

ACRIN NEWSLETTER

Advancing Clinical Care Through Imaging Research

Fall 2011

From the Network Chair **ECOG and ACRIN Research Strategy Builds Upon Strong Scientific Synergies**



Mitchell Schnall, MD, PhD

The National Cancer Institute's (NCI's) plan, announced late last year, to restructure its Cooperative Group Program has engaged ACRIN leadership in considerable dialogue about what components of ACRIN's mission and culture were critical to preserve as we considered strategic alliances. Of overriding importance was engaging in a partnership that would promote conducting the continuum of imaging research—from screening and early detection to treatment monitoring—while maintaining a culture of scientific innovation and transparency.

In our initial discussions with Eastern Cooperative Oncology Group (ECOG) leadership, we learned about the group's similarly broad interests. As we engaged in more focused discussion about respective research goals, the groups' extensive complementary expertise and similar commitment to scientific innovation became readily apparent. Through many productive discussions, a scientific framework was constructed that builds upon each group's strengths and results in a scientific integration that has enormous potential to be greater than the sum of its parts.

This new construct has three core areas. ACRIN and ECOG investigators working on early cancer detection and prevention will develop strategies that address such issues as identification of subpopulations that most benefit from specific screening interventions. In the area of cancer therapeutics, researchers will work to develop innovative clinical trial designs for multiple cancer types and stages, such as the current collaboration underway of the phase 2 adaptive therapy trial based on PET imaging for patients with Hodgkin's lymphoma (see sidebar). At the heart of the collaboration, the Biomarker Study Group brings together prominent scientists from ECOG's Laboratory Science Committee and Developmental Therapeutics Committee and ACRIN's Experimental Imaging Sciences Committee to collaborate on integrating imaging and in vitro biomarkers for therapeutic development. These scientists also will help guide the biomarker strategies for all research initiatives.

In addition to the scientific synergies, this merger also brings together the energy and innovativeness of each group's research associate and patient advocate committees. I have every confidence that the integration of these ECOG and ACRIN committees will result in enhanced coordination across disciplines and outreach to study participants.

This integrated model offers enormous potential to better serve cancer patients and the scientific community. There is a lot of hard work ahead of us; however, I believe this alliance offers an opportunity to strengthen our research programs. I am gratified by the pervasive enthusiasm I've seen across both organizations, and look forward to a very successful future together.

ECOG and ACRIN Collaborate on Hodgkin's Lymphoma Trial

In early discussions about mutual scientific interests, ECOG and ACRIN investigators quickly identified a clinical trial that offered an excellent collaborative opportunity. The ECOG 2410 protocol incorporates FDG-PET imaging to stratify patients with stage I and II bulky Hodgkin's lymphoma into one of two treatment arms. The trial leadership welcomed a partnership with ACRIN investigators to incorporate several imaging aims. The ECOG 2410/ACRIN 6700 protocol was recently approved by the National Cancer Institute.

The adaptive trial design seeks to determine whether FDG-PET, after two cycles of the chemotherapy regimen ABVD, can accurately determine the optimal continuing course of patient therapy. If the FDG-PET scan is negative, the patient completes the ABVD therapy regimen; if the FDG-PET scan is positive, the more aggressive therapy BEACOPP is pursued. The trial's primary end point is to evaluate the progression-free survival (PFS) of patients in both arms at 36 months following registration. Imaging end points include assessment of the predictive value of FDG uptake with respect to response at the end of chemotherapy and PFS, as well as FDG-PET's predictive value alone versus in combination with CT and with serum and tissue molecular biomarkers.

"The study has significant potential to advance both therapeutic and imaging science and is a good example of the exciting potential for future collaborative efforts," says Barry Siegel, MD (Washington University, St. Louis), ACRIN co-chair for the trial with Lale Kostakoglu, MD, MPH (Mount Sinai Hospital, New York).

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Aiding the Development of Lung Cancer Screening Guidelines

Following the publication of the National Lung Screening Trial (NLST) primary results this past summer, Denise Aberle, MD (Radiological Sciences, University of California, Los Angeles), the NLST-ACRIN principal investigator and ACRIN deputy co-chair, provides insight regarding future NLST analyses and other important uses of the NLST data.

Newsletter: What additional NLST data will be reported that will have an impact on screening guideline formation?

Aberle: A much-anticipated paper is the CT screening cost-effectiveness analysis (CEA), headed by William Black, MD (Dartmouth College, Hanover, NH). The CEA examines costs associated with screening, including subsequent diagnostic and treatment interventions, time missed from work, follow-up of false-positive screens, and tests for those not screened who later became symptomatic and required treatment. These broader data will place CT screening into units of measure for comparing it with other approved screening strategies, such as breast cancer screening. This analysis' most important contribution will be its impact on decisions by health policy organizations about whether to recommend CT lung cancer screening and by insurers—especially the Centers for Medicare & Medicaid Services—about whether to pay for the screening examination.

In addition, a trial-wide Epidemiology Working Group is asking questions not addressed by the NLST design, such as what is the most appropriate risk group to undergo CT screening. This group, which includes epidemiologists, such as Ilana Gareen, PhD (Brown University, Providence, RI), as well as statistical specialists, will develop risk predictors regarding different age ranges or smoking history, extrapolate NLST data, and then develop a mathematical model to determine the cost effectiveness of these criteria changes.

The working group will consider the optimal frequency and time period for screening from not only a cost, but also a patient outcome, perspective. Once a common NLST data set is developed, the possibilities for researchers to ask questions or make predictions using these data are quite large.

Newsletter: Can policy be built using models alone or are additional trials necessary to provide adequate data?

Aberle: Models are very helpful in providing insights to guide policy. The NLST was designed to address a mortality endpoint, and cannot answer all questions. Nonetheless, it provides a rich and minable data source with which to populate mathematical models to address some outstanding questions. Demonstration projects and registries in which we capture longitudinal data on screening will also be critical to inform policy.

The definition of CT screen positivity is one major unresolved question. The NLST used a binary decision tree to identify screens as either positive or negative based primarily on nodule size. However, an ongoing European randomized trial of lung cancer screening uses a two-step approach based on nodule size in which screen results are positive, negative, or indeterminate. Those individuals with indeterminate screens

undergo follow-up screening at 3 months, the results of which determine whether the screen is positive or negative. This approach has significantly reduced the total number of positive screens and, importantly, the number of false-positive screens. This design better appropriates the perceived risk of lung cancer, influences participant anxiety, and minimizes some of the guesswork of primary care physicians when managing patients. We can learn much from this trial, which will be publishing its mortality endpoint in the next few years.



Denise Aberle, MD

Newsletter: What is the potential for biomarkers and the role of the NLST-ACRIN Biorepository in helping to identify the most appropriate population for screening?

Aberle: A number of potential biomarkers have been identified in preliminary tests that may help with risk prediction and early lung cancer identification: methylation, tumor and germ cell mutations, and proteins in blood and sputum secretions. Biospecimens were acquired longitudinally in the high-risk NLST population for the purpose of validating such biomarkers for risk assessment. In the future, molecular biomarkers analyzed in readily accessible specimens like blood or sputum may help identify the optimal risk groups for screening, or the individuals with positive screens who should undergo biopsy. These biomarkers must be validated first before they can be promoted as primary screening methodologies.

Unlike in prostate cancer, for which one biomarker (prostate-specific antigen [PSA]) is currently used for screening, biomarkers for lung cancer screening will likely involve a panel of multiple individual biomarkers. Although cancers ultimately exploit many of the same mechanisms for initiation and progression, they are dependent upon multiple different key biological “drivers” to trigger and sustain these

continued on page 6

Judy Johnson: Passionate About Advocating

When an opportunity to advocate for ACRIN breast cancer trial participants appeared in 2010, Judy Johnson, MBA, CCRP (St. Louis, MO) thought, “That has my name all over it. Let’s see if I can do it.” Taking risks and following nontraditional paths have been themes throughout her career journey. Johnson, who completed her undergraduate and graduate degrees while working full time, worked as a career and human services consultant within academic and private sector settings. A personal cancer experience, however, opened the door for her to pursue another passion.



Judy Johnson, MBA, CCRP

In 2003, Johnson underwent successful treatment for early-stage breast cancer at Washington University’s Siteman Cancer Center, where she met volunteers from the local St. Louis affiliate of Susan G. Komen for the Cure. She became interested in breast cancer research advocacy and co-founded the Komen St. Louis Research Advocacy Committee, which recruits survivors and other supporters to serve on institutional review boards, and conduct consumer peer reviews for the Department of Defense Congressionally Directed Medical Research Programs and Komen National Headquarters. “The Komen peer review Research Advocacy Committee created a formal structure for the breast cancer research advocacy efforts in St. Louis and continues to serve as a model for other Komen affiliates,” notes Johnson.

Applying a business background to her new passion, Johnson pursued a career change and became a clinical trials coordinator at Siteman Cancer Center. There she oversaw patient enrollment and collaborated in protocol development and activation of trials for lung, esophageal, glioblastoma, and rectal cancers for 5 years. “I preferred not to be assigned to breast cancer trials, initially because it seemed too soon after my treatment, and later because

of my research expertise in other cancers,” explains Johnson. The ACRIN 6668 study of pretreatment and posttreatment PET scans for lung cancer was one of the many National Cancer Institute Cooperative Group trials she coordinated at Siteman.

Upon retiring early, Johnson was encouraged by Siteman colleagues to apply for an available position on the ACRIN Patient Advocacy Committee (PAC) for which Johnson was selected in July 2010. “It seemed like a logical step, given my ACRIN clinical trials and volunteer advocacy experience, and broadened my scope to the national level,” Johnson reflects. “The mentoring I received from PAC members was very helpful in guiding my involvement in ACRIN’s breast cancer research activities.” The first trial she reviewed was ACRIN 6694, a study of preoperative magnetic resonance imaging (MRI) to select patients for breast-conserving therapy. “I provided input regarding the potential problems of accruing participants to a trial in which one randomized group would not have access to an MRI,” she recalls. She has also aided in development of the ACRIN PA 4006 study brochure with a focus on describing the differences between the two research arms.

Providing input when new trial concepts are presented is particularly rewarding for Johnson. “It can be difficult for science-focused investigators to understand how specific trial requirements may discourage patients from participating in a trial. As people touched by cancer, we are better able to consider the patient perspective and evaluate a trial concept’s practicality,” she notes. Johnson hopes that the well-structured ACRIN PAC continues to serve as a model when ACRIN merges with the Eastern Cooperative Oncology Group (ECOG).

“Breast cancer has changed my life in a good way,” reflects Johnson. “I’m making a difference in the world now. Knowing I have input regarding the monies spent and concepts discussed as research is developed for breast cancer means I have a direct impact on helping to save lives.”

CQIE Winds Up Initial Site Qualifications

ACR imaging core laboratory personnel have been on the move this past summer working with physicists, technologists, radiology department administrators and others to complete the Center for Quantitative Imaging Excellence (CQIE) initial qualification process, which began in August 2010. All 58 NCI-designated cancer centers in the continental United States are expected to be qualified by the end of 2011.

The CQIE program’s purpose is to establish a network of sites qualified to participate in upcoming NCI-sponsored clinical trials that include a quantitative imaging component specifically focused on body volumetric CT, brain volumetric MRI, body and brain DCE-MRI, and body and brain PET (or PET/CT). These advanced imaging techniques play a pivotal role in cancer care by providing the ability to detect tumors early, guide therapy, and monitor treatment.

“We were truly impressed by the level of engagement in the CQIE process at so many sites,” comments core lab imaging analyst Jim Gimpel. “The interest in the CQIE specific approaches to quantitative imaging was substantial and we look forward to working with these sites over the next several years.”

With only a few more sites to qualify, the CQIE core lab team has begun planning the process for ongoing qualification. As Gimpel emphasizes, “By establishing a common benchmark to quantitative imaging approaches and educating imaging personnel on the importance of standardization and protocol compliance, we hope to have sites better prepared to participate in imaging multi-center clinical trials.”

For more information about the program, visit www.acrin.org/NCI-CQIE.aspx.

ACRIN Receives Contract to Support Lung Cancer Biomarkers Consortium

ACRIN was notified in April 2011 of a 5-year, \$3.9 million contract from Boston University to carry out an integral component of the Detection of Early lung Cancer Among Military Personnel (DECAMP) consortium which is funded by a grant from the U.S. Department of Defense (DOD). DECAMP is a multidisciplinary, translational research program spearheaded by Avrum Spira, MD, MSc, director of the Translational Bioinformatics Program of the Clinical and Translational Science Institute at Boston University. It is designed to develop and validate molecular biomarkers for the early detection of lung cancer among active military personnel and veterans.

ACRIN brings to the consortium experience managing the National Lung Screening Trial (NLST) and an extensive infrastructure for conducting multicenter clinical trials. ACRIN Network Chair Mitchell Schnall, MD, PhD, Matthew J. Wilson Professor of Radiology at the University of Pennsylvania, will serve as a co-principal investigator with Spira. Other consortium members include leading lung cancer biomarker groups in the academic community, pathology laboratories with longstanding experience supporting biospecimen collection and storage, biostatistics groups highly regarded for data management and analysis, and clinical leaders with lung cancer diagnosis and management specialties at military and veteran hospitals across the country (see Figure 1).

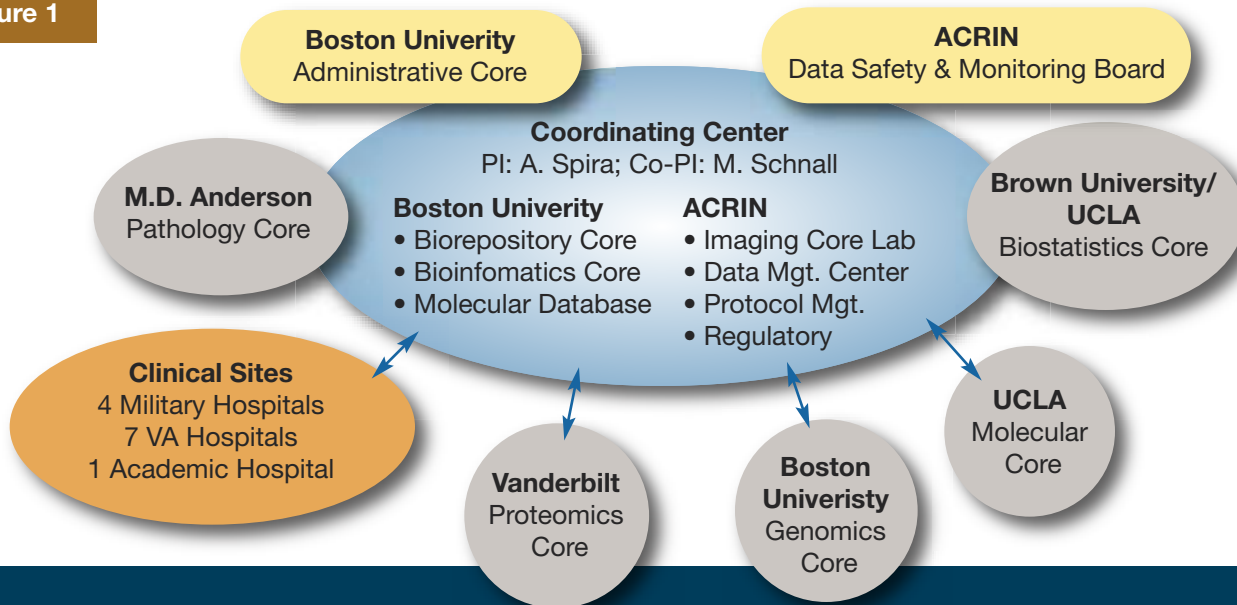
Several significant factors motivated the consortium's development. The mounting evidence of the significantly higher rate of lung cancer among military personnel and veterans—as much as two times higher than in the general population—

caused by smoking and exposure to other carcinogenic substances such as radon, asbestos, fuel exhaust, and other battlefield emissions. Conservative estimates place the cost of lung cancer to the military at \$1 billion a year. Lung cancer-associated mortality has remained essentially unchanged over the last 3 decades, in part because the majority of lung cancers present at an advanced stage. Another major factor is the evidence the NLST results provided that, for current and former smokers, screening with low-dose CT scans decreased lung cancer mortality by 20%. However, 39% of all NLST participants screened with CT had a positive test result, and 96% of those 39% positive screens were found to be false, resulting in a false-positive rate of approximately 37%. Currently, there are no effective biomarkers to identify the subset of smokers most likely to benefit from CT screening.

As a result of these factors, the DECAMP consortium will address two important challenges: 1) evaluate airway and blood-based molecular biomarkers for distinguishing benign vs. malignant diseases among smokers with indeterminate pulmonary nodules found on CT chest, and 2) develop and test noninvasive molecular markers in the airway and blood to identify those smokers at highest risk for developing cancer. In addition, the DECAMP consortium will establish a unique high-quality repository of lung cancer biospecimens, clinical data, and imaging data obtained from patients at 4 military and 7 veteran hospitals and 1 academic hospital that have all agreed to participate in the consortium.

For more information, contact project manager Irene Mahon, RN, MPH (imahon@acr.org).

Figure 1



Medidata Rave Implementation Underway

The Long-Awaited Clinical Data Management System Will Offer Many New Efficiencies

The timely collection of accurate data is at the heart of clinical trials research. Currently, site research personnel participating in National Cancer Institute (NCI)-sponsored trials need to be proficient in using multiple clinical data management systems (CDMS). Fortunately, relief from managing the complexities of multiple systems is in sight. Expected for rollout in 2012, Medidata Rave, a state-of-the-art CDMS, will become available to research sites across the NCI clinical trials network. After coordinating extensive review of available systems, NCI is facilitating the Cooperative Groups' move to Medidata Rave through user licenses and implementation financial support.

Data manager Lindsey Dymond, BS, who is leading the Medidata Rave implementation for ACRIN, is very excited about the new functionality it will offer sites. "The CDMS will have a single sign-on for all NCI clinical trials and, once a site user logs on, all studies in which the site is participating will be available. Having the same interface and functionality for all NCI trials will make the end user's life much easier," explains Dymond.

Ed Kellar, a consultant with over 15 years experience in information technology project management including implementation of electronic data capture systems such as Medidata Rave, is guiding the CDMS implementation for both ACRIN and the Radiation Therapy Oncology Group (RTOG) and emphasizes that Medidata Rave is a very intuitive system, which helps with end-user training and adoption. Kellar comments, "A significant benefit is reduced training time required with a single CDMS, and Medidata Rave offers a comprehensive, self-paced training online." The first time an end user logs into the system, an invitation will be sent to complete the one-time required online training.

"A significant benefit is reduced training time required with a single CDMS, and Medidata Rave offers a comprehensive, self-paced training online."

Dymond also is enthusiastic about the new system's potential for saving data entry time and minimizing errors. "The vast majority of data entry issues will be handled at the point of entry. The data entry fields will have 'edit checks' to help prevent data entry errors. For example, if a value is entered that

is out of acceptable range, an error message will pop up," she elaborates. Once a completed case report form is saved, the end user will receive immediate confirmation of the successful data submission or notification of missing or inconsistent data.

All queries will be resolved electronically, either immediately, or at a later time through a trial-specific task list that itemizes data issues that need to be reviewed, data forms past due, and study notification alerts and messages. Medidata Rave also features an interactive calendar to help keep track of critical imaging time points.

NCI project coordinator for Medidata Rave implementation, Mike Montello, PharmD, MBA, associate branch chief of the NCI's Clinical Investigations Branch, predicts a significant impact from the new system. "It touches every aspect of clinical trials research to include the science, patient safety, and regulatory issues," says Montello. Emphasizing the significant savings of time and effort the system presents for site users, he adds, "Reducing research personnel's administrative burden and increasing the focus on patient care is one of the most significant benefits of Medidata Rave implementation."

While Montello is confident that Medidata Rave will have a huge positive effect for sites participating in NCI's oncology clinical trial research, he acknowledges NCI's acute awareness of the need for a thoughtful deployment to ensure a positive experience for site users from the start.



"Reducing research personnel's administrative burden and increasing the focus on patient care is one of the most significant benefits of Medidata Rave implementation."

The Next Phase for the NLST *(continued from page 2)*

mechanisms. These panels will need to capture the heterogeneity of molecular signatures in lung cancer.

It is critically important that researchers take advantage of the NLST-ACRIN Biorepository. The process for receiving and reviewing applications was developed by a panel of experts in lung cancer. Proposals for use of the specimens are distributed for peer review to various lung cancer specialists in clinical oncology, pathology, molecular biology, epidemiology, radiology, and other disciplines who have agreed to review applications on an ad hoc basis. Five independent groups have submitted proposals to date. The goal is not to use the specimens to discover new biomarkers but to validate those proven promising in preliminary testing.

Newsletter: What other research issues must be addressed before CT screening can be implemented into public policy?

Aberle: There is an extraordinary amount of work to be done in lung cancer screening implementation. We need to establish guidelines for what constitutes a screening center and to

implement screening as a multidisciplinary effort. Standardized image quality, radiation dose monitoring, definitions of screen positivity, diagnostic follow-up procedures, and outcomes collection will be necessary to ensure quality control. Low-dose CT screening will likely require some degree of regulation, as ultimately occurred with mammography for breast cancer screening. The emerging ACRIN-ECOG alliance will provide opportunities for sensitizing the medical oncology community to the need for image quality standards, standardized interpretations, and the development of processes and new technologies to validate improved outcomes in community practice.

Nesting CT screening within broader programs of smoking cessation and risk modification could substantially reduce the burden of lung cancer worldwide. If we want to maximize the risk-to-benefit ratio with low-dose CT screening, it is critical to systematically address these various post-NLST issues while we have the funds and wherewithal to do so.

CT Dose Reduction Project

Four Pennsylvania-based health care networks will participate in a research project investigating the radiation dose variances of CT scans performed throughout the networks and whether specific interventions can reduce radiation exposure.

Medical diagnostic procedures are now the major source of radiation exposure to the US population, with computed tomography (CT) scans being the largest contributor. CT radiation exposure has been headline news during the past several years, and startling reports of burns, hair loss, and other CT-scan related complications have raised patients' concern. Many studies have documented a wide range of doses for the same types of scans performed at different centers or on different scanners.

A research project funded by the Pennsylvania Department of Health and led by Harold Litt, MD, PhD (University of Pennsylvania, Philadelphia, PA) will collect radiation dose information from CT scanners used throughout four health care networks in Pennsylvania. The project research team expects to observe significant variation in the doses received by patients for the same types of CT studies—the majority related to factors under operator control.

CT radiation dose information will be collected from CT scanners at all participating network sites for 6 months. Each network and the associated sites will then be randomized to one of several dose-reduction strategies, and interventions will be implemented accordingly. Following the intervention, the CT dose rate data will be collected for another year to determine how effective the intervention was in lowering dose. The investigators predict, by the end of the 6-month intervention period, an estimated 25% decrease in overall radiation dose and a 60% reduction in dose resulting from the intervention with the greatest effect.

After the intervention period, data will continue to be collected for a 1-year follow-up period. During the follow-up period, network sites will be randomized to either receive or not receive monthly dose reports. Investigators hypothesize that sites that receive continuing feedback will maintain greater net dose reductions than those that do not receive continuing feedback.

For more information, contact project manager Irene Mahon (imahon@acr.org).

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