid evaluation of technologies and biomarkers before initiating large, expensive validation trials.
- Commence partnerships with Human Proteome Organization (HUPO) and its US affiliates on proposed Gene-centric Human Proteome Project and Peptide Atlas.
- Work with the American Association of Clinical Chemistry, the FDA, and the ASCO to set up clinical standards for diagnostic markers and assays.
- Collaborate with NCI cooperative groups to develop collaborative studies on prognostic and predictive markers.

BREAST AND GYNECOLOGIC CANCERS

- Breast • Ovarian • Cervical

Breast Cancer

Strategic Goals

The increase in incidence of breast cancer observed over the past 20 years is almost entirely attributable to the detection of ductal carcinoma in situ (DCIS) and stage I cancer by imaging. The large majority of these lesions remain indolent. At the same time, there are many cancers that are being missed by the current screening modalities, many of which tend to be aggressive disease, such as “interval” and hormone-receptor negative or triple-negative breast cancers (TNBC). The incidence of the latter is significantly higher in premenopausal women where imaging screening modalities are significantly less effective. The ultimate goal is to develop non-invasive methods for detecting and characterizing pre-cancerous and cancerous breast lesions with poor prognosis with certainty when they are small and more easily treatable. Specifically, biomarkers are needed that can either augment mammography in the short term, or replace mammography in the long term. Biomarkers are also sought for the assessment of risk of progression from benign breast disease (BBD) or DCIS to invasive breast cancer (IBC), and for the detection of aggressive cancers, such as TNBC, the majority of which are not detected by routine imaging.

- Can biomarkers further improve the interpretation of conventional mammography or other computer-aided technologies?
- Can biomarkers detect characteristics of specific types of benign and malignant breast lesions and stratify benign disease into high and low risk for progression?
- Can tumor-specific biomarkers be identified and used as contrast agents to improve the performance of any imaging modality?

The Plan

Identification and validation of:

- Biomarkers to further improve the interpretation of conventional mammography or other computer-aided technologies;
- Biomarkers that detect characteristics of benign and malignant breast lesions and stratify benign disease into high and low risk for progression;

- Biomarkers which, in conjunction with mammography, can distinguish malignant from benign lesions in order to reduce or eliminate unnecessary biopsies;
- Biomarkers to detect highly proliferative early malignant lesions associated with increased mortality; and
- Tumor-specific biomarkers that could be used as contrast agents to improve the performance of existing imaging modalities.

Ovarian Cancer

Strategic Goals

The absence of accurate screening biomarkers, coupled with the typical late stage diagnosis of ovarian cancer contributes to the significant lethality of the disease. Thus, early detection is important as currently there are no reliable biomarkers available for screening for ovarian cancer. Transvaginal ultrasound and the serum tumor marker CA-125 have been explored as a strategy for the early detection of ovarian cancer, but the sensitivity, specificity, and lead time (earliness of detection) are not optimal. For example, increased CA-125 levels are found in about three percent of post-menopausal women, resulting in false positives for this biomarker. Recent morphologic and molecular genetic studies have resulted in a paradigm shift with regard to the origin of ovarian cancer and its pathogenesis. This has important implications for research and for radically changing our approaches to early detection, prevention, and treatment of the disease. The development of new circulating biomarkers to be used as a first-tier screening modality for the general or high risk population is a strategic goal that would improve the early detection of the most lethal, high-grade serous ovarian cancers is of utmost importance. Hence, there are two key questions:

- Can biomarkers further improve the interpretation of conventional transvaginal ultrasound or other computer-aided technologies?
- Could a strategy involving the use of risk stratification, accurate biomarkers, and secondary diagnostic imaging tests be a cost-effective model for ovarian cancer screening in a high risk or even general population?

The Plan

- Identification and validation of biomarkers that can further improve the interpretation of conventional transvaginal ultrasonography or other computer-aided imaging technologies;
- Identification and validation of biomarkers that can identify and stratify early ovarian lesions as benign and at high risk of progression to ovarian cancer;
- Building a consolidated pre-diagnostic specimen repository (PLCO, WHI, CARET, Nurses' Health Study, UKCTOCS), statistically powered for discovery and rapid pre-validation of candidate markers;
- Utilizing the NCI TCGA data on ovarian cancer somatic genetics to inform early detection biomarker development; and
- Focusing biomarker discovery efforts on a better understanding of the natural history of the disease and better characterization of putative pre-malignant ovarian lesions.

Cervical Cancer

Strategic Goals

Cervical cancer remains a significant public health problem. Worldwide, cervical cancer is a leading cause of cancer mortality in women. In the United States, cervical cancer screening and follow-up and treatment cost an estimated 2.3 billion dollars, annually. Newly approved HPV vaccines promise to provide primary prevention of cervical cancer, but as only ~70% of cancers are targeted, screening cannot be eliminated. In addition, the best-case scenario for the time-frame in which an impact on the incidence of cervical cancer will be seen is on the order of 20 years. If successful, vaccination will significantly reduce true disease, but have much less impact on transient abnormalities that contribute to the large number of women referred to colposcopy, who do not need treatment.

Developing countries without screening programs stand to benefit the most by the introduction of vaccination. Implementation is being delayed because of the cost of the vaccine and because vaccination without screening is unacceptable to most countries. We need to develop markers that will improve the efficiency of current screening based on high risk HPV detection and cytology so that health care costs can be shifted to other areas of need. The assays for these markers should be robust and easy to perform in low resource settings. Strategic goals are to:

- Improve the effectiveness of cervical cancer screening in the United States.
- Improve on risk-stratification provided by HPV testing to allow screening intervals to be increased in order to reach unscreened populations by using a more culturally acceptable sampling method (self-sampling, urine, blood).

The Plan

- Use EDRN Cervical Cancer biorepository as the basis of a “screening sample” reference set (i.e., serum, plasma, PBMCs, cervical mucous, exfoliated cervical cell DNA/RNA extracts) to evaluate a panel of new markers targeting multiple sample and analyte formats (e.g., methylation in cervical cells, protein markers in cervical mucous, etc.).
- Develop biomarkers for cervical mucous using integrated approaches and multiple platforms (i.e., genomics, proteomics, etc.) using the samples assembled above.

COLORECTAL AND OTHER GASTROINTESTINAL CANCERS

Colon • Liver • Pancreatic

Colon Cancer

Strategic Goals

Colon cancer is both the third most frequently diagnosed cancer and the third cause of cancer deaths in the United States. Successful prevention of colon cancer depends on early detection. Current screening technologies include fecal occult blood test, fecal immunochemical test, sigmoidoscopy, and colonoscopy. Although screening has been shown to reduce cancer deaths, all of the current screening methods have limitations that reduce their effectiveness. Fecal occult blood test and fecal immunochemical test fail to detect a significant fraction of colon cancers and advanced adenomas and have high rate of false positive rates. Sigmoidoscopy and colonoscopy are invasive, expensive, and cause patient discomfort. Consequently, many individuals who should be screened are not. Thus, there is a need to develop biomarkers that more accurately identify individuals that are at risk of having colon cancer or advanced adenomas and that need further testing by colonoscopy. Genetic, epigenetic, and proteomic methods are being used to identify potential colon cancer biomarkers.

- Can biomarkers be used to accurately determine which patients are at risk and in need of further testing (i.e., colonoscopy)?
- Can biomarkers detect characteristics of benign and malignant lesions and stratify benign disease into high and low risk for progression?

The Plan

- Identify, develop and validate both blood based and stool based protein and DNA biomarkers for early colon cancer detection that compliment or perform better than the fecal immunochemical test.
- Develop colon cancer reference sets comprised of serum, plasma, urine, DNA from WBC (white blood cells), and paraffin embedded tissues from normal colon, adenomas, inflammatory bowel disease, and colorectal cancer.

Liver Cancer

Strategic Goals

Hepatocellular carcinoma has a high mortality rate due to late stage diagnosis, when therapy is not as successful. The 5-year survival rate for liver cancer is less than five percent.

Hepatocellular carcinoma incidence is rising in the United States. Infection with HBV (Hepatitis B virus) or HCV (Hepatitis C virus) is responsible for at least 80% of liver cancers. Although there is a vaccine for HBV, currently there is no effective preventative therapy for HCV infections. Cirrhosis of the liver (with or without HBV or HCV infection) is a risk factor for the development of hepatocellular carcinoma. Surveillance of patients with cirrhosis is an important goal for early detection of hepatocellular carcinoma. AFP (alpha-fetoprotein) level in the blood is the current standard used to detect liver cancer. This biomarker has a high false positive rate and can miss many early stage cancers. Better biomarkers need to be developed for hepatocellular carcinoma for early detection and diagnosis, which will reduce the mortality of this cancer.

- Can genome-wide association studies be combined with biomarkers to identify populations at risk for the development of hepatocellular carcinoma?
- Can changes in the HCV viral genome be used to identify cirrhotic patients at high risk from low risk for progression to liver cancer?
- Can imaging be combined with biomarkers to develop a better method to screen cirrhotic patients?
- Can biomarkers be developed that have better sensitivity and specificity than AFP or be used in combination with AFP?

The Plan

- Develop a serially collected liver cancer reference set comprised of serum and plasma from patients at high risk, patients with cirrhosis. These patients will also be monitored with imaging (ultrasound) followed until the development of hepatocellular carcinoma. The serially collected reference set will be valuable for validation of biomarkers for the early detection of liver cancer.
- Use the reference sets to test the ability of previously developed biomarkers (e.g., AFP, DCP and AFPL3%) and newly discovered biomarkers to detect early stage cancer in cirrhotic patients and determine which patients with cirrhosis are likely to progress to cancer.

Pancreatic Cancer

Strategic Goals

Pancreatic cancer has a very high mortality rate, with the mean survival time of less than six months, largely due to the late diagnosis. The current standard biomarker for the diagnosis of pancreatic cancer is the serum marker, CA 19-9. In an asymptomatic population, this biomarker has a positive predictive value below one percent. Currently, universal screening for pancreatic cancer is not recommended. Identification of high risk populations and better biomarkers are needed for the early detection and diagnosis of pancreatic cancer. Diabetes, secondary to pancreatic diseases, is commonly referred to as Type 3c diabetes. Approximately 75% of Type 3c diabetes is due to chronic pancreatitis, which carries a high risk for pancreatic carcinoma. Understanding the link between Type 3c diabetes and pancreatic cancer has the potential to identify individuals at greater risk for pancreatic cancer.

Precursors of invasive ductal adenocarcinoma of the pancreas include pancreatic intraepithelial neoplasias (PanINs), intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms. PanIN's are classified from PanIN1-3, with PanIN-3 being clinically significant because of its potential to progress to invasive cancer. Commonly used imaging methods include endoscopic ultrasound, abdominal CT scan, or MRI. PanINs are difficult to detect using current imaging modalities. However, these methods are increasingly detecting mucinous cystic lesions (IPMNs) in the pancreas. Clinically, the study of IPMNs that have the potential to progress to pancreatic cancer is important and has potential in early detection in identifying asymptomatic patients.

- What is the link of other diseases in increasing the risk for pancreatic cancer, especially Type 3c diabetes?
- Can imaging be used to identify or stratify populations at risk for the development of pancreatic cancer (e.g. IPMNs)? Furthermore, can biomarkers be used to improve imaging techniques and better identify cysts with potential to progress toward pancreatic cancer?
- Can biomarkers be identified and used with CA 19-9 to better identify pancreatic precursor lesions with the potential to progress toward pancreatic cancer?

The Plan

- Determine the relationship between Type 3c diabetes and the development of pancreatic cancer.
- Identify patients at high risk for developing pancreatic cancer and develop methods (*in vitro* diagnostic and/or imaging) to detect early stage pancreatic cancer and PanINs in these patients.

- Develop biomarkers to distinguish IPMNs with high risk of developing pancreatic cancer from those with low risk of developing cancer.
- Use panels of markers to identify profiles for precursor lesions associated with pancreatic cancer (IPMNs or PanINs).
- Develop imaging and biomarkers to stratify populations at risk for developing pancreatic cancer.
- Establish and maintain biorepositories with specimens from patients with early stages of pancreatic cancer (Stage IA, IB, and Stage IIA and IIB), with pancreatic cancer precursor lesions (IPMNs, PanINs), and with benign pancreatic conditions (acute and chronic pancreatitis, biliary obstruction).

LUNG CANCER

Strategic Goals

Lung cancer continues to be the most lethal cancer in the US with over 160,000 deaths per year. The incidence of lung cancer is driven predominantly by smoking with a prevalence of lung cancer in the smoking and former smoker populations in the range of 10–15%. About 90% of patients with lung cancer have a significant smoking history. In the EDRN, a variety of lung cancer markers have been pursued including panels of gene methylation markers, mitochondrial DNA mutations, mitochondrial number, chromosomal abnormalities, proteomic profiling, autoantibodies to defined proteins or glycans, miRNAs, and gene expression profiles. Within a high risk population of smokers, many markers were not able to distinguish non-diseased smokers from lung cancer patients; however, they clearly differentiate smokers from nonsmokers. These molecular alterations persist later in life as evidenced in cohorts who ceased smoking five years previously. These findings highlight how smoking induces profound molecular alterations in the epithelial linings of the lungs setting them on a path towards neoplasia. Recently, interest has arisen to characterize the sequence of driver mutations that occur during oncogenesis from the earliest stages of atypical adenomatous hyperplasia (AAH) to invasive cancer. Understanding how somatic gene defects accumulate over time and determine which critical genes are responsible for progression to invasive cancer will yield greater insights into predicting and stratifying those smokers that may be at greater risk for developing lung cancer.

Results from the National Lung Screening Trial (NLST) found that screening by low-dose CT decreased lung cancer mortality by 20% highlighting the benefits that can be achieved with more frequent detection of early stage lung cancers. It is noteworthy that 25% of the subjects presented with nodules of which 96% were benign. Current management of abnormalities found by chest CT can lead to expensive and invasive diagnostic follow-up. The utilization of non-invasive biomarkers to discriminate between early stage malignancies and benign nodules could greatly reduce the need and costs associated with clinical follow-up of subjects with indeterminate nodules.

To address these challenges the strategic goals are to:

- Develop biomarkers that will be used in combination with CT imaging in patients presenting with small pulmonary nodules to stratify those that will need to undergo further work up for diagnosis of lung cancer from those with benign disease. This test could spare follow-up on many subjects who do not have an early stage malignancy.
- Classify gene mutations occurring from early stages of hyperplasia through successive stages to invasive adenocarcinoma in an attempt to understand the sequence of genetic insults that drive lung cancer progression.

The Plan

- Validate all promising lung cancer biomarkers on a prospectively collected cohort of 200 subjects with indeterminate pulmonary nodules. Approximately 30 lung cancer cases are estimated to be found in this cohort after 2 year follow-up. Biomarkers to be tested among EDNRN BDLs are gene methylation markers, gene expression profiles, a host of serum protein markers, anti-glycan autoantibodies, and miRNAs.
- Recruitment of 200 subjects for this prospective study will occur at four sites for current or former smokers greater than 45 years of age and over 25 pack-years of smoking. Subjects must have noncalcified pulmonary nodules on chest CT in the range of 7–20 mm in diameter. Specimens to be obtained from each subject are serum/plasma, bronchial brushings during bronchoscopy, and nasal brushings. All subjects will be followed up for two years until a diagnosis of lung cancer is determined. All samples will be sent to one site where relabeling and blinding will occur before being sent out to all biomarker testing labs.
- Perform deep genomic sequencing of heterogeneous sites within a single subject to uncover the sequence of genetic mutations that lead to progression of invasive adenocarcinoma. Two strategies are used in this paradigm. The first is to sample adenocarcinoma tissue, premalignant lesions, and adjacent normal lung tissue from individual lung cancer patients. The second approach is to sample various histological zones of progression from subjects presenting with lesions characterized as atypical adenomatous hyperplasia, adenocarcinoma in situ, or minimally invasive adenocarcinoma. DNA obtained by laser capture microdissection will be analyzed by deep sequencing methods where comparisons of the similarities or heterogeneity in the mutational landscape within each lesion should reveal the important cascade of mutational events leading to invasive adenocarcinoma.

PROSTATE AND OTHER UROLOGIC CANCERS

- Prostate • Bladder and Other Urogenital Cancers

Prostate Cancer

Strategic Goals

Prostate-specific antigen (PSA) had a remarkable effect on the detection diagnosis and monitoring of prostate cancer. Although clinically localized prostate cancer has become highly curable, the overall death toll remains high due to recurrence and progression to hormone-refractory and metastatic disease, which remains incurable. PSA tests resulted in detection of a large number of false positive prostate cancers, leading to the phenomena known as “overdiagnosis” and repeated biopsies.

There is an urgent need for predictive markers for early detection of aggressive prostate cancer, which would be distinguished from the less aggressive non-lethal forms of prostate cancer. Markers should be developed based on recent advances in cancer biology with application of Omics related approaches (genomics, epigenomics, metabolomics, and proteomics).

The recently discovered fusion transcripts (TMPRSS2-ETS), which are frequently (~50%) expressed in prostate cancers, are promising markers that were or are being validated for early detection; as a prognostic markers for the development of aggressive cancer; or as risk markers. Those include TMPRSS2-ERG, TMPRSS2-ETV1, TMPRSS2-ETV4 as well as genes, which are exclusively expressed in fusion negative prostate cancers such as the mutant SPOP and the overexpressed SPINK1. In addition, a recently discovered marker, SchLAP-1, a long non-coding RNA, that is highly correlated with ~20% of aggressive prostate cancers.

In light of unmet needs of minimizing false positives, differentiating between aggressive and non-aggressive forms of prostate cancer, and estimating risk, EDNRN investigators are trying to address the following areas:

- Further development and validation of promising markers for early detection of significant cancers; for risk assessment and for prostate cancer stratification (e.g., fusion genes positive as compared to fusion genes negative cancers).
- Development and validation of markers based on recent advances in cancer biology (e.g., markers associated with prostate cancer stem cells; markers associated with reactive stroma adjacent to a cancer focus; and application of integrative approaches to biomarker development for early and aggressive forms of prostate cancer.

- Development and validation of biomarkers for prostate cancer risk assessment based on recent results of whole genome association studies; and provide guidelines for integration of risk markers into clinical practice.
- Improve the performance of existing markers (e.g., PSA by evaluating its molecular forms, such as [-2]proPSA or combining it with a panel of tumor specific markers such as TMPRSS2-ERG and mutant SPOP.
- Combining biomarkers with imaging to improve the diagnostic performance of imaging – reducing the false positive rate; improving the detection of significant cancers; and to improve testing of same foci for patients on active surveillance.
- Reduce the number of unnecessary biopsies (primary and repeat biopsies).
- Develop and validate biomarkers associated with grade and stage upgrading.
- Continue to assemble prostate cancer “reference sets” for biomarkers discovery and validation studies. Composition of each collection of “reference set” should be tailored to answer specific clinical question.
 - Body fluids to include, plasma, serum, urine, EPS (Expressed Prostatic Secretions)
 - Circulating tumor cells, WBC
 - Tissue

The Plan

- Reference Sets and Cohorts:
 - EDNRN will assemble reference sets based on tissue and body fluids to discover and test candidate biomarker/s that may assist in answering specific clinical needs.
- Biopsy positive reference sets will be necessary for:
 - For general population screening with marker/s adding or replacing PSA, all cases and controls should have a biopsy. This collection should not be triggered by elevated PSA.
 - For identification and testing markers that will be used to assist in clinical decisions (i.e., whether a patient needs a radical prostatectomy). One need to keep in mind that the current practice is based on clinical predictors (e.g., Gleason score).
 - For prediction of cancer progression, including the development of metastasis and mortality, there is a need for specimens from cohorts with many years of follow up. For this purpose we will collaborate with the appropriate programs (i.e., collaborative groups, PLCO).
 - Expand the collection biopsy from high risk individuals, men with elevated PSA, or abnormal DRE (Digital Rectal Exam).
 - For Biopsy negative population. There is a need to develop a tissue resource and combine tissue based marker with body fluid markers to increase negative predictive value.

- Develop and identify differential expressed markers for detection of prostates cancer perpetuating cells – prostate cancer stem cells.
 - Detection of cancer stem cells among exfoliated cells (for cancers of the urological system such as prostate and bladder).
 - *In vivo* early detection of early stage prostate cancer by detection of prostate cancer stem cells. This approach will be based on combination of affinity reagents, specific for the cancer stem markers, with imaging technologies. The proof of principle will be established in animal models. Similar approaches should be conducted for other cancers as well.
- Development of biomarkers based on cancer stroma cells associate markers.
 - Identification of prostate cancer stoma markers in tissue culture, 3-D cultures, cancer tissue, and in animal models.
 - Detection of cancer reactive stroma markers in prostatectomy specimens.
 - Detection of cancer stroma markers in body fluids
- Application of Systems Biology approach to integrate variety of cancerous processes as detected by Omic technologies [e.g., differential expression of genes, non-coding RNAs including miRNAs, fusion transcripts (TMPSS2-ERG), mutant or amplified oncogenes, inactivation of tumor suppressor genes; mutations / inactivation of DNA repair mechanisms; differential proteomics; and abnormal PTMs; differential expression of epigenomic markers (signatures for abnormal DNA methylation; signatures of abnormal histone methylation and acetylation; differential expression of metabolites, etc] to identify perturbed biochemical pathways and processes that could be used for early detection and early prediction of aggressive cancers. .
- Initiate validation studies based on new generation of biomarkers, such as gene fusion product (TMPRSS2-ETS); mutant genes and differentially overexpressed coding and non-coding genes and or metabolites in tissue and body fluids (biopsy and prostatectomy specimens as well as in urine, EPS and blood).
- Circulating Tumor Cells (CTCs) to estimate cancer progression and early recurrence. CTCs could be early indicators for the development of an aggressive cancer.
- To develop surrogate markers, the GU (Genitourinary) collaborative group will assemble a collection of WBC from cancer and control patients, which could be used to develop surrogate markers, such as functional biochemical tests, and polymorphism, which correlate well with risk; e.g., the capacity to repair damaged DNA by certain DNA repair enzymes like OGG1 was recently correlated with risk of developing lung cancer due to smoking. The activity of this enzyme was identical in the surrogate tissue, WBC, and lung epithelia cells in the same individuals.
- Continue to establish collection of body fluids (plasma, serum, urine, EPS) as “reference sets” for rapid evaluation of biomarkers before entering the validation trials; and for discovery purpose using well annotated and well represented collection of specimens to minimize the presence of confounders and bias.

Bladder and Other Urogenital Cancers

Bladder Cancer

Strategic Goals

Bladder cancer is the fifth most common cancer in the Western world, affecting about 4% of all cancer patients and is the cause of about 3% of all cancer-related deaths. The estimated life probability of developing bladder cancer in the United States is 1 in 28 for men and 1 in 87 for women. Bladder cancer occurs in two clinically significant forms: Superficial (TNM: Ta, TIS, T1) and Invasive (TNM: >T2). Seventy-five percent of the patients are diagnosed with superficial disease, and only a minority (about 15%) is at risk for progression. Approximately 70% of these patients will experience recurrence of the disease within 10 years. The majority of recurrences occur within the first two years after diagnosis. The vast majority of invasive bladder cancers occur in patients without a prior history of papillary tumors. Although urine cytology and cystoscopy are considered standards of care, these are less than optimal in detecting all forms of bladder cancer. The sensitivity and specificity of urinary cytology are 25-50% and 90-100%, respectively. The sensitivity and specificity of cystoscopy is 90-100% and 75%, respectively. In recent years, several new biomarkers and tests for detection of bladder cancer gained acceptance and FDA approval (BTA™, BTA stat™ FDP™ NMP22™ and the UroVysion). Most of these FDA-approved tests can augment, but not replace, the cystoscopy for diagnosis of bladder cancer. Consequently, there is a need to improve the current practice of bladder cancer detection and surveillance. Strategic goals are to:

- Develop non-invasive diagnostic tests for early detection of superficial bladder cancer (to minimize the number of unnecessary cystoscopies) and for early recurrence of superficial bladder cancer.

The Plan

- Develop biomarkers associated with the four major subtypes of bladder cancer: (1) transitional cell carcinoma; (2) squamous cell carcinoma; (3) adenocarcinoma; and (4) small cell carcinoma. Also, identify biomarkers associated with bladder cancer stem cells, bladder stroma cells, and others.
- Validate (analytical and clinical validation) promising biomarkers for the various subtypes of bladder cancer [i.e., methylated DNA sequences, genetic alterations (mutations, amplifications, and deletions) in candidate oncogenes and tumor suppressor genes, and alterations in mtDNA, etc.].
- Assemble bladder cancer “reference sets” and appropriate controls for biomarker discovery and validation studies. The composition of each collection of “reference sets” should be tailored to answer specific clinical questions.

- For prediction of cancer progression, including the development of metastasis and mortality, there is a need for specimens from cohorts with many years of follow-up. For this purpose, EDNRN will collaborate with the appropriate programs (i.e., collaborative groups). Collected specimens will include body fluids (urine, plasma, and serum), tissues, circulating tumor cells, and WBCs.
- Develop biomarkers including biomarkers derived from stromal and stem cells for molecular classification of bladder cancer subtypes.
 - Use circulating tumor cells (CTCs) to estimate cancer progression and early recurrence. CTCs could be early indicators for the development of an aggressive cancer.

Other Urogenital Cancers

At present, there is no established serum or urinary biomarker for the diagnosis or management of kidney cancer as well as a lack of specific symptoms in people with early stage disease. Furthermore, an increasingly larger subgroup of patients with small renal masses are not treated but are instead monitored for disease progression by CT or MRI.

The Plan

- Priorities for kidney cancer are the development of biomarkers for non-invasive early detection and as prognostic indicators of aggressiveness of disease.

DATA SHARING AND INFORMATICS

Informatics/Information Science

Strategic Goals

Informatics plays a key role in supporting the scientific discovery process by building the infrastructure and tools that connect the EDRN research institutions together into a virtual knowledge portal. The objective is to provide an essential and critical core infrastructure that builds and connects database knowledge systems, where bio-specimens, scientific data, study specific data, and biomarker data can be captured, accessed, and shared within the EDRN and at a national level via a transparent, grid-type architecture. Therefore, the goal is to support collaborations in biomarker discovery and clinical application by linkage of various database implementations, scientists, and other researchers to discoveries by means of different data sets through use of a data portal that is similar to a single, large repository of knowledge. Strategic goals:

- Does software interfaces adequately capture discovery and access of science data resources across the knowledge system, and can informatics provide software interfaces to capture and annotate biomarkers into the EDRN Biomarker Database?
- What advances does informatics entail that will implement an integrated portal environment across the distributed EDRN?
- Will a secure transfer and distribution infrastructure meet United States Federal regulations for data sharing?

The Plan

- Produce and unify bio-specimen interoperability among groups across the EDRN and participating institutions by coordinating discovery of biomarkers across cancer research centers.
- Capture, catalog and annotate the EDRN science data into the EDRN Science Data Warehouse, EDRN Catalog and Archive System (eCAS) and associate the Biomarker Database and eCAS with the EDRN Knowledge Environment (EKE).
- Review the Data Sharing Policy and Data Disclaimer.
- Develop a biomarker database and set-up a PDQ-like review system to evaluate published biomarkers for inclusion in the database. The plan is that the data base provides pre-competitive data sharing with the extramural community.

CONCLUSION

The EDRN assesses organ-specific cancers and identifies promising markers that can be further tested and validated for early detection and diagnosis of aggressive cancers. The evidence is clear that it is essential to estimate early cancer progression and early cancer recurrence.

Therefore, EDRN investigators will research organ-specific cancers in order to identify early, new detection and surveillance theories worthy of further research to identify markers and reference sets. As a result, each organ-specific area proposes strategic goals and a plan to assemble reference sets and appropriate controls to answer EDRN strategic goals that validates (analytical and clinical validation) development of promising biomarkers for a variety of subtypes of cancers.

In addition, the EDRN's Strategic Plan includes both short and long-term goals. While the biomarkers for population-level early detection and screening remains part of the long-term goals, the improvement of current detection and diagnostic modalities are achievable short-term goals.

Translation of biomarker discovery into cancer early detection and diagnostics requires a broad spectrum of disciplinary expertise. The EDRN has focused on this since its inception and has thus established a unique group of multidisciplinary investigators dedicated to the EDRN Strategic Plan. This group includes basic scientists, epidemiologic and population researchers, and physician scientists, who are on the front line of patient care. Collaborative projects amongst these EDRN investigators facilitate biomarker research and its translation into clinical application. Equally important, EDRN collaborations have a long-standing relationship with industry and private sectors, which are changing their business model to support biomarker discovery for early detection and diagnostics.

EDRN is also developing strategic alliances with non-profit foundations, such as the Canary Foundation and the Lustgarten Foundation, Federal agencies, such as NIST (National Institute of Standards and Technology) and the FDA (Food and Drug Administration); and professional organizations, such as ASCO (American Society of Clinical Oncology) to develop a transparent process for creating well-defined consensus standards and guidelines for biomarker development, validation and qualification to reduce the uncertainty in adoption of biomarkers for clinical use. In the future, the EDRN proposes to work with CMS (Centers for Medicare and Medicaid Services) to review new biomarkers and to reach consensus on coverage and pricing.

Stakeholder's Meeting on Research Priorities for the Future
May 20-21, 2010
Hilton Hotel, Rockville, MD
Draft Agenda

Thursday, May 20, 2010

- 8:30-8:45 a.m.** Welcome
Sudhir Srivastava, Ph.D., National Cancer Institute
- 8:45-9:00 a.m. Introduction
Richard Schilsky, M.D., University of Chicago Medical Center
Sam Hanash, M.D., Ph.D., Fred Hutchinson Cancer Research Center
- 9:00 a.m.-12:00 p.m.** **Session 1: Biomarkers for Early Detection and Diagnosis**
Moderators:

William Rom, M.D., NYU
Michael Goggins, M.D., Johns Hopkins University
- 9:00- 9:15 a.m. Remarks by Moderators
- 9:15- 9:30 a.m. Early Detection: Case Study
Dan Cramer, M.D., ScD, Dana-Farber Cancer Institute
- 9:30 – 9:45 Challenges faced by a Biomarker Development lab in delivering a clinical application
Jeff Marks, Ph.D., Duke University
- 9:45 a.m. -11:45 p.m. High Priority Applications Pertaining to Unmet Medical Needs: Detection and Diagnosis Discussion Topics

Speakers are to suggest for their assigned organ types one or two high priority applications pertaining to detection and diagnosis that they consider within reach near term. Criteria to be considered in prioritizing applications include:

1. What are the known risk factors that define the population to be screened for early detection?
2. What are the ways to integrate with imaging modalities to improve diagnostic accuracy?

3. How can we reduce the need for invasive procedures?

9:45 – 10:00 Dean Brenner, M.D., University of Michigan/ GI

10: 00 – 10:15 David Sidransky, M.D., Johns Hopkins University/ Head & Neck

10:15 – 10:30 John Minna, M.D., University of Texas Southwestern Medical Center at Dallas/ Lung

10:30-10:45a.m. Break

10:45 -11:00 Peter Nelson, M.D., Fred Hutchinson Cancer Research Center/ Prostate

11:00 – 11:15 Sandra Swain, M.D., Washington Hospital/Breast

11:15 – 11:30 Beth Karlan, M.D., Cedar-Sinai Medical Center/ Ovarian

11:30 – 11:45 Margaret Tempero, M.D., University of California, San Francisco/ Pancreas

11:45- 1:00 p.m. Lunch break (on your own)

1:00 p.m. – 3:00 p.m. Session 2: Biomarkers for Refining Prognosis, Selecting Therapy, or Monitoring Response

Moderators:

George Coukos, M.D., Ph.D., University of Pennsylvania
Steven Dubinett, M.D., University of California at Los Angeles

1:00 p.m. -1:15 p.m. Remarks by Moderators

Discussion Topics:

1. Potential to affect patient management through better assessment of prognosis
2. potential to affect patient management through early assessment of response or resistance to treatment
3. Potential to affect patient management by providing an early indication of disease recurrence.
4. Potential to contribute to clinical trials

1:15 p.m. -1:45 p.m. Development and use of Oncotype Dx in Breast and Colon Cancer: Case Study
Steve Shak, M.D., Genomic Health

1:45- 2:45 p.m. Unmet Medical Needs

1: 45 – 2:00 David Gandara, M.D., UC Davis Cancer Center/ Lung

2:00 – 2:15 Dean Brenner, M.D., University of Michigan/ Colon

2:15 – 2:30 Peter Nelson, M.D., Fred Hutchinson Cancer Research Center/ Prostate

2:30 – 2:45 Jenny Chang, M.D., Baylor College of Medicine/ Breast

2:45- 3:15 p.m. Break

3:15-4:15 p.m. Strategies to Accelerate Biomarker Development in Areas of Unmet Medical Needs

3:15- 3:30 p.m. Harvey Pass, M.D., New York University Medical Center/Lung

3:30- 3:45 p.m. Raju Kucherlapati, Ph.D., Harvard University/ Colon

3:45- 4:00 p.m. William Nelson, M.D., Johns Hopkins University/ Prostate

4:00- 4:15 p.m. Jenny Chang, M.D., Baylor College of Medicine/ Breast

4:15-5:15 p.m. Role of Imaging in Cancer Detection, Response Assessment and Monitoring Recurrence

4:15- 4:45 p.m. Dr. Ralph Weissleder, M.D., Ph.D., Center for Molecular Imaging Research

Clinical and Molecular Imaging (proteomics, genomics, metabolomics) in a Systems Approach to Cancer Detection and Diagnosis

4:45- 5:15 p.m. Steven Larson, M.D., Memorial Sloan-Kettering Cancer Center

Imaging as an Adjunct to Early Detection and Diagnosis

5:15-5:30 p.m. Summary and Wrap-up of Day 1

Richard Schilsky, M.D., University of Chicago Medical Center
Sam Hanash, M.D., Ph.D., Fred Hutchinson Cancer Research Center

Friday, May 21, 2010

8:30-10:10 a.m.

Session 3: Roadmap for Developing Clinical Applications that are Achievable Near Term

Moderators:

George Poste, Ph.D., Arizona State University
William Nelson M.D., Johns Hopkins University

8:30 – 8:45 am

Remarks by Moderators

Discussion Topics:

Efficient discovery strategies, needs and use of specimens (preclinical versus clinical samples), partnership with cohort consortia and cooperative groups and access to quality samples.

8:45- 9:00 a.m.

Efficient Study Designs

Ziding Feng, Ph.D., Fred Hutchinson Cancer Research Center

9:00- 9:15 a.m.

Single Investigator vs. Collaborative Approaches to Discovery and Validation: EDRN Experience

Adi Gazdar, M.B.B.S, University of Texas Southwestern Medical Center

9:15- 9:30 a.m.

Development of Biomarkers and Related Challenges

Nita Maihle, Ph.D., Yale University

9:30- 9:50 a.m.

Partnerships with Cohort Study Groups

Sam Hanash, M.D., Ph.D., Fred Hutchinson Cancer Research Center

9:50 - 10:10 a.m.

Partnerships with Clinical Trial Groups

Richard Schilsky, M.D., University of Chicago Medical Center

10:10-10:30 a.m.

Break

10:30 a.m.-12:00 p.m.

Public-Private Partnerships

Moderators:

David Sidransky, M.D., Johns Hopkins University
David Parkinson M.D., Nodality Inc.

10:30 – 10:45

Remarks by Moderators

Discussion Topics:

1. Are there common or standard interests that are shared among partners? If so, how can these be the cornerstone of agreements?
2. How can each partner assist in achieving these goals?
3. What considerations need to be made when the relationship involves “discovery” projects vs. “validation” projects?
4. How are the relationships different in partnering with a platform company vs. a content company?
5. How can alliance among industry and academia be strengthened? What types of programs can be developed? What role might EDRN play?
6. What are the barriers to industry-other collaborations?
7. What are the issues surrounding commercialization of a discovery product or new biomarker? For multiplex marker panels? When is a biomarker or panel ready to hand over for commercialization?
8. How can EDRN specifically facilitate partnership among all of these groups and among industry: industry partnerships?

10:45-11:15 a.m.

Foundations' Perspective

Don Listwin, Founder, Chairman, Canary Foundation

11:15 - 11:30 a.m.

Private Sector's Perspective

David Parkinson, M.D., President, Nodality, Inc.

11:30 a.m.- 12:00 p.m.

Global Perspective

George Poste, Ph.D., Arizona State University

12:00 – 12:15

Experience Working With Private Sectors

William Rom, M.D., NYU

12:15 -12:30 p.m.

Summary and Moving Forward

Sudhir Srivastava, Ph.D., M.P.H, National Cancer Institute

12:30 p.m.

Adjourn

Think-Tank Mini Workshop: Companion Imaging and Molecular Diagnostics

U.S. Department of Health and Human Services (DHHS)

National Institutes of Health (NIH)

National Cancer Institute (NCI)

Division of Cancer Prevention (DCP)

Cancer Biomarkers Research Group (CBRG)

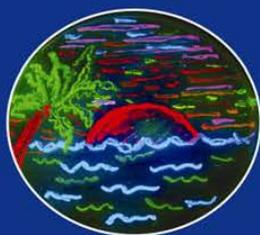
Early Detection Research Network (EDRN)

Endorsed by:

American College of Radiology Imaging Network (ACRIN)

The Society for Molecular Imaging (SMI)

Academy of Molecular Imaging (AMI)



Think-Tank Mini Workshop: Companion Imaging and Molecular Diagnostics

February 28, 2011 • Hyatt Regency Bethesda • Bethesda, Maryland

AGENDA

Chair: Sanjiv Sam Gambhir, M.D., Ph.D.

Moderator: Juri Gelovani, M.D., Ph.D.

7:30 a.m. – 8:00 a.m.

Registration

8:00 a.m. - 8:05 a.m.

Welcome

Richard Mazurchuk, Ph.D.
National Cancer Institute

Baccarat Room

8:05 a.m. - 8:30 a.m.

EDRN Overview

Sudhir Srivastava, Ph.D., M.P.H., M.S.
National Cancer Institute

8:30 a.m. - 8:50 a.m.

EDRN Perspective:

Companion Imaging and Molecular Diagnostics (CIMD)

Richard Mazurchuk, Ph.D.
National Cancer Institute

8:50 a.m. - 9:25 a.m.

Emerging Strategies for the Merger of *In Vitro* and *In Vivo* Diagnostics

Sanjiv Sam Gambhir, M.D., Ph.D.
Stanford University

9:25 a.m. - 10:00 a.m.

New Molecules and Mechanisms for Early Detection and Image-Guided Surgery of Tumors

Roger Tsien, Ph.D.
University of California, San Diego

10:00 a.m. - 10:15 a.m.

BREAK

10:15 a.m. - 10:50 a.m.

Cancer Genomes and Their Diagnostic Implications

Bert Vogelstein, M.D.
Johns Hopkins University

10:50 a.m. - 11:00 a.m.	<p>Overview: Discussion Group Breakout Sessions Richard Mazurchuk, Ph.D. National Cancer Institute</p>	
11:00 a.m. - 1:30 p.m.	<p>Parallel Breakout Session Discussion Groups 1 and 2</p> <p>Group 1: Companion Imaging and Molecular Diagnostics</p> <p>Moderator: David Mankoff, M.D., Ph.D. Co-Moderator: Peter Choyke, M.D.</p> <p>Group 2: Multi Targeted, Multi Disciplinary Molecular Imaging Approaches</p> <p>Moderator: Robert Gillies, Ph.D. Co-Moderator: Rebecca Richards-Kortum, Ph.D.</p>	<p><i>Baccarat Room</i></p> <p><i>Haverford Room</i></p>
1:30 p.m. - 1:45 p.m.	BREAK	
1:45 p.m. - 2:45 p.m.	<p>Groups 1 and 2: Summary Presentation and Discussion</p> <p>Preliminary report and discussion with input from both groups Group 1: David Mankoff, M.D., Ph.D. Group 2: Robert Gillies, Ph.D.</p>	<i>Baccarat Room</i>
2:45 p.m. - 3:45 p.m.	<p>Group Discussion and Action Items Proposed Group 1 and 2 Updates with consensus based on discussion input</p> <p>Moderator: Juri Gelovani, M.D., Ph.D.</p>	
3:45 p.m. - 4:00 p.m.	BREAK	
4:00 p.m. - 4:55 p.m.	<p>Summary, Questions, and Answers/Next Step(s)</p> <p>Sanjiv Sam Gambhir, M.D., Ph.D.</p>	
4:55 p.m. - 5:00 p.m.	<p>CONCLUDING REMARKS AND ADJOURNMENT</p> <p>Richard Mazurchuk, Ph.D. National Cancer Institute</p>	

National Cancer Institute
National Institutes of Health
U.S. Department of Health and Human Services

Defining Molecularly-Informed Natural History of Occult Neoplasms

The Hilton Washington DC/Rockville Hotel and Executive Meeting Center

Rockville, MD

March 8-9, 2012

DRAFT AGENDA

Thursday, March 8, 2012

7:30 a.m. - 8:00 a.m. **Registration** *Regency Foyer*

8:00 a.m. - 8:10 a.m. **Workshop Overview** *Regency*
R. Rhey Palmer, Ph.D.
National Cancer Institute/Division of Cancer Prevention
Consultant and Workshop Facilitator

8:10 a.m. - 8:30 a.m. **Welcome and Charge to the Workshop**
Sudhir Srivastava, Ph.D., M.P.H.
Chief
Cancer Biomarkers Research Group
National Cancer Institute, NIH

8:30 a.m. - 9:00 a.m. **Impact of Overdiagnosis on Prevention and Treatment**
Barnett S. Kramer, M.D., M.P.H.
Director
Division of Cancer Prevention
National Cancer Institute, NIH

9:00 a.m. - 9:30 a.m.

Biology of Missed and Interval Cancers

Patrick Brown, M.D., Ph.D.

Stanford School of Medicine

9:30 a.m. - 10:00 a.m.

Molecular Basis of Screening and Early Detection

Kenneth Kinzler, Ph.D.

Johns Hopkins University

10:00 a.m. - 10:20 a.m.

Break

10:20 a.m. - 12:40 p.m.

Overdiagnosis and Clinical Implications

10:20 a.m. - 10:40 a.m.

Orientation

Chairs:

Ian Thompson, M.D.

University of Texas San Antonio

Laura Esserman, M.D., M.B.A.

University of California at San Francisco

10:40 a.m. - 11:10 a.m.

Discussants:

David Ransohoff, M.D.

University of North Carolina at Chapel Hill

Barnett Kramer, M.D., M.P.H.

National Cancer Institute, NIH

Peter Nelson, M.D.

Fred Hutchinson Cancer Research Center

Peter Bach, M.D., M.A.P.P.

New York University

Michael Hollingsworth, Ph.D.

University of Nebraska

H. Gilbert Welch, M.D., M.P.H.

Dartmouth University

11:10 a.m. - 12:10 p.m.	Breakout Session 1	
11:10 a.m. - 11:15 a.m.	<i>Charge to Discussion Groups</i> R. Rhey Palmer, Ph.D.	
11:15 a.m. - 12 noon	<i>Discussion</i> Breakout Group 1 Breakout Group 2 Breakout Group 3 Breakout Group 4	Regency Monroe Truman Wilson
12 noon - 12:10 p.m.	<i>Group Leaders prepare 5 minute summary for plenary</i>	
12:10 p.m. - 12:40 p.m.	Reconvene in Plenary Session/Summation of Discussions David Ransohoff, M.D. University of North Carolina at Chapel Hill Donald Berry, Ph.D. University of Texas MD Anderson Cancer Center Slyvia Plevritis, Ph.D. Stanford University Peter Nelson, M.D. Fred Hutchinson Cancer Center Plenary Summary of Conclusions R. Rhey Palmer, Ph.D.	Regency
12:40 p.m. - 1:40 p.m.	Lunch (On your own)	
1:40 p.m. - 5:00 p.m.	Molecular Characteristics of Missed and Interval Cancers	Regency
1:40 p.m. - 2:00 p.m.	Orientation <i>Chairs:</i> Brian Reid, M.D., Ph.D. Fred Hutchinson Cancer Research Center	

Sudhir Srivastava, Ph.D., MPH
National Cancer Institute, NIH

2:00 p.m. - 2:30 p.m.

Discussants:

Kenneth Kinzler, Ph.D.

Johns Hopkins University

Mina Bissell, Ph.D.

Lawrence Berkeley National Laboratory

Douglas Brash, Ph.D.

Yale University

John Pepper, Ph.D.

National Cancer Institute, NIH

2:30 p.m. - 3:30 p.m.

Breakout Session 2

2:30 p.m. - 2:35 p.m.

Charge to Discussion Groups

R. Rhey Palmer, Ph.D.

2:35 p.m. - 3:20 p.m.

Discussion

Breakout Group 1

Regency

Breakout Group 2

Monroe

Breakout Group 3

Truman

Breakout Group 4

Wilson

3:20 p.m. - 3:30 p.m.

Group Leaders prepare 5 minute summary for plenary

3:30 p.m. - 3:50 p.m.

Break

3:50 p.m. - 4:20 p.m.

Reconvene in Plenary Session/ Summation of Discussions

Regency

Darryl Shibata, M.D.

University of Southern California

David Threadgill, Ph.D.

North Carolina State University

Laura Esserman, M.D., M.B.A.

University of California, San Francisco

Kenneth Pienta, M.D.

University of Michigan

Plenary Summary of Conclusions

R. Rhey Palmer, Ph.D.

4:20 p.m. - 5:00 p.m.

Summary of the Day

R. Rhey Palmer, Ph.D.

5:00 p.m.

Adjournment

5:00 p.m. - 7:00 p.m.

Dinner (on your own)

7:00 p.m.

**Chairs reconvene to participate in write-up for Day 1
with facilitator and science writer**

Regency