

# ACRIN NEWSLETTER

Advancing Clinical Care Through Imaging Research

August 2010

## From the Network Chair NCI Commissioned Reports Call for Change



Mitchell Schnall, MD, PhD, ACRIN Network Chair

*Two important National Cancer Center- (NCI) sponsored reports were released this past spring that will have significant influence on the operation of its Clinical Trial Cooperative Groups. ACRIN's network chair, Mitchell Schnall, MD, PhD, is a member of the Operational Efficiency Working Group (OEWG) and shares his perspective on the OEWG and the Institute of Medicine (IOM) reports.*

### Operational Efficiency Working Group (OEWG) Report

I was asked to join the OEWG because of my role as ACRIN network chair and also because ACRIN has consistently shown an interest in the issues of operational efficiency. The charge of OEWG was to develop strategies for significantly reducing the time it typically takes to activate NCI-sponsored clinical trials. I joined a broad base of stakeholders, including representatives of other cooperative groups, cancer centers, NCI entities, the Food and Drug Administration (FDA), and the Centers for Medicare & Medicaid Services (CMS), as well as biotechnology companies, and patient advocacy organizations, in collaborating on this first phase of the OEWG mission.

The full report, containing 14 initiatives and associated implementation plans, was made available this past spring. The second phase—addressing timely completion of activated studies—will be reported on by OEWG at a future time.

Front and center throughout the consensus-building process was an awareness of the important balance between the need for rigorous debate and interplay to advance science and the need to expeditiously move forward and make progress. Much discussion focused on how to compress the timeline for trial activation without sacrificing critical science and embarking on trials with little potential benefit. After acknowledging the variations in challenges presented by the different types of trials, the OEWG set a goal of reducing the time to trial activation by at least 50% (for the full report, visit <http://ccct.cancer.gov/files/OEWG-Report.pdf>).

Integral to the commitment to set aggressive timelines was a two-pronged underlying philosophy that (1) a scientifically rigorous and important trial should garner the time and energy of key stakeholders necessary to move it forward; the fact that such support is not forthcoming and stakeholders are “voting with their feet” suggests that a trial is lacking in importance, and (2) a trial concept that is not working serves as a drag on the system and should be terminated early in the process. With this in mind, the OEWG set a target of 300 days for initial activation of cooperative group phase 3 trials, also determining that such protocol concepts not fully activated with complete issue resolution within 24 months will be terminated. These timelines for activation and review are aggressive but achievable, and there was broad support for enforcing them without exceptions.

(continued on page 5)

### UPENN is First CQIE Site

The Abramson Cancer Center of the University of Pennsylvania is the first NCI-designated cancer center to receive the “Center of Quantitative Imaging Excellence” (CQIE) attribute. CQIE was developed to establish a resource of ‘trial ready’ sites within the NCI Cancer Centers Program that are capable of conducting clinical trials in which there is an integral molecular and functional advanced imaging endpoint.

CQIE participation is open only to the 58 NCI-designated Cancer Centers and, through an NCI contract award, ACRIN developed and is implementing a process for qualifying the centers to perform the advanced quantitative imaging procedures. For more, visit [www.acrin.org/NCI-CQIE.aspx](http://www.acrin.org/NCI-CQIE.aspx).

### ACRIN Seeks Sites for Cardiovascular Trial

The Agency for Healthcare Research and Quality (AHRQ) awarded ACRIN a grant to conduct the ACRIN 4701 trial: Randomized Evaluation of Patients with Stable Angina Comparing Utilization of Noninvasive Examinations (RESCUE). The trial will compare outcomes of participants with symptoms of stable angina undergoing cardiac CT angiography as an initial method of coronary artery disease diagnosis (Group A) to single photon emission tomography myocardial perfusion imaging (Group B) as a guide to optimal medical therapy.

Interested? Submit a survey at [www.surveymonkey.com/s/8ND299D](http://www.surveymonkey.com/s/8ND299D) or contact ACRIN 4701 project manager Cynthia Olson ([colson@acr-ars.org](mailto:colson@acr-ars.org)).

**ACRIN**  
AMERICAN COLLEGE OF  
RADIOLOGY  
IMAGING NETWORK

## Introducing Ann Kolker

### Increasing Resources and Survival for Patients With Gynecologic Cancers



*Ann Kolker, ACRIN Gynecologic Patient Advocate*

Ann Kolker began a new chapter in a career focused extensively on women’s health issues when she became a patient advocate for ACRIN gynecologic cancer clinical trials in November 2009. Her early experience included monitoring women’s health and reproductive rights issues in Congress and federal agencies, and leading women’s health coalitions, for the National Women’s Law Center.

She credits her astute obstetrician-gynecologist with taking her family breast cancer history into account and immediately referring her for testing of an ovarian cyst found 14 years ago. When a computed tomography (CT) scan, transvaginal ultrasound (TVU), and CA125 tumor marker blood test were inconclusive, Kolker underwent surgery, was diagnosed with early-stage ovarian cancer,

and completed 6 months of chemotherapy near her Washington, DC home. She has since undergone surgery and chemotherapy for two recurrences and is now monitored with periodic scans and CA125 testing.

Realizing that “the low incidence of ovarian cancer made it more difficult for patients to connect with each other,” in 1997 she co-founded and directed the Ovarian Cancer National Alliance (OCNA). The early years of this renowned patient-led organization were a time of planting and growing its activities, including an annual conference for patients and family, comprehensive education of medical professionals, and support of cutting-edge treatment research. Confident that OCNA was self-sustaining, Kolker stepped down from her leadership role in 2004 to spend time with her first grandchild. She continued to consult on selected projects, including an Ovarian Cancer Research Funding Directory for the Gynecologic Cancer Foundation.

The opportunity to serve as a patient advocate for ACRIN clinical trials appealed to Kolker on many levels. “We knew from the get-go with OCNA that the use of radiology imaging was important in the diagnosis of and treatment monitoring for ovarian cancer.” Kolker has long advocated for radiation oncologists reading CT and TVU scans to provide a more precise assessment of whether a gynecologic mass is malignant and surgery is justified. “With the exception of cervical cancer,” she notes, “survival rates for gynecologic cancer have been flat for many years, and there is a desperate need for the type of cross-discipline collaboration that occurs in ACRIN trials to advance treatment modalities for these diseases.”

Kolker’s experience of becoming an ACRIN patient advocate has been positive—from the clear and organized Web site instructions to the assignment of a more experienced mentor, “which provided a road map of the various ACRIN subdivisions and lead players.” Her first task was to participate in a Patient Advocacy Committee conference call about continued improvements to the patient section of the ACRIN Web site. She later participated in a review of an ACRIN/Gynecologic Oncology Group (GOG) ovarian cancer protocol, to which she brought tools learned from institutional review board (IRB) assessments of government programs. Paying close attention to the informed consent section, Kolker understands the need to “strike a balance between a form that is clear but not dumbed down, and that clearly explains the risks and benefits of trial participation without appearing formulaic.”

Kolker is struck by the increased scientific understanding, diagnostic tools, treatment options, and patient materials available for other cancers, particularly breast cancer. “It would be nice to see that same kind of evolution in ovarian cancer,” she muses. “I am excited about this new opportunity to help the patient advocacy community move forward, identify new audiences, and be on the ground floor of developing new protocols that provide new diagnosis and monitoring tools for gynecologic cancers.”

## AccrualNet Online Resource

The National Cancer Institute (NCI) has launched AccrualNet, an online resource designed for practicing professionals to support clinical trial accrual needs.

AccrualNet includes:

- Linkable access to existing tools and materials
- A searchable, annotated list of published journal articles on clinical trial recruitment
- A space to ask questions, post tips, share experiences, insight, materials and strategies

To learn more about AccrualNet, visit <http://accrualnet.cancer.gov>.

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## Improving Oncologic Image Interpretation: A project of the ACRIN Biomedical Imaging Informatics Committee and the ACRIN MRI/CT Core Laboratory

### Overview

A critical keystone in biomedicine, radiologic images can show physical abnormalities, disease progression, and clinical laboratory test results. Of primary importance is an interpretation of whether the anatomic structures appear abnormal, which makes up the visual image's semantic content.

Current clinical practice involves a radiologist reading images to identify lesions and describe their location and features. Comparing images from a current study to those from prior studies allows the reader to assess any overall change in the size or number of lesions observed, which helps determine whether a patient's disease is progressing.

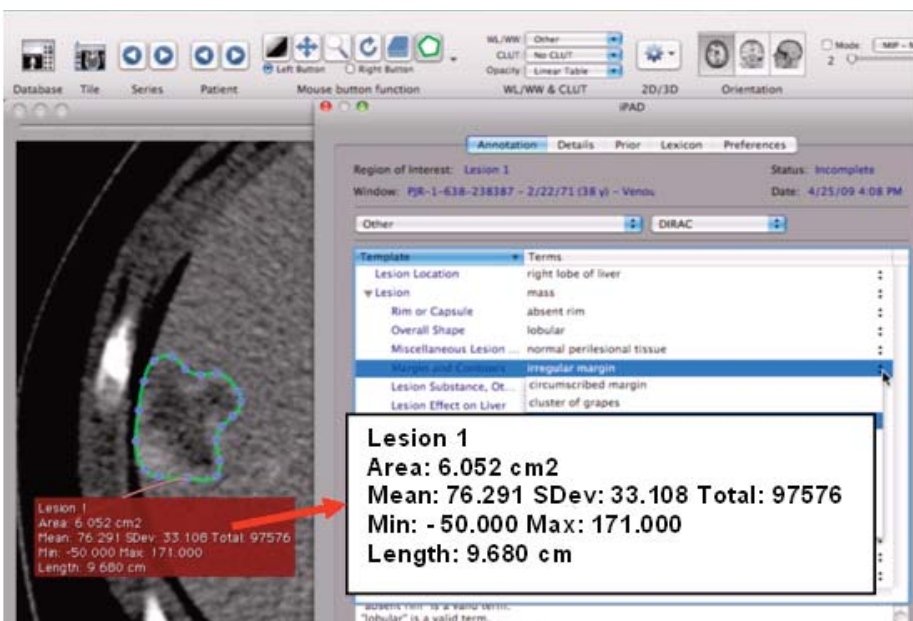
Because this semantic information is usually recorded textually or verbally, the oncologist must read the report or

listen to the recording in order to recover the reader's described observations and interpret their meaning. This often necessitates verifying or reevaluating the original image. Moreover, because the semantic information associated with the images is rarely noted within the image itself, other image reviewers must consult the separately stored text reports. This workflow hinders time efficiency and introduces great potential for error or miscommunication.

One solution for improving the current image interpretation process is to allow the meaningful information contained within the images to be organized, stored, and made accessible by computer. By linking this information directly to the image, upon subsequent image review, a radiologist or other physician could also review the essential semantic content.

In addition, storing this linked electronic content in a structured and quantitative manner would allow users to more efficiently search and analyze the important information stored within radiologic images. Instead of being recorded in a large block of text within a text report, image descriptions would be stored in categories, and description types would be standardized across images. This would make it possible to perform image-based analysis (eg, data mining) across large collections of images. Retrieving content-based images (eg, viewing the diagnosis for all lesions with a certain shape) would become a simple proposition. A researcher, for example, could use this technology to find the probabilities of specific diagnoses associated with certain image features, or to compute the average lesion size over a large image repository—tasks that would be intractable without machine-searchable semantic content.

### Introducing iPad: An Annotated Image Mark Up (AIM) Tool



**Figure A** (above) shows the graphical interface of iPad. In this image, the reader has circumscribed a lesion in an image of the liver (left) and is using the reporting template to completely describe the visual features of that lesion (right). Each imaging observation, including the lesion name, is automatically prompted by the iPad tool.

The image Physician Annotation Device (iPad) is an open-source tool that serves as a bridge linking the semantic content of a radiologic image with the image itself, enabling physicians to annotate images such that descriptions are recorded into the computer in a machine-accessible way. iPad has the following important functions and components:

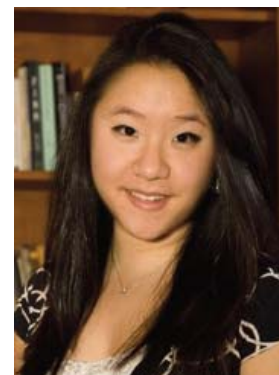
- The ability to split valuable information into meaningful object-oriented structures (categories) (eg, patients, studies, image series, annotations) and to use these structures to dynamically interact with both the images and annotations (ie, providing the link between image annotations and the image file itself)
- A guided, user-friendly interface that allows readers to describe the images while viewing the markup of the images in real time

(continued on page 4)

## Katie Hsieh and Brett Lullo Provide Informatics Support through the Princeton Internships in Civic Service Program

For the past five years, Princeton University interns have provided support for a variety of ACRIN projects. Brett Lullo and Katie Hsieh provide an overview of their work with project mentor Daniel Rubin, MD, MS, chair of the ACRIN Biomedical Imaging Informatics Committee.

A significant project for Princeton senior Katie Hsieh involved the creation of a tool that recognizes variability in the labeling of identified lesions by readers. Users reading the same set of radiologic images might choose to annotate different lesions or to annotate the same lesions differently. In addition, the same reader may describe images across studies within the same case such that similarly identified lesions do not correspond to one another. By alerting the user to such inconsistencies and eliminating user disagreement, this tool paves the way for the automation of the tracking and evaluation of lesion changes over time, which is integral to assessing response to treatment. The goal is to include this recognition feature in iPAD in order to improve the accuracy of image analysis.



*ACRIN Summer Intern  
Katie Hsieh, Graduate  
Princeton University*



*ACRIN Summer Intern  
Brett Lullo, Senior  
Princeton University*

Hsieh also initiated a pilot study comparing the reading of images with and without the iPAD tool in 20 different radiologic cases. This study analyzes the differential in both the change in lesion size over time and the length of time required to do the readings. Radiologists currently participating in this study include Daniel Rubin MD, MS and Grace Tye, PhD (Stanford University), and Mark Rosen, MD, PhD (University of Pennsylvania). Proctoring the reading sessions with the first two physicians, Hsieh instructed readers in the use of iPAD, provided support for technical or other iPAD-related issues, and timed the individual image readings. The readings for this study are nearly complete, and analysis of the data will begin shortly.

Brett Lullo focused his time at ACRIN headquarters further developing the iPAD tool, building upon a version developed by last year's Princeton intern Chris Baldassano. Receiving direct feedback from Rosen, Lullo programmed enhancements to make the tool more intuitive for radiologists to use. After several iterations for adding additional functionality, including input from Ruben, Lullo helped to develop the pilot study described above and provided training on the tool's use. Acting as a facilitator early on in the study, he also incorporated other functionality so that the iPAD tool could be used for several studies at the University of Pennsylvania. A future goal is to increase the popularity and use of iPAD in the radiology community. Fortunately, Lullo plans to continue working on the project for his senior thesis at Princeton with the aim of creating a completely Web-based version of the iPAD tool which will allow for easy tool access.

### AIM Tool...*(continued from page 3)*

(The tool itself is a plugin to OsiriX, an open-source imaging platform mimicking the commercial Picture Archiving and Communication System [PACS] workstations used in most medical facilities, but it allows for more flexible functionality)

- The ability to store annotations in a standard file format that can be accessed and integrated across different hospital systems and other technologies that are used to store semantic information. iPAD makes it possible to standardize the terminology and syntax used to describe radiologic images. The current practice of radiologists annotating the same images differently makes comparing

annotations by different readers difficult and limits the degree to which health professionals can communicate effectively with one another. Because iPAD stores data in a quantitative manner, it automatically provides a standard annotation vocabulary across the image repository and between readers (Figure A on page 3).

This tool could enable researchers and physicians to exploit images on a very large scale, by gathering the significance of image content for a large image repository and analyzing the data quantitatively. iPAD makes it possible to reduce the time involved in annotating medical images while increasing accuracy and reducing opportunities for human error.

iPAD was designed to be adjusted according to the needs of the users and professional community. Examples include a more sophisticated system that provides immediate feedback based on a user's annotations (sometimes called "annotation content check") or eventually incorporates voice recognition, rendering manual data input unnecessary.

The goal of iPAD is to achieve quantitative lesion measurement and tracking, which is the core of evaluating cancer treatment response. Although this may include clinical or research-oriented projects, its dominant use will most likely be in clinical trials.

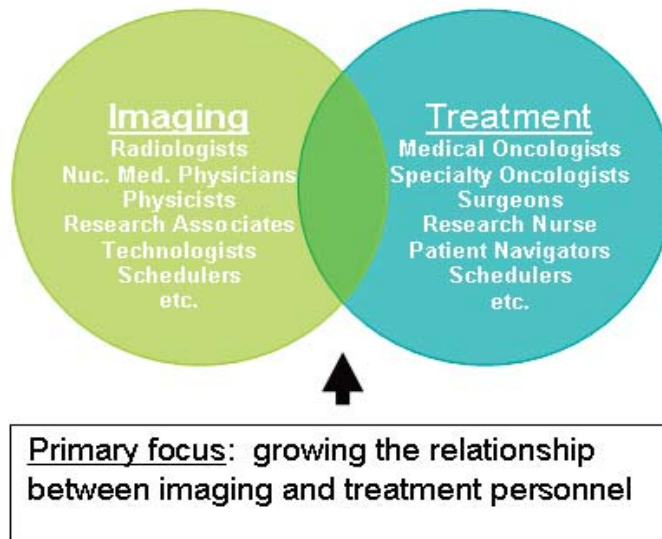
## Network Chair...(continued from page 1)

The report also recommends a fundamental change in how the NCI Steering Committees and Cancer Therapy Evaluation Program (CTEP) review research concepts. The current process of lengthy cycles of written review and response is often fraught with communication problems and delay tactics. Something I personally championed is the recommendation to break this cycle of written communication and set up calls between

the review committee and protocol team to discuss the critical issues raised. By the end of the conversation, it should be determined if the protocol is going forward or not. Providing a rapid response to the groups about the merits of the core scientific idea should go a long way toward streamlining the existing process.

Many of the OEWG recommendations reflect procedures already in place within ACRIN, including the occasional use of even more stringent timelines. Modest new NCI funding is available for hiring program managers, medicalwriters and other staff to support implementation of OEWG initiatives. However, ACRIN's greatest barrier relates to what I call the "Venn Diagram site recruitment problem" (see diagram) rather than a lack of personnel.

The complex imaging requirements involved in many ACRIN trials necessitate a cohesive relationship between imaging personnel and personnel involved with providing patient treatment. Therefore, ACRIN's focus will be to put resources in place that help grow this relationship by ensuring that all personnel supporting a trial understand their unique roles and are



*To effectively "grow the relationship" all personnel involved with supporting a trial need to understand their unique role and be committed to the study.*

committed to carrying them out. Such intra-site collaboration can foster the cultural change necessary for sites to effectively accrue study participants.

### Institute of Medicine (IOM) Report

The IOM, also initiated by NCI to assess the Cooperative Group Program and offer strategies for improvement, recently released its findings (A National Cancer Clinical Trials System for the 21<sup>st</sup> Century: Reinvigorating the NCI Cooperative Group Program). The IOM report calls for improving the speed and efficiency of the design, launch, and conduct of clinical trials. Specifically, the report recommends consolidating some administrative functions and processes, streamlining government oversight, and enhancing collaboration among stakeholders.

The report also highlights the need to make optimal use of scientific innovations, such as mandating standardized storage and assessment of biospecimens collected from patients in trials involving the use of biomarkers. A shift in NCI focus from oversight to facilitation of Cooperative Group trials is

encouraged to support highly effective protocol concepts. Assessing whether investigators and sites are adequately resourced, the report recommends increasing incentives for broader physician participation and strategically enhancing funding. As well, public and private health insurers should establish consistent payment policies to cover patient care costs in NCI clinical trials. In this way, expanded participation of both patients and physicians can be fostered. The IOM report offers broad concepts for improvement rather than specific actions; however, the recommendations involve every element of the cancer clinical trials system and are presented with a certain sense of urgency.

What specific changes are put in place will depend upon the focus and direction of the new NCI director Harold Varmus, MD, and his leadership team.

### ACRIN Publications Process and Policy Revisions

Revisions have been made to the ACRIN Publications Policy and process. A few key new and existing policies include:

- Writing teams are required to notify ACRIN headquarters of any external manuscript reviews by collaborators, and the outcome of the review
- The newly created Manuscript Submission Form is to be completed and submitted by the manuscript's lead author
- Lead authors are responsible for copying the writing team on critical correspondences, including reviewer comments, submissions, acceptance status, galley reviews and journal article print date/citation

The revised policy and forms are available on the ACRIN Web site at [www.acrin.org/PublicationsPolicy.aspx](http://www.acrin.org/PublicationsPolicy.aspx).

## ACRIN Conducts Site Recruitment Survey

Earlier this year, the ACRIN Recruitment Subcommittee distributed a survey to research personnel who supported ACRIN studies that have since closed to accrual. The goal of this project was to assess major accrual barriers and determine how ACRIN can assist in supporting sites with trial activation and participant enrollment.

**“ The IRB at my institution seems to review each study as something that is originating at my own institution, rather than being a site in a national, multicenter trial.”**

*Survey respondent about general IRB-related barriers*

Responses received from 133 survey recipients included 45 (34%) trial and/or site principal investigators and 81 (61%) research associates or nurses. The top studies represented are shown in Table 1. Insight into major accrual barriers are reported below.

- The most common reason eligible patients declined to participate in a trial:
  - Study procedures were too demanding
  - Apprehensive about the study procedures such as additional needle sticks or claustrophobia
  - Time constraints
- Most significant facility-specific barriers (Table 2):
  - Referring/treating physicians had little interest in supporting the trial
  - Limited access to other department’s scheduling for potential participants
  - Communication between treating/referring physician and imaging staff is difficult
- IRB issues affecting accrual:
  - Internal processes were complex and required extended time
  - The language required to be included in the participant consent

Trial	Response Count	Response Percent
ACRIN 6654 (NLST)	40	31%
ACRIN 6668 (PET for survival prediction)	16	12%
ACRIN 6666 (US + mammo vs mammo alone)	13	10%
ACRIN 6652 (DMIST)	11	8%
ACRIN 6660 (Pediatric whole body MRI)	11	8%
<b>Total Response Count: 133</b>	<b>91</b>	<b>68%</b>

Barrier	Response Count	Response Percent	Total Response Count
Referring/Treating physicians have minimal interest in supporting trial	36	36%	101
Access to other departmental scheduling for potential participant identification is limited	34	33%	103
Communication between treating/referring physician and imaging staff is difficult	29	28%	102
Site PI has limited time to focus on study-related activities	28	27%	102
Access is difficult due to parking and/or location of imaging services	25	25%	102

form negatively affects the patients’ willingness to participate

Additionally, survey respondents reported that the departmental leadership was supportive of ACRIN trials and time constraints on the part of the site principal investigator and research associate did not negatively impact accrual.

**“ The major barrier for our institution [was that we] had so few patients being treated according to the required protocol.”**

*Survey respondent about recruitment barriers*

The monthly site calls and study participant brochures provided by ACRIN were cited as the most helpful accrual tools. In response to the question about whether study participants were compensated for time and travel or offered amenities such as free parking, the majority of respondents reported these would not be allowed by the site’s institutional review board. The most common amenity given to patients was free or valet parking.

This survey will be reviewed by the Recruitment Subcommittee to help formulate strategies that can be offered to sites to increase their accrual goals. Our aim is to assist sites with achieving their maximum accrual by offering a variety of tools and strategies.

Thank you to all who took the time to responded to the survey.