

NWX-NCI

**Moderator: Shannon Silkensen
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1:00 pm CT**

Coordinator: Welcome and thank you for standing by. During today's conference, all lines will remain in listen only mode. This conference is being recorded. If you have any objections, you may disconnect at this time. I would like to turn the meeting over to Dr. Shannon Silkensen. You may now begin.

Shannon Silkensen: Thanks, Julie. Hello, I'm Shannon Silkensen, a Program Director with the NCI Office of Cancer Centers. Welcome to this webinar entitled "Bringing Quantitative Imaging to the Cancer Center's Clinical Trials," the NCI Quantitative Imaging Network or QIN. To ensure uninterrupted streaming of the online portion of this presentation, please consider closing all additional programs and windows on your desktop.

As a reminder, this webinar is being recorded and will be archived on the Office of Cancer Center's website. So if you have any objections, please disconnect at this time. One last piece of housekeeping, all participants are in a listen only mode so you may submit questions in the Q&A box on the right hand side of your screen at any time during today's presentation. And we will

try to answer them either during the webinar or later offline if they are of a more specific nature.

And now I would like to introduce today's speakers, Bob Nordstrom and David Mankoff. Bob is a program director in the Cancer Imaging Program within the NCI's division of cancer diagnosis and treatment. He will provide you with an overview of the NCI's quantitative imaging program to tell you about open funding announcements in this area.

David is a professor of Radiology at the University of Washington in Seattle. He will share with you how he used the QIN to bring imaging modalities into clinical trials. Remember, our goal here is to disseminate useful information so please ask questions and engage your speakers in conversations about the QIN. We reserved about 15 minutes at the end of each presentation for these questions. And now Bob will begin his presentation titled, "The Quantitative Imaging Network - Building Resources for NCI Cancer Centers." Thank you.

Bob Nordstrom: Thank you, Shannon. I'd like to welcome you all to this web seminar today. It's my pleasure to be a part of it. I've been invited to discuss a relatively new program we have underway dealing with the uses of quantitative imaging to predict and measure response to cancer tumors to therapy. We call the program "The Quantitative Imaging Network" or QIN. You know it's not my intent to drill down into the science of the QIN program today.

We have Dr. David Mankoff from the University of Washington as an additional speaker to this web seminar. He is a principle investigator on QIN and he'll discuss his prospectives on the network and approaches to quantitative images being taken at the University of Washington. I'll discuss the overall missions and goals of the program, the organization of the network and I'll try to present its value as a resource to the Cancer Centers.

To start, just let me make a brief word about myself and why I'm the one giving the seminar today. I'm a member of the Cancer Imaging Program as Shannon said in the Division of Cancer Treatment and Diagnosis. As the lead Program Director of the Quantitative Imaging Network, I'm responsible for monitoring the progress made by each of the teams on the program and for bringing new applications that scored well in peer review to the attention of the scientific program leaders committee here at NCI for their consideration.

My background includes algorithm development and validation of methods and biomedical instrument design through clinical trials. You know, Hillary Clinton said it takes a village to raise a child. Well, on that note, it takes a cast of characters to make a successful QIN program. These individuals have provided much needed support for the QIN. The Cancer Imaging Program is the home to the Quantitative Imaging Network. It's divided into four branches.

QIN is a part of the Imaging Technology Development Branch headed by Dr. Larry Clarke. But participation by the other branches and also from programs within our division of NCI, most notably the Radiation Research Program, is extensive.

Translational research, that is all aspects of taking an idea from the concept stage to standard of care in the clinical environment, is the theme that permeates several programs supported by the Cancer Imaging Program.

This slide shows a stylized pipeline with the concept stage at the far left and standard of care at the right. In between there are a number of milestones that can be identified. We recognize that there may be others and that the orders of these regions identified along the pipeline can vary depending on the nature of

the project. But for the most part, this is a reasonable first approximation that will serve as well to map out the challenges and hurdles present along the transactional research path.

Using this translational scale, we can chart the locations of several different programs within CIP as they relate to translational research. Traditional R01 research, for example falls near the concept and feasibility end of the spectrum. These programs can extend into the prototyping of hardware or software and might even extend into the feasibility testing with some pilot clinical studies. Another program familiar to the Cancer Centers is the ACRIN Program where imaging clinical trials are explored. This program is located near the other end of the pipeline spectrum

The Cancer Imaging Program is attempting to extend basic R01 research further down the translational pipeline by requiring academic researchers to team with industrial partners in a program we call “Academic Industrial Partnerships.” The goal of this R01 program is to create an environment for dialogue between academic and industrial researchers that will extend imaging research efforts into areas such as standardization of methods and validation procedures needed before controlled clinical trials can take place.

The NCI Experimental Therapeutics or NExT program of the Division of Cancer - Treatment & Diagnosis consolidates NCI’s anti-cancer drug discovery and development resources. And can support discovery and development from initial concept through Phase II clinical trial evaluation. This is not a grant mechanism. Instead, the NCI allocates various contract and grant resources toward the implementation of projects selected from submitted applications. NCI partners with successful applicants to facilitate progress in the development of anti-cancer drugs.

The Quantitative Imaging Network, that's our topic for today, occupies a region on the translational research spectrum from feasibility testing through clinical trials as shown here. So, the discussion today will be on imaging and particular on quantitative imaging. Medical imaging was forever changed in the late 19th century when Wilhelm Roentgen discovered x-rays while studying cathode rays in his laboratory.

This now famous photograph of his wife's hand caused her to say, "I have seen my death." The first Nobel Prize in physics was awarded to Rankin in 1901 for his work on x-rays. I dare say this is very different from what the Nobel Prize was awarded for today. From that time on, there's been an explosion in imaging technology. And imaging has moved to a finer and finer resolution scale aiming for the nano-environment and below. As this has taken place, the cost for imaging has increased dramatically.

It's important to pause in this frantic race for finer and finer resolution to remember that imaging can play important roles in the clinical environment without new and costly technology. One area in particular where this is true is the use of imaging as a quantitative marker for prediction or measurement of response to therapies. The latest and most expensive imaging equipment is not needed. What is needed as we will see later is a thorough understanding of the operating characteristics of the equipment and how they are transportable to other devices.

So what exactly do we mean by quantitative imaging? This is a paraphrase of the definition provided by the Quantitative Imaging Biomarker Alliance or QIBA of the RSNA. As you can see, the definition covers the acquisition and manipulation of numerically measurable features from medical images. This excludes observer base decisions such as, "well the tumor appears to be

denser than before” or “the size of the tumor is somewhat smaller than the baseline image.”

Quantitative imaging is needed for the measurement and prediction of therapy response. And quantitative imaging is also a necessary advancement if imaging is to become an integral part of the greater picture of cancer research in which genomics and proteomics play key roles. So, we get ourselves set on a quest to extract numerical information from the medical images. That doesn't seem too difficult. Here are two images of the same lung cancer patient taken 21 days apart during treatment.

These images were taken at the Memorial Sloan-Kettering Cancer Center a few years ago. A particular lung nodule has been identified in both images. Using the segmentation scheme, we can highlight the tumor in the first image. Similarly, we can highlight the tumor in the second image. In both highlighted images, we can extract quantitative information regarding the tumor size by drawing lines along the longest axis of the tumor regions.

Similarly, we can create lines at 90 degrees from those lines in regions where the tumor is broad. Using the information from the long axis only, this method is known as “RECIST” or Responsive Evaluation Criteria in Solid Tumors. A World Health Organization method uses information from both axes. Measuring the length of the lines in each image gives us a quantitative measure. That is, a numerical measure of the tumor size. Looking at the results, we can see that there is a 3% decrease in the size of the tumor after the 21 days.

While this exercise does lead to a quantitative result, it raises a number of very important questions. First and foremost is the change that was measured a true indication of the therapy response? The imaging scientist may ask the

following: What are the sources of variance in the device? What would an additional image show? Would the 3% decrease in size be confirmed? Or would a different result occur?

The oncologist would certainly ask: Should the therapy be continued? Or should the current therapy be discontinued in favor of a different approach? A host of underlying questions are important to ask. Are we measuring the right quantitative parameter? What about other biomarkers? Hypoxia? Angiogenesis? Tissue elasticity? Metabolic function of the tumor region? These are all legitimate biomarkers that could indicate tumor response and can be measured quantitatively.

And what about the possibility of combining measurements of several different biomarkers? This might lead to a synergistic determination of therapy response. Raising these questions unfortunately raises questions of a more subtle nature. If the sources of error are known, how can they be reduced? And once we understand the physical characteristics of the errors produced by one imaging platform, how can that knowledge be translated to other platforms or imaging modalities?

Once the images are recorded, what analysis schemes work best? What do we even mean by best? And ultimately if the software tools are created and validated using one form of imaging modality or cancer problem, is it possible to use the same tool on images collected using a different modality or cancer challenge? These are but a few questions that come to mind from even a cursory look at the quantitative imaging problem.

To answer the end-user's other questions, the NCI created a program announcement that was given the number PAR-08-225. Its official title is "Quantitative Imaging for Evaluation of Response to Cancer Therapies." We

prefer to call it “the Quantitative Imaging Network” or simply QIN. The announcement has recently been reissued as PAR-11-150. It calls for multi-disciplinary teams to attack a problem of the team’s choice in the area of quantitative imaging of cancer.

Using the U01 mechanism rather than the traditional R01 mechanism, the program is actually a cooperative agreement rather than a grant. This permits a certain amount of program involvement with the administration of the program and creates a network of research teams each working on different problems, but working in cooperation with each other.

The program has a mission statement created by the investigators themselves. It was drafted by the program investigators at their first face-to-face meeting. It specifically focuses on quantitative imaging for clinical decision making in oncology, and speaks of tools to tailor cancer treatment in individual patients and to predict or monitor response to therapy. To do everything requested in the program announcement, it was decided that networking the success for the successful awardees was the best approach.

First of all, cancer is a complex and adaptive problem. Not only are there a number of tumor sites, but there are number of different tumor types and conditions such as heterogeneity as well. In addition, to imaging, there are a number of different imaging modalities that can be used to visualize the tumor and its surroundings. While each team is approaching a different problem, it’s recognized that there are a number of similar challenges that confront all of the teams: issues of software validation and standardization methods for tools; open science approaches and data sharing are all common to all the teams.

Therefore, networking can create consensus building in these areas. In addition, multi-disciplinary teams are needed to cover the full range of

challenges and end-user needs for quantitative imaging. Oncologists represent the ultimate end-user of software tools designed and validated for clinical decision making. So their input in the research is essential. At the same time, radiologists, imaging scientists, bioinformatics specialists and other disciplines are needed for success.

By networking the teams funded under the program, team/team interactions can occur, creating links at the technical level among the various Cancer Centers. As will be seen in a few minutes, the organization of the QIN facilitates this cross-network interaction through specific working groups in specialty areas.

The QIN is built on a history of past programs with strong track records for success. The IRAT program, “Image Response Assessment Teams” is one that many Cancer Centers are familiar with. Several years ago, we funded eight groups with the mission to promote imaging in cancer center clinical trials. Another successful program was RIDER, “Reference Imaging Database to Evaluate Response.” Long image data and images from other organ sites had been posted in the database.

A number of informatics issues, including open access and web-accessible database development were addressed. The images stored on the RIDER database are used to support algorithm development for software tools focused on large tumor studies and response to therapy. The Cancer Centers are familiar with the program we call “Centers for Quantitative Imaging Excellence,” or the CQIE, where standards are being set for specific imaging modalities.

And prequalification of cancer center imaging in PET CT and diffusion image MRI across all manufacturers is being completed making these centers trial

ready. ACRIN is doing the qualifications on an annual basis. The QIN is also focused on issues as standardization of imaging. While the COIE focuses on standardization as a method for prequalification, QIN is working on the technical issues of standards to reduce variance and bias in imaging across platforms in order to improve imaging contributions in future clinical trials.

Looking specifically at the QIN program now, it was designed to add value to the Cancer Centers. By linking the imaging research activities of academic institutes associated with the Cancer Centers, it's anticipated that the network can become a common imaging resource for future clinical trials involving imaging. Also, results being generated by the QIN have potential for reducing costs for imaging trials. We'll look at this in more detail in just a few minutes.

Another area of QIN is the creation of imaging standards to reduce error across platforms. These standards can become important in creating confidence in imaging result, enabling imaging to be linked to other cancer activities such as genomic research. As the QIN grows, it has the potential to make a positive influence on the incorporation of imaging within and across Cancer Centers. In addition to these values, participation in the Quantitative Imaging Network offering extensive collaboration with other imaging scientists and should position researchers to be more competitive in the NIH/R01 funding for future grants.

A brief look at the organization of the QIN network is now warranted. The structure is set up to accept any number of technical teams. Applications are accepted on the same schedule as R01 grant applications. That is, receipt dates are October 5, February 5 and June 5. Applications are reviewed in the special study section convened by NCI, not the Center for Scientific Review. Governance of the network is the responsibility of the steering committee

consisting of the principle investigator from each team and selected NCI program staff.

Monthly teleconference meetings and an annual face-to-face meeting are scheduled. One of the important organization features of the QIN is its working groups. Rather than have the working groups organized within each technical team, the network has created working groups that transcend the teams and are separate from them. Each team assigns delegates to each of the five working groups. A chairperson for the working groups sets the agenda and holds monthly teleconference meetings of the group.

Each working group is autonomous from the technical teams and has created its own mission statement consistent of course with the mission of QIN. Activities of the working groups included creation of white papers that discuss issues where consensus among the research teams is important. The working groups are listed here. Rather than organizing the groups by imaging modality or cancer organ site, the steering committee chose to organize the groups around issues involved with quantitative imaging.

Therefore, activities of data collection, image analysis, performance metrics, bioinformatics, and data sharing were identified. In addition, it was recognized that quantitative imaging will have the potential for changing the design of future clinical trials, so a working group was organized to begin discussions on that topic. Finally, an outreach group was formed to interface the QIN with potential industrial parties, professional organization such as RSNA, SNM, ISMRM and others, and possible academic associate members.

Here's the geographic view of the current teams in the QIN program. Newsflash, three more teams are just now entering the QIN bringing the total number to 12. As I mentioned earlier, the program announcement for the

participation in QIN has been reissued and will stay active until May 2014, offering the opportunity for many more teams to enter the program. Here's a list of the first nine teams and the cancer problem each has chosen along with the imaging modality or modalities selected by each team.

QIN applications are reviewed by special study section that examines them for response to the program announcement and for overall scientific merit. Hypotheses driving the research are relevant to the review and to the direction of QIN. A few of the hypothesis behind the current research teams are listed here. You can see that some teams are motivated by more esoteric statements such as "medical imaging has been thwarted by a lack of standardized image analysis tools." Other teams are motivated by the very pragmatic such as "quantitative analysis of routine PAT and CT images of lung cancer can be prognostic."

Each is profound in its own way and they all usher in extensive amount of multi-disciplinary research on the topic of quantitative imaging. This slide shows that although the program began back in 2008, a compliment of teams was not available for true interaction and networking until about the middle of 2010 to the beginning of 2011. As a result, the network is still in its early stages of functioning. We held an initial face-to-face meeting in early 2010 with only 4 or 5 teams onboard.

A second face-to-face meeting was held in March 2011 where a larger group discussed process and planned coordinated activities for the coming year. Our third meeting is scheduled for March 2012. Now that the structure and organization of QIN had been discussed, I want to look into some of the early highlights of the network. To do so, I want to focus on three of the relevant features of quantitative imaging, namely data collection and investigations of

variance in the data, data analysis and validation of software tools; and informatics and data sharing across the network.

We begin with the problem of data collection and the task of measuring and reducing measurement uncertainty. It's not difficult to grasp that the overall measurement uncertainty that is present in any quantitative measurement is the collection of all sources of uncertainty, taking the appropriate statistics into account when combining the errors of course. Two of the most prominent ones are the physical uncertainties presented by instrumentation and data collection process and the biological uncertainty presented by differences in human subjects such as age, body weight, patient genetics, tumor biology and staging, time of imaging relative to therapy, et cetera.

This second effect can be very large relative to the measurement error and must be controlled as much as possible during the trials. These data from the University of Washington show how measurement errors affect the sample size in a clinical trial. These curves were generated for a desired sensitivity of 80% and a significance of 5 parts in 100. Other desired outcomes would generate different curves. What is seen, is the influence the physical error has on the needed sample size.

Now if the true effect size, that is the difference in a measureable parameter between two tissues states - for example, normal and neoplastic - is say 20%, then if the physical error from a system is on the order of 10%, the sample size on the order of 10 subjects would be sufficient to achieve the desired sensitivity at the desired significance. If however, the physical error is as high as 40%, the sample size would have to be 13 times greater to achieve the same result.

As the change in the measured perimeter and tissue space becomes a smaller fraction of the initial perimeter value, that is as we move the vertical dotted line to the left closer to the origin of the plot, the required sample size grows very rapidly as a function of measurement error as seen by the steepness in these curves. In another view of data, this is stylized waterfall plot showing, hypothetical data of percent decrease in a measured parameter across a complete patient set when therapy is applied.

The data have been arranged in decreasing response. The population is divided into three regions. The responders are here because a measured decrease in the tumor perimeter is seen. Non-responders are here because the parameter continues to increase despite the application of therapy. In the middle are those patients where it is not possible to determine a response because the measured response is actually less than the measurement error. The results from these patients cannot be used in making a response implication.

If the variance in the measurement is large, the region of undetermined results is potentially large, adversely affecting the study. If the physical measurement area is reduced, the region of unknown responders is decreased so that more of the data from the trial are available for analysis. So, reducing measurement uncertainty has a potential for reducing the number of patients required for a clinical trial and may increase the amount of useful data that can be obtained.

This can reduce costs in clinical trials and may permit the idea of the adaptive trials such as the I-Spy 2 trial. Of course, the biological variable still remains and must be considered during all of these studies. The question confronting the QIN teams is this: How are measurement uncertainties reduced?

One very important activity for reducing uncertainty is the standardization of the data collection protocols for each imaging modality. This is achieved through the use of phantoms designed to mimic the clinical measurement. In particular, measurements intended to study the physical variance that will occur over the timeline of a clinical study are important. The QIN team is working with phantoms for PET/CT and MRI to gain insight on imaging platform performance characteristics over multiple sites, multiple vendors using repeat and longitudinal studies in order to quantify physical sources of variance.

The goal is to understand and thus reduce the physical sources of variance. In PET/CT data presented by the team from the University of Washington, it was shown that improper calibration of the PET component lead to the incorrect SUV measurement with 20% bias. That's on the top. In another study, using a modified phantom with the background in all 6 spheres filled with 9-month half-life Ge-68 epoxy, 8 different PET sites were scanned by the same phantom.

The bottom data show the normalized PET measurements as a function of sphere diameter and you can see that there all very much different. The set of curves demonstrates measurement bias in the data. The shape of the curve is caused by the partial volume effect. Unknown individual PET measurement biases between scanners at different sites leads to higher overall PET measurement error for multi-center trials.

In diffusion weighted MRI, a study has been done looking at three different vendors of MRI machines at both 1.5 T and 3 T in both the UK and the United States. A phantom was used to determine the measured apparent diffusion coefficient under different diffusion gradient from 500 to 2,000 units. The results of several measurements on several different devices of the same

manufacturer are shown. For the most part, repetition of the measurements fell well within the plus or minus $\pm 5\%$ margin although one measurement from vendor 1 was askew. The study of physical variance sources and their reduction will continue in QIN.

Moving forward, the use of standardized or model-based data collection protocols has a potential to reduce imaging platform dependence and create a common resource across Cancer Centers for imaging technology. It will certainly provide a level of quality control for future imaging clinical trials. In addition, a common data collection protocol will provide a format for sharing data across Cancer Centers and for using commonly collected data in testing of value rhythms for therapy response.

Next, we turn to data analysis and tool validation. For the sake of this presentation, I define a tool as a software procedure that can do one or more of the following functions. It can search for images according to specific input criteria and/or isolate a region or regions of interest of one or more images, that's segmentation. It can combine different images in a desired way, that's registration. And/or it can extract quantitative information from regions of interest for analysis including whole body tumor burden if that's the challenge. Then, it can perform an analysis leading to the measurement of prediction of therapy response. It is these last two functions that brings quantitative imaging to the role of true support of clinical decision making.

The type of program envisioned at the time the program announcement was written is similar to the types of programs created to validate various assays. The individual QIN member has a concept for particular software tool. A separate database exists with sufficient information to subject the tool to testing at the development stage.

The tool is refined through an iterative process until it's deemed ready for clinical validation. If an appropriate database does not exist, a clinical trial can be used to collect the information on the performance of the tool during development. Once a tool is developed, it must be validated through an ongoing clinical trial.

The data and results are then available to the QIN member for final analysis. I need to say a word about the clinical trials associated with the QIN program. QIN investigators are expected to develop, optimize and validate clinical decision tools. To do that, they will require access to clinical data. As mentioned, this maybe in the form of retrospective data from past trials that is accessed through databases.

The clinical data can also be prospective from ongoing clinical trials. If this is the case, the QIN program will not support the trial. But will support the collection of additional data required for optimization and/or validation of the clinical tools. Of course, appropriate IRB approval must be obtained. In addition, QIN is very interested in supporting correlative studies that link quantitative imaging to other research thrusts such as genomic research.

At the most recent meeting of ACRIN, the comment was made and discussed that it is difficult to design and execute clinical trials for the sole purpose of discovering a disease biomarker. I want to make it clear that the QIN program is not doing this. The clinical trials is used by the QIN members have their own goals and endpoints. These are usually testing the therapeutic effect of a drug or other therapy regimen. QIN teams access existing imaging data and metadata from the trials as needed.

Or they petition to add specific imaging protocols to a trial in order to obtain the required imaging data for tool development or validation. The tools

created in this matter can become useful as support for clinical decision making in future clinical trials. The trials used by QIN investigators are in no way anticipated to create an imaging biomarker.

So, the following picture emerges. As the QIN program progresses, we fully anticipate the future cancer center's clinical trials and clinical trial groups such as ACRIN which is now merged with EGOG will begin to receive important resource information from QIN. A few of those possibilities are shown here. Looking at some of the quantitative approaches being taken by the QIN teams, we return to the set of images shown earlier.

We can reexamine the quantitative changes in the tumor in a different light. Because these particular images are each only one slice of the set of many slices recorded at the time of the scan, it's possible to extract information from multiple slices to create a 3D rendition of the tumor. And from that, the volume of the tumor can be computed. The volume change can then be measured. This maybe a more accurate measure of the response to therapy than the straight forward linear measure shown earlier.

Several teams in QIN are looking at the volume metrics has a way to make quantitative measures a tumor responsive therapy. In a completely different approach taken by the group as H. Lee Moffitt Cancer Center, traditional CT images of lung cancer are being broken down into large numbers of features including common metrics such as tumor size and location; along with more esoteric measurements such as the values of various moments in a wavelet decomposition of the image.

In the words of Dr. Robert Gatenby in a lecture given here just last week, "the images are awash in data and information. It's a matter of extracting and displaying the information correctly and efficiently." Here, each of the

measured quantitative perimeters is displayed horizontally. Individual patients are shown vertically. The perimeters are medium centered, normalized from -1 to +1 and plotted in green for negative numbers and red for positive numbers with intensities at each grid location corresponding to the value of the normalized perimeter for that particular patient.

Heat maps such as these are useful for determining correlations in large numbers of seemingly independent perimeters. And offer visual similarities to genomic array results. Patterns and heat maps such as these are being studied for their ability to predict response. At Vanderbilt University, breast cancer is being studied during neoadjuvant therapy using the combination of PET/ CT and MRI imaging. In particular, they are combining FDG-PET/CT with dynamic contrast enhanced MRI or diffusion weighted MRI. They are using the combined data to perform longitudinal registration of PET CT on the lesion segment obtained from MR imaging. The registration allows for voxel-by-voxel assessment of the changes as shown here.

While it will be possible to spend more time talking about the technologies being studied in the QIN program, other aspects of building a complete quantitative imaging capability demand our attention. In particular, bioinformatics and its potential to create methods for data sharing critical components in the quantitative imaging challenge.

A broad definition of bioinformatics would include these and probably some other activities. In particular for QIN, the types of activities being discussed include data mining capabilities and querying data to locate information; lesion identification and segmentation; standardizing annotation; facilitating storage of imaging and metadata so that data sharing is possible; and providing an open source environment for all of this to happen.

The goal of the informatics activities is to convert data to knowledge. To give you an idea of the commitment of resources and activities to the area of informatics, I show this schematic of the University of Iowa's informatics effort. At the bottom of the diagram is the outside world including the Cancer Centers. Above the demarcation line are the bits and pieces of the informatics effort along with the connecting arrows of activities that make everything work. Similar effects are underway at other QIN sites.

One of the necessary tasks in informatics related to quantitative imaging is the development of a usable semantic structure to give descriptors to all of the relevant quantitative features in the images. Stanford University is focusing on this issue. And they have joined with Moffitt through the network to begin creating a naming convention that includes not only phenotype information from Moffitt, but also semantic representations in a single string vocabulary.

An important asset just now available for data archiving is The Cancer Imaging Archive, the TCIA. It's an archive of DICOM images and metadata. This extensive database is being hosted by Washington University through a contract from the Cancer Imaging Program. Although it's separate from QIN, the QIN is providing pilot data to the archive and will be a strong supporter in the future.

The Cancer Genome Atlas (TCGA) is another supporter of this archive, offering a central location for both image and genome data. As QIN moves forward in the next generation, it's anticipated that more investigators will link their imaging data to genomic data, further strengthening the TCIA as a resource for both bodies of data.

You could see that for the present, the data supplied by the QIN members are restricted. This is because the QIN program is still new and the investigators

have not yet had a chance to perform full and complete analyses of their data. After a while, these data will become available to others for algorithm development and analysis.

So in conclusion, we've discussed how the QIN program can reduce costs of clinical trials, create imaging standards that will link imaging activities across the Cancer Centers, promote adaptive trials, which have the potential for reducing costs, and create leveraging in imaging technologies across Cancer Centers.

The QIN was developed to provide deliverables useful to the Cancer Centers and the Cancer Center community. The deliverables include methods for understanding and more importantly, for overcoming physical measurement uncertainties in imaging platforms, reducing and hopefully eliminating observer-based estimates of trends in therapy response, providing validated imaging methods for prediction and measurement of therapy response, and database development for current and future use.

We emphasize database development and the TCIA in this presentation because it has a special value to the Cancer Centers. In particular, TCIA will make data available to test new imaging hypotheses and to develop new analytical methods to advance our understanding of cancer in a cancer micro-environment. Databases will help engineers build new tools and validate them through the use of accurate data. And of course, educators can use validated databases with confidence when introducing students to medical imaging technology and cancer treatment types.

The QIN will continue its pursuit of quantitative tools to support clinical decision making, and the number of research teams in the network will grow. We encourage additional applications from Cancer Centers. This

announcement is not due to expire to May, 2014. This offers a number of future opportunities for submission of applications that will broaden the base for which consensus decisions can be made and will strengthen the overall QIN program. In addition, our goal is to encourage participation of industrial partners either directly connected with research teams or as associate members to the QIN. They can help to accelerate the commercialization and dissemination of FDA-approved support tools.

Finally, we are working to link QIN to international cancer research organizations as recommended in a recent workshop held in 2011 in London and attended by Canadian, UK and NCI officials. Ultimately, we're looking to have quantitative imaging reshape the clinical trials involving imaging. And with that, I will turn it back to Shannon for discussion.

Shannon Silkensen: Great. Thank you very much Bob. We have a few minutes for questions. And one of the questions we received was somebody who applied for funding through the initial PAR for QIN and didn't receive funding. Do you recommend that they apply again over this open funding announcement?

Bob Nordstrom: Yes. What I recommend you do is give me a call and we'll discuss it privately over the telephone. We encourage people that have applied in the past to reapply. Of course, there are rules about that and we have to discuss that on an individual basis.

Shannon Silkensen: Great. Another question that we had was does the PAR use the multiple PI mechanism? Is it advantageous for a PhD and MD to team up for one of these grants?

Bob Nordstrom: Good question. And the answer is yes. The multiple PI option is available. We certainly encourage multi-disciplinary teams if MDs and PhDs are together, that's fine.

Shannon Silkensen: We also received a couple of questions about equipment. Does the QIN grant pay for equipment or for imaging studies?

Bob Nordstrom: The QIN will pay for some equipment. If you have equipment that needs to be purchased, it needs to be stated in the application. We do not - we will not cover are the costs for the clinical trial itself. We'll cover costs for additional images if it's a PET image or an MRI image or series of images. We will cover those costs. If you have specific pieces of equipment again, I'd like you to talk to me specifically about that so that we can understand more about it.

Shannon Silkensen: Great. Can you talk a little about the data sharing requirements among network members?

Bob Nordstrom: That's a tough one. Good question. Data sharing requirements - requirements is probably too strong a word - data sharing recommendations is probably what I would choose to call it. We certainly would like data sharing to be a part of the network and unfortunately, we can't require it per se. But we certainly encourage through the annual meetings and through the monthly teleconferences that certain parts of the data can be shared.

Larry - Larry Clarke is here with me. Maybe you want to say something particular about that.

Larry Clarke: Only in the sense that almost every team so far has agreed to share data because they see the common value in sharing data and the context of

software tools. And also sharing has very little intellectual property, so there isn't really a strong resistant to share the data.

Shannon Silkensen: I guess along those lines, people are curious about your interactions with caBIG. And so people are wondering how the trial data and image information will be made available for key linkage variables made available through CaBIG or another standard suppository?

Bob Nordstrom: Well right now the standard depository that we're working with is the TCIA. CaBIG is of course an option. We're not working closely with it right now. We have a number of members on our team that have experience with caBIG and have worked particularly in the imaging workspace of caBIG. And we will continue as caBIG reinvents itself in the next year.

Shannon Silkensen: Great. Thank you Bob. At this time, we're going to transfer the presentation over to Dave Mankoff at the University of Washington. David is a professor of Radiology at the University of Washington in Seattle. And he will share with you how he's used the QIN to bring new imaging modalities to clinical trials and build off some of some of Bob's presentation. Thank you Dr. Mankoff.

Dave Mankoff: Thanks very much Shannon. I hope I'm talking loud enough so that you can hear me. Let me know if not. First of all I wanted to thank the QIN and NCI for the support for our center to be able to participate in this very worthwhile program. So that's much appreciated. I also wanted to thank Shannon and Bob and Larry for the chance for us to present some aspects of our program.

On the first slide I did want to acknowledge a number of members of our team, many of whom are represented here. We're a multiple PI grant. My co-PIs are Hannah Linden and Paul Kinahan. And on the second line you see a

number of folks that have also been pretty active in the program and you'll see some of their work as I go through.

In response to a lot of questions that came up, I'll point out that we are a group that has physicists and engineers, basic scientists, imaging specialists, physicians like myself, oncology specialist like Hannah Linden and Evan Yu who are also part of our team. And we even have a card-carrying biostatistician, Brenda Kurland, who has a good portion of her research focusing on image-related processes.

So it really does, as was mentioned before, take a village to have one of these programs. I want to give you a little bit about how this fits in with our cancer center especially since this is a program directed towards the Cancer Centers. In Seattle, our comprehensive cancer center is listed as the Fred Hutchinson Cancer Research Center to which is the organization that holds it. A number of years ago, this turned into a consortium of a number of institutions, perhaps the largest of which is the University of Washington.

We practice under the Fred Hutchinson UW Cancer Consortium. One of the important contributions of the university program was in fact a Cancer Imaging Program that is within this consortium. It is co-led by Janet Eary, Ken Krohn and Connie Lehman. This Cancer Imaging Program was anchored by some long standing grants including Ken Krohn's long standing P01 which has been focusing on cancer PET imaging for some time.

And the focus of our program as was seen in Bob's slide is PET. This also had a number of associated cancer imaging R01's as well as more recently cancer clinical trials including an active participation in ACRIN. At the same time, through collaborations that had been established for some time, there were a number of disease site programs that have questions to which imaging can be

addressed. And these include SPOREs in breast, ovarian and prostate, all of which have imaging components to varying extents; clinical trials, many of which especially our local clinical trials include imaging, and then increasingly part of clinical practice. So we decided to focus our program and QIN to actually bring resources to these efforts that we are supplying many of those resources themselves. However, as these programs appropriately grew, and as the use of imaging appropriately grew, the QIN was seen as a very important and valuable resource to not only refine but support those tools for these ongoing efforts.

Now this fit quite nicely with the science that already existed at our center which used molecular imaging as a way to measure *in vivo* cancer biology. And again, echoing one of the themes in Bob's talk, using the molecular imaging and quantitative imaging to guide cancer - targeted therapy both in the trial and development stage, and eventually into clinical practice.

So the specific aims of our QIN U01 are centered on three components. The first component centers around measurement uncertainty and much of that related to the instrumentation that we use and the way in which we use it. Particularly, making sure that PET instruments (that can be rather sensitive) are cross-calibrated from site to site. And this picked up very nicely on an effort that Bob mentioned in his slides that Paul Kinahan and Robert Doot and others at our center were already involved in. And I'll show you an update on that.

Secondly, once we get the data, we'd like to make the best possible use of it. And our center had focused, for some time, in efforts that are led by a number of folks including Mark Muzi on detailed dynamic image analysis through kinetic modeling. Again, that's not a resource that's available throughout the center uniformly and is not available at every center. But a particular area of

focus for us and as you'll see, provides some in capabilities that what otherwise might not be available.

And then finally taking a cue from both the calibration and the analysis echoing on a slide that you saw earlier; with the help of Brenda Kurland, Robert Doot and others, we've really used this to begin the process of formalizing this into basic study design. That is once we have a better understanding of the noise, which is related to calibration uncertainty as well as the effect size. We can tease from an image, then we can do a much better job of designing our clinical trials.

So let me start with our first aim which is measurement uncertainty. And here I need to give you a little bit of background on the SUV measure in PET. Now this is not a gas guzzling large vehicle in this case. But rather the Standardized Uptake Value which has become an emerging standard in the way that PET uptake values are measured. This involves three measurements. We typically think of the measurement in the upper right hand corner which is represented by acquiring the data on the PET CT in the calibrated fashion so that we can get our measurement in hard units of microcuries per mL or as shown my slide, per gram.

However, there are two other important components. On the lower right is the scale. For the moment we're going to assume that most centers can do a decent job of weighing patients. But on the left is an often overlooked device: the dose calibrator which tells how much we injected into the patient. And to be able to make this measurement worthwhile, we really need to compare what got to different parts of the body which we measured to the scanner to the dose calibrator.

The dose calibrator is an often overlooked component of the uncertainty measurement. And that's a lot of what our approach has focused on. So, work again with Paul Kinahan and Robert Doot, we have generated a second generation approach to a phantom to be able to provide this calibration. You saw the first generation in the slide that had been highlighted by Bob earlier. Now for those of you that are not familiar with calibration for PET imaging, you need a piece of plastic for a phantom to do this.

You may be familiar with the idea that you need laboratory standards to be able to standardize any laboratory assay. Those standards typically come from a central and reliable source so that different labs can make sure they get the same answer when they make measurements in a multi-site trial. And that's really the exact same concept that has been part of the approach that's been oncoming from our center. And what you're now seeing is a modified approach where there are two important components.

One is the white thing that is at the bottom of the top left diagram which contains germanium 68 - I'll show you a little bit more about this in a second. Germanium-68 is a long-lived isotope that serves as a very useful way of measuring and calibrating PET scanners. On the bottom left is a little test-tube like structure that is filled with the same material that can be used to calibrate the dose calibrator in the same way that you would calibrate your system.

Again because these are long lived isotopes that can be shipped from a central source, they can, in fact, be NIST-traceable. Paul and Robert have done a lot of very nice work, in this aspect of the U01 project as an outgrowth work they've done before.

Now in particular, one of the innovations of this approach is to take a single batch of an epoxy that's made with these long-lived resins and put them into

both imaging and dose calibrator standards that can be shipped from a common source and again be NIST traceable. Now while this may seem uninteresting to somebody who is wondering how you image a cancer patient, this is a really fundamental innovation that I think will allow us to have a tracking system for calibrating PET imaging across Centers.

So, what are we doing with this device now that it's been developed? Well as you saw before an earlier device had been tested by a number of academic centers with reasonably good results, proving the value of using one of these long lived isotope phantoms in the cross calibration process. We next turn that back to the next level using our local Seattle Cancer Care Alliance network. The Seattle Cancer Care Alliance is conglomeration of the University of Washington, Fred Hutch and Children's Hospital.

It has a network of other sites in a "clinical centers of practice network feel" similar to that of other major Cancer Centers around the country. Each of these organizations can participate in our clinical trials. In particular we want to make sure that when they do participate in the clinical trials, especially if they participate in some of our PET clinical trials, we can accurately represent data in one site versus another and minimize a number of errors that come from having multiple centers involved in the sensitive imaging approach.

This seemed to us the next logical test, to test the calibration approach that had been developed at Academic Cancer Centers. So on my next slide which is popping up now, I'll show you some of our earlier results that were presented by Robert Doot at the Society of Nuclear Medicine meeting in 2010. The equipment used for the calibration study is again seen on the left; the phantom set has components for both the dose calibrator and the imaging divider. In these tests, we saw that there was a range of errors across a number of sites. For the most part, these errors were relatively small but the important

thing is this allowed us to measure what that size of those errors were and also identify what the biases were between centers so that they could be corrected for. The middle column is equally important and shows you what happens over time. Robert Doot did a lot of this work and noted that when he came to do the first calibration measurement, many of the sites had decided that was a good time to get their system serviced and recalibrated. Results looked pretty spiffy on the first error measurement.

But as you can see, some centers had drifted in the second measurement. This touches on another important theme for the first aim, namely to make sure calibration not only works once but works well over time. The approach provides a method for recognizing errors early and correcting for them. We are now in the process of taking the next step and implementing this across our network.

These tests will lead to test/retest patient trials, where we will in addition, test the uncertainty of the instrument, test the uncertainty of the actual imaging procedure with patient preparation involved.

As we move onto the second aim and tell you a little bit about our image analysis approach. I'll give you a little bit of background about how dynamic imaging and PET works. We typically will take snapshots with PET imaging of a single time point. That's represented by the blue rectangle in the bottom right. I will explain that again in a second. But in fact, the imaging data from PET emissions occur the time and it doesn't expose the patient to any extra radiation to collect those emission data as they come out of the patient. And so in fact, if you have the scanner time and the patient is willing to lie under the scanner, big important ifs, you can collect a moving series of pictures that allow you not only to track the spatial distribution of the tracer at any one time point but changes in quantitative spatial distribution over time.

We can also make a measurement of the activity or the amount of tracer that's in the blood as an indication of the availability to the tumor. We can make a tissue time-activity measurement in the tumor site and normal tissues. And then we can then apply to a kinetic model to these data to not only measure snapshots of tracer uptake, like the SUV, but also to calculate important physiologic parameters. For example, we can measure the glucose metabolic rate when we're using fludeoxyglucose (FDG).

Now let me show you the next slide to motivate why somebody would want to do all this. Number 1, you get a lot more information about your system by taking a full set of data rather than just a snapshot. But importantly, this allows you to be much more sensitive in your measures of response. And I'll explain why in this slide and the next one. So when we look at an image of FDG - and back step for a second, to note that FDG is a commonly used clinical tracer and it's a tracer of tissue glycolytic rate.

The important information from FDG comes at the far right of this diagram - that is the rate at which we see FDG that has been phosphorylated as it moves down the glycolytic pass way making this the best and robust estimate of the glycolytic rate for tissues in particular tumors. Now when we do a PET image, all of this is labeled with F-18. We can't tell from a single snapshot whether we're looking at tracer that is sitting in blood at a microscopic level or contained within the tissue. We can't tell whether we simply looking as FDG that is moving back and forth between the blood and the tissue, but has not been phosphorylated, or whether in fact we're looking at trapped FDG 6P - the phosphorylated FDG that gives us the most information possible about glycolysis.

Now in high metabolic rate tissues, and those tissues that are burning glucose, on a PET scan, most of what we're looking at in the image is in the form of that trapped component. So it's not a big problem. However, when we look at lower uptake tissues and tumors, or perhaps equally importantly, when we see the glycolytic rate going down at the end of treatment and we want to measure that change, we're very much looking at a mixture of FDG and FDG 6P, very much a mixture of something that's just simply sitting there in the background versus the carrier that gives us information on glycolysis.

Without a more sophisticated analysis, we can't tell that difference. However, if we've collected dynamic data and do a kinetic analysis, we can make a measurement of the metabolic rate of FDG represented by the dashed yellow line which is the flux of glucose or measurement of the flux of glucose along this pathway.

So we can get a much more robust measurement from dynamic imaging than we can from a single snapshot. But what does this do for you? And so I move to the next page and show you a paper that Robert Doot published that comes from our center that was actually one of the important pieces of data leading to this aim within our U01 grant proposal. These data come from a series of breast cancer patients that underwent FDG imaging at two time points over the course of treatment.

What we did was to just simply look at the change in FDG uptake that is measured on the vertical axis by the SUV, so again, that's just a simple snapshot, versus the more complex dynamic imaging kinetic analysis and metabolic rate estimates that you see on the horizontal axis. What Robert discovered was very interesting.

If we look at patients with high initial uptake, those that had an SUV of at least 3 or higher, we were able to see that SUV as a fairly effective method for capturing the change in glycolysis over time. However, because of increased background when we looked at the lower uptake tumors, we found that the change in uptake measured by a simple static measure underestimated the change in the rate of glycolysis by about 35%. That is we lost about 35% sensitivity to change with treatment, which can be very important in the investigation of early effects of new drugs (which is much of what we focused on in our recent research).

And it really demonstrated that if you have the ability; and the time; and the resources to be able to collect more sophisticated data, you'll get a more robust answer. So, where have we taken this? This was a precursor. We've now taken this approach to ACRIN which you heard about earlier. And my one correction to Bob is it's actually now ECOG-ACRIN. So they're now 2 equal organizations but together that are merging. And we've been working with ACRIN for some time in this area, where ACRIN is an NCI-supported cooperative network with its headquarters based in Philadelphia.

And at the time of this slide, ACRIN had 118 clinical sites conducting trials but there's actually a few more at this time. I have a vested interest in this as I chair the experimental imaging scientists committee with ACRIN, which is a committee designed to bring new techniques, especially those that would be beneficial to looking at early drug trials and the kind of adaptive trials that Bob had mentioned earlier into early multi-center trials. So this was a nice marriage and a nice place to be able to test out some of the approaches that had been developed within the QIN.

And importantly, ACRIN needed a resource to be able to carry out these early trials. We turned our efforts to a different tracer in this case, Fluorothymidine

(FLT), which you may have heard of through the Cancer Imaging Program. Fluorothymidine is a thymidine analog that traces through the external or salvage pathway of thymidine incorporation into DNA.

As such, it is a very robust tracer of DNA synthesis and thus, the proliferation. And the whole idea here is that if we're measuring the change in the rate of tumor growth as assessed by proliferation; which should prove as an extraordinarily robust way of measuring early response to therapy. Now on the right see you see some examples from the work of Dr. Laura Kenny and her colleagues at Imperial College in London that show for breast cancer, within a week of therapy, we can see a complete shutdown in tumor uptake on the top in a responder and no change in the bottom, again demonstrating this value.

Now if you turn your attention to the diagram on the left again, you'll notice there's some analogy between the kinetics of FLT and that of FDG. FLT is trapped by a phosphorylation step and that's what carries the specific information. So we run into some of the same issues that we ran into with FDG. We also know from the experience at a number of centers the very nature of breast cancer can be quite variable and that some of these tumors can have fairly moderate uptake of FDG reflecting their relatively modest proliferation.

So this was an important place to bring the processes developed within the QIN and within our center into this multi-center trial. And in fact we were able to join forces with ACRIN 6688, that's an ongoing trial. It's just actually been approved. And you can see that this trial follows patients over the course of chemotherapy in the neo-adjuvant or pre-surgical setting. The measurement at point number 2 in the trial is after a single cycle of chemotherapy, testing the very exciting preliminary results that have been

seen by a big London group and others that shown early prediction of treatment response.

Now I'm going to show some slides that were put together by Mark Muzi who has been spearheading the effort and working with ACRIN and running a satellite core lab in conjunction with the ACRIN core lab. This illustrates the kind of infrastructure that was necessary to be able to carry this out. So, what we were able to do, and what Mark was able to do working with ACRIN, was to take advantage of existing resources from ACRIN and the ACRIN central server.

Working with a commercial modeling program optimized for PET (PMOD), the dynamic core analysis effort is housed on a local server at the University of Washington. We worked out a number of data sharing schemes back and forth with ACRIN to be able to enable sophisticated data analysis on this trial. This would have been very difficult to carry out at the individual Centers. There were 21 Centers involved through this trial, and they range from academic Centers to community practice.

So this was really a place in which central analysis was strongly needed. The next slide shows you an example of the kind of forms that Mark has put together working with the ACRIN core lab, stat center and data team that provide the centralized resource to the analysis of these dynamic images in the center of clinical trial. We're very excited to take this forward now that this trial is just about complete and work this through the data analysis and onto the analysis results.

Thus far, I think this nicely demonstrates how the QIN resources can work together in everywhere from individual centers down to clinical trials into

multi-center trials to be able to provide an importantly optimize these resources.

Finally, I want to go back to our last specific aim which was highlighted briefly in Robert's talk and talk a little about how we put this all together. We're going to go back and show you the slide that you saw before which is as Brenda Kurland tells us, kind of stats 101. It tells us that our sample size depends on the effect size and the amount of noise or error that we have in our system. The larger the error, the more patients we need. The smaller the effect size, the more patients we need.

So how do we take this basic statistical diagram and turn this into something that is useful in trying to design clinical trials and involve quantitative imaging? Well, we return to a hypothetical case that was modeled on our breast cancer experience of a patient undergoing a treatment measurement in 2 time courses.

What we simply wanted to do was identify what size we would need to be able to identify some punitive effects in this case, an effect of 20- to 30% which has been typical in many of the trials that have been published. And so I've got - the two axes represented. On the vertical side on the left, we're looking a different noise levels based upon different calibrations. But our assumption is that the single site is going to be able to do the best job of minimizing errors. With good multi-center collaboration and again this is hypothetical, we might reduce error - we might reduce variable to 20%. And in matter of fact, I think we could a lot more than that.

However, if there's bad multi-center collaboration, we certainly seen some published examples of this, then that error may be as large as 40% and unfortunately, that has some realism in some of the real world experience that

has happened so far. So that's the variance size of the noise slide on the left. In the other direction, horizontally, represented at the top, we look at the ability of this exercise based upon how we analyze this.

And again, going back on some of the original work I've done in our center, if the SUV is low or you haven't selected your patient's properly then we're going to have a decreased effect based upon the background factors that I showed you before. And if we go all the way to the right and use detailed kinetic modeling, we can assure that in every single patient we can tease the maximum signal out by being able to use the kinetic modeling to look at the very specific rate of FDG 6P formation and a better estimate of the change in glucose consumption

So what does this mean? Well, if we –put together a trial where we can have good multi-center collaboration and have sites that can perform and at least ship centrally their data analysis from dynamic imaging, we might be able to get away with a trial in this hypothetical scenario of as few as 34 patients. Not a whole lot more than the single site of 12 patients. And really quite achievable within the type of approach we're taking at ACRIN.

However, if we're not careful about how we analyze the data, the requirement for patients may go up by a factor of 3-4 or even up to 10 if we look at the lower left hand corner where required sample size reaches 300. So this is important in a number of regards.

One important tool in trying to design trials is to minimize their overall costs. Secondly, I think these are the kind of tools that will allow us to look at the tradeoffs between using simpler quantification on such as an SUV or more detailed analysis that may provide more robust approach.

So with that, I again thank Bob and the QIN for the chance to present some of our analysis and some of our approaches. And I want to thank a number of the folks involved in these both locally as well as some our collaborating organizations and institutions. So I'll stop and be happy to take some questions, Shannon.

Shannon Silkensen: Thanks David. That was a really great talk. I think one of the questions that several people actually asked has to do with this work you've shown about cross calibration between sites. And there's been sort of a variety of questions in terms of the process that you went through to do this work as well as do you think any of your work has really changed policy or really changed the way people are including imaging within trials?

David Mankoff: Sure. Those are excellent questions. I don't think we've gotten far enough to change policy yet. But there are a number of organizations involved in this in addition to the QIN and some of the cooperative groups like ACRIN have been involved in this. And there is an organization called the QIBA which originally sponsored by the RSNA which is brand new groups together.

There's also a UPICT organization that is another standard bearer. And all of these organizations right now are realizing the need for cross-calibration. So I think that need is out there. Exactly how to do it is an evolving story but we're beginning to develop some standards. And I think that whether it's exactly like the phantoms that we showed you here or whether it's the next general evolution of that process the ability to have central traceable quantities that can be used to do this; cross-calibration is absolutely key.

You know, the people in laboratory science have known this forever. I think sometimes they look at us imagers and say, "what took you so long?" But I

think that that's going to be a major innovation in quantitative imaging in general.

Shannon Silkensen: Another question that we received is what are the concurrent efforts underway to evaluate controllable biologic variation?

David Mankoff: Excellent question. I can talk about 2 efforts in that regard. Our local effort is now going and talking the next step beyond what I showed you. And we're actually taking patients that are imaged outside the network and then reimaging them in one of our central hospital scanners where those 2 scanners have been physically cross-calibrated using our phantom device.

And so that's going to allow us to measure biologic variation. And then importantly, we're going to have a technologist visit to make sure we're operating using the same patient protocols to minimize the biologic variation. PET, especially FDG PET, depends quite a bit on patient preparation scanning procedure. And so we're recognized that.

We just figured we had to make sure we have the instruments cross-calibrated before doing that. There have also been some efforts on a national scale to do that as well. The NCI took that upon themselves a number of years ago and published a standards document that Lalthia Shankar was the first author for, published in 2006 in the Journal of Nuclear Medicine. There have been a number of other ongoing efforts. Lalthia also directed other efforts to bring organizations together to continue to refine that standardization. I think it's an excellent question, because even if we can make our physical devices beautifully aligned, if we can't calibrate the biologic variation or eliminated the unwanted biologic variation, we'll have equally unreliable result.

Shannon Silkensen: One of the things that you mentioned - we had a question about collaborating within the cooperative group. And I guess it was made a little bit smoother because of your active role within ACRIN. So maybe you can talk a little bit about the process for collaboration between the QIN and cooperative groups. And also a little about the issue of data ownership. Who owns the data at the end of the day here? Is it QIN or with the groups?

David Mankoff: So let me answer the second question first. Both for our local trials and ACRIN, the people who are running the clinical trials have primary ownership of the data. And at least in those trials that have been started by those groups. Now one of the things we're working on both in the cooperative groups and locally is making sure that we can export de-identified data through the QIN to be made available for analysis.

In fact, ACRIN does that as well. It has a formalized process for requesting data including requesting access to images. In terms of calibrating with the cooperative groups, we're in a nice position because our center has been active in them as ACRIN participants and as leaders. I chair an ACRIN committee; my colleague Connie Lehman chairs the breast committee. We've been quite active in some of the central roles in ACRIN. So that seems natural for us to bridge the QIN and ACRIN.

I think because of that, ACRIN is the group that we've made the most progress with thus far. The interesting news and I think the good news is that as people may know, the whole cooperative group system is realigning. And I think that is going to bring about some changes in the way the groups work with each other. This change will have the advantage that groups like ACRIN that are an imaging center group. For example, CALGB has its own imaging core lab; these changes may make this kind of resources more widely available.

That's an evolving story. I don't want to pretend to know what the final version is or understand it yet. But I think that access in the cooperative groups is going to widely available. And, starting with its connection in ACRIN, but expanding to the other groups, I think the QIN play a key role there.

Shannon Silkensen: Well thank you very much David. I feel like these excellent questions have been really good to get us thinking about the QIN. Again, from the NCI Cancer Centers, I want to thank both David and Bob for their time and knowledge and for joining us for the Cancer Centers Learning Series. If anybody on the line has any additional questions, please feel free to email them to the NCI cancer center's email address.

Thank you so much.

Coordinator: Thank you for participating in today's conference. You may disconnect at this time.

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