

Fourth National Forum on Biomedical Imaging in Oncology

February 6-7, 2003

Hyatt Regency Bethesda – Crystal Ballroom

Presented by: National Cancer Institute, Food and Drug Administration, Centers for Medicare and Medicaid Services and National Electrical Manufacturers Association

Sponsored by: National Institutes of Health/Foundation for Advanced Education in the Sciences (NIH/FAES)



Meeting Summary

Introduction/Objectives

The National Forum on Biomedical Imaging in Oncology (NFBIO) was created to facilitate partnerships with the imaging industry and government agencies to address new biomedical opportunities and challenges in oncology, and to focus on the regulatory, coverage, and reimbursement issues for more developed and established technologies. During the 2003 NFBIO, speakers focused on imaging for screening, diagnosis and therapy (including monitoring of drug therapy), along with technology assessment issues related to these topics. Breast cancer, lung cancer, and the development of protease molecular targets were used as case studies. In addition, the [National Cancer Institute \(NCI\)](#), [Food and Drug Administration \(FDA\)](#), and [Center for Medicare and Medicaid Services \(CMS\)](#) summarized progress made on issues raised at the 2002 Forum.

Imaging continues to evolve and is becoming integral to diagnostic and therapeutic medical care. This NFBIO focused on: 1) the use of imaging devices for screening and diagnosis of disease, 2) the use of evidence based medicine as payers continue to demand proven outcomes, and 3) image guided procedures.

FORUM ISSUES: UPDATES

Food and Drug Administration (FDA) [[presentation slides](#)]

An overview of the issues surrounding drug, biologic, and device products regulated by the [FDA](#) was presented. Dr. Mark McClellan was recently appointed FDA Commissioner. The [Combination Product Office](#) has been established in the Office of the Commissioner to streamline the processing of complex drug-device, drug-biologic, and device-biologic combination products that play an increasingly significant role in health care. This is intended to improve the review process for combination products and promptly assign a center with primary jurisdiction for a combination product based on the mode of action. The FDA continues to expand its development of guidances and encouraged public discussion of their draft guidances. The [Center for Drug Evaluation and Research](#), [Center for Devices and Radiological Health](#) and NCI continue to build a strong relationship in order to be ready for innovation in the advancing field of imaging.

Centers for Medicare and Medicaid Services (CMS) [slides not available, contact rdeicas@cms.hhs.gov]

An overview of the Medicare process was provided. Improvements are underway in the areas of Federal Register process, appeals regulation, technology assessment from the [Association for Healthcare Research and Quality \(AHRQ\)](#), guidance documents, and research design consultations. [CMS](#) is eager to speak with industry to discuss research and health outcomes that would be helpful to CMS before a company applies for national coverage. Coverage decisions for FDG-PET are on going.

National Cancer Institute (NCI) [[presentation slides](#)]

An overview of [NCI](#)'s current investment in biomedical imaging, including budget, contract support, grant initiatives, and platforms to interact with other Institutes, government agencies, and with technology developers in academia and industry was discussed. The investments span from early discovery to development and application in clinical trials. The [NCI initiatives](#) include those in molecular imaging, novel imaging agents (Development of Clinical Imaging Drugs and Enhancers), early and confirmatory clinical trials (American College of Radiology Imaging Network), and research resources including preclinical models and imaging databases. A high priority for NCI is the [National Lung Screening Trial \(NLST\)](#) in lung cancer, the largest cancer killer. This 50,000 person trial was launched in September 2002 and is designed to determine if lung cancer screening using two different imaging

modalities, spiral CT or CXR, reduces lung cancer-specific mortality. Another high priority trial, the [Digital Mammography Imaging Screening Trial \(DMIST\)](#) was launched in October 2001. This 49,500 women trial is designed to determine the screening efficacy of screen film vs. digital mammography. The [Interagency Council on Biomedical Imaging in Oncology \(ICBIO\)](#) continues to hold confidential meetings between technology developers, NCI, FDA, and CMS with the aim of facilitating the entry of medical imaging technologies to market by providing multi-agency advice on scientific, clinical, regulatory, and reimbursement issues. The next receipt date to present before the Interagency Council is June 6.

National Institute of Biomedical Imaging and Bioengineering (NIBIB) [[presentation slides](#)]

A brief history, structure and future directions of the [NIBIB](#) were presented. Its primary focus is on the development and translation of technologies. Several Requests For Applications (RFAs) have been published. The new Director, Dr. Roderic Pettigrew, has taken office. An advisory council was formed and held its first meeting. There has been a change in its organizational structure. The NIBIB has been involved with organizing several imaging workshops during the past year.

IMAGING AGENTS AS COMPLEMENTS TO THERAPEUTICS [[article](#)]

Imaging the Inner Workings of Solid Tumors: A Twenty-five Year Odyssey

Imaging is a vital, important part of seeing cancer pathogenesis pathways. Two problems have plagued cancer treatment: physiologic barriers impede drug delivery and genetic instability leads to drug resistance. Through the use of intravital microscopy (IVM), Dr. Rakesh Jain has investigated gene expression and function in tumors, as well as host-tumor interactions in the biology of tumors and their responses to therapy. IVM is a promising clinical tool for the diagnosis and treatment of cancer. Further information on IVM can be found by clicking on Dr. Jain's article/pdf document below. PDF documents can be viewed by anyone with Adobe Acrobat Reader.

Case Studies - Experience in Development of Protease Therapeutics

Are Proteases Valid Therapeutic Targets in Cancer? [[presentation slides](#)]

Imaging is used to monitor responses to treatment and helps identify which patients are more likely to benefit from a particular therapeutic intervention. Preclinical studies revealed that matrix metalloproteinases (MMPs) are involved in tumor invasion and metastasis, but clinical trials showed that matrix metalloproteinase inhibitors (MMPIs) were not efficacious. Is this because MMPIs were used at late stages of diseases? The selection of patient population, knowledge that target is modulated by drug, and clinical endpoint assessment are factors being considered to address whether MMPs and other proteases are appropriate targets for cancer and when to administer protease inhibitors during tumor progression. Ongoing research efforts are focused on protease profiling and using in vivo imaging in preclinical models to further investigate proteases.

Approaches and Challenges in Imaging the Protease Pathways

Certain tumors are responsive to certain inhibitors. Near infrared fluorescence probes are being used to image MMP activity. Multi photon excitation microscopy, another technique, allows for deeper imaging in intact tissues. Infrared probes with high quantum efficiency and new light sources for specific excitation in infrared may provide further insight into protease pathways.

Discussion of Protease Pathway research– Key Points

- Profiling at the genomic level and then selecting tumors may provide improved success for targeted therapy.
- Given that all preclinical models have shown MMPs to be effective in early stage disease, proteases may be a preventive agent as opposed to a therapeutic.
- Imaging to further define a drug's capabilities and limitations in the preclinical arena may help define the appropriate clinical setting.
- In the case of combination therapy, imaging can be used to attribute effect due to drug. A study with Herceptin in combination with anti-angiogenesis therapy will soon be published.

IMAGING FOR SCREENING: CASE STUDY – BREAST CANCER

Introduction to Clinical Dilemma [[presentation slides](#)]

Screening mammography has decreased mortality from breast cancer. Randomized mammography trials have shown decreased mortality for women, 40-74 years old. Screening has an enormous impact economically and emotionally. The organization of care affects the quality of screening. Steps to improve the quality of breast cancer screening with mammography include: requirements of annual volume, 'double reading', computer assisted

programming, and digital mammography. Not all cancers can be imaged with mammography, so other technologies and combinations of tests/tools will also play a role in the future of breast imaging.

New Technology for Breast Cancer Screening

Breast imaging is used in the clinical setting for screening, diagnosis, evaluating extent of tumor, and follow-up after breast conservation therapy. Mammography has improved over the past ten years with the evolution of digital mammography, tomo-synthesis, computer aided detection, and contrast enhanced digital subtraction. The use of ultrasound, MRI, nuclear techniques (PET, Sestamibi), and optical imaging techniques has also brought innovation to the field of breast imaging.

Discussion of Imaging Technology for Breast Cancer Screening– Key Points

- Combination technology may drive down costs and change the field of screening. Small PET cameras (FDG PET) in combination with ultrasound and x-ray may help solve MR access problems. PET is also being combined with mammography.
- PET is being evaluated for diagnosis, staging, and follow-up.
- The inability to image and localize abnormalities is problematic for several of the newer systems.
- The clinical environment often provides too much information. What is done about all the lesions detected? Malpractice and reimbursement issues come into play.

TECHNOLOGY ASSESSMENT – ISSUES RAISED BY BREAST CANCER SCREENING AND IMAGING AGENTS IN THERAPY

Technology Assessment – Bringing Evidence-Based Medicine to Medical Policy [[presentation slides](#)]

The [Blue Cross Blue Shield Association’s Technology Evaluation Center \(TEC\)](#) was presented as an example of how cancer imaging technology is evaluated. New technologies are evaluated with priority based on clinical importance and national interest. The effect of a diagnostic technology on health outcomes might ideally be studied in randomized trials; however, in most cases, such direct evidence does not exist and indirect evidence may be linked together to demonstrate effectiveness using decision analysis. Clinical effectiveness is based on the performance of the diagnostic test, effect on patient management and effect on health outcomes. An evaluation against the TEC criteria is performed. An expert panel is the next step in the TEC assessment cycle followed by publication. Literature continues to be monitored. Current knowledge on three breast imaging technologies was discussed. Many new technologies fail because the available evidence is not of sufficient quality and quantity to permit conclusions regarding health outcomes. Once the evidence is sufficient, then a determination is made on whether the beneficial effects of the technology on health outcomes outweigh the harms and whether the improvements from the new technology are at least as beneficial as available alternatives.

Methodologic Issues [[presentation slides](#)]

Receiver Operating Characteristics (ROC) methodology can be used to evaluate diagnostic (imaging) systems based on diagnostic accuracy. ROC analysis is necessary because of the limitations of other available methods for evaluating two-group classification performance. Diagnostic tests are evaluated in terms of sensitivity (probability of calling an actually-positive case ‘positive’) and specificity (probability of calling an actually-negative case ‘negative’). ROC-based indices of performance were presented along with a historical background on ROC analysis. Statistical significance tests were reviewed. The tests that analyze data from multiple readers and multiple cases (MRMC) allow for conclusions to be drawn regarding populations of readers and cases. Many advances have been made in ROC methodology and more are needed.

Center for Radiological Health/FDA Research Perspectives on Medical Imaging and Computer-aided

Diagnosis (CAD) [[presentation slides](#)]

The variables when comparing imaging technologies are vast. Full analysis requires MRMC ROC analysis whereby every reader reads every case. The MRMC ROC approach leads to ‘least burdensome’ study designs. CAD has greatly reduced the range of variation in reader skills and the dependence of this range on the case. Expected benefit function and statistical pattern recognition are other assessment methods. The MRMC ROC approach has been used in several industry submissions to FDA and is being presented to sponsors of medical imaging, CAD, and CADx systems as a potential framework.

Cancer Imaging Informatics [[presentation slides](#)]

Images are important for cancer research, but they are disconnected from other forms of biological knowledge. Medical imaging knowledge is unique in that there are few publicly accessible databases, links to mainstream

biological knowledge collections are absent, and there are few software tools available that allow one to use heterogeneous databases. An open cancer imaging database has the potential to open the field to rapid technological advancement, coalesce the scientific community, and address questions that could not otherwise be answered. When compared to genomics and proteomics, imaging has few, if any, public repositories, few links to primary data in publications, rarely available primary data, and few open source tools that operate on images in conjunction with other forms of biological knowledge/databases. The failure to integrate data sources has serious consequences for cancer imaging science and related applications. Narrow channels for communication and unwillingness to share data pose barriers. Four approaches for imaging science informatics were discussed:

Lung Image Database Consortium – sponsored by [Biomedical Imaging Program, NCI, NIH](#)

Medical Image Resource Center – sponsored by [Radiological Society of North America](#)

National Digital Mammography Archive – sponsored by [National Library of Medicine, NIH](#)

Biomedical Informatics Research Network - sponsored by [National Center for Research Resources, NIH](#)

The sharing of primary data from investigations that generate and collect images is new, and will require a change in culture, organizational effort, and persistent infrastructure.

Discussion of Technology Assessment and Cancer Imaging Informatics – Key Points

- A disconnect exists between the development of a medical product, dissemination of that product to a provider and application of technology/clinical outcomes. A company cannot tell a provider how to use a technology in the practice of medicine.
- The FDA needs to make sure clinical outcomes are the true performance of a device.
- A consensus driven process may need to take place in order to minimize observer availability.
- ROC allows for analysis of individual practitioners.
- Accreditation is important and mammography has been a leader in this process.
- The patient advocacy community is incorporated in the TEC assessment by the presence of a biomedical ethicist who sits on the expert panel.

IMAGING IN DIAGNOSIS AND THERAPY OF SCREEN-DETECTED LESIONS: CASE STUDY – LUNG

CT Screening for Lung Cancer--Mayo Clinic Experience

Mayo Clinic's findings answer some questions and raise many others. Screening of patients at high risk for lung cancer with low-dose spiral CT allows detection of many early stage lung cancers. It is not clear if this is a true stage shift or over-diagnosis. Will there be a decrease in the number of advanced stage cancers detected with CT screening? CT screening allows detection of a very large number of benign, but uncalcified lung nodules (false positive result) that will be expensive to diagnosis and may negatively impact quality of life. Clearly, CT is much more sensitive than chest radiography for detection of small lung cancers. Unproven is whether CT meets the criteria for an effective screening test. There are serious issues regarding quality of life and radiation exposure that are raised by false-positive findings. Surgery for false-positive findings could lead to more morbidity and mortality among the screened group than could be saved by any gain in disease-specific mortality. Additional findings raise hopes for decreased mortality from many conditions including abdominal aortic aneurysms and renal-cell carcinoma, but over-diagnosis and operative mortality issues mute the enthusiasm here as well. Further study is needed. A randomized control trial that shows disease-specific mortality benefit may be the best way to settle the controversy. The [NLST](#) funded by the NCI is a randomized controlled trial that is now underway.

Image-guided Diagnostic Procedures for Screen-detected Lung Lesions

CT is replacing x-ray in some hospital emergency departments. A screening CT can reveal small nodules in the lung, causing a physician to make new decisions in patient management. The use of CT during a biopsy procedure to obtain tissue for a diagnosis is being investigated. What is being learned by obtaining tissue? How much tissue is needed to make a diagnosis? How is the tissue obtained? With CT technology, radiologists are able to steer beveled needles into the lung and obtain tissue for histologic analysis. Imaging has become a valuable tool in selecting the appropriate lesions for biopsy, thus yielding a higher rate of malignancy in nodules being biopsied and sparing patients from a procedure that may not be beneficial.

Image-guided Therapeutic Non-surgical Interventions for Screen-detected Lung Lesions

Cryoablation, microwave ablation, and radiofrequency ablation (RFA) were discussed as minimally invasive alternatives to surgical interventions for lung neoplasms. With RFA, an insulated electrode shaft with an uninsulated tip is placed in lung tissue. An electrical generator is attached to the electrode and electrical impedance of tissue allows a current to flow from the generator to the tissue. This alternating current causes local ion agitation.

Resistance (friction) of tissue causes heat generation from the flowing current. Heating then occurs in the tissue leading to coagulation necrosis of >50 degrees. RFA causes disruption of tumor equilibrium of recruiting cells into mitosis and also destroys the more central hypoxic tumor, resulting in reactive neo/revascularization of surviving adjacent tissue/tumor. Several clinical trials with RFA alone and in combination with radiation or radiotherapy or XRT or high dose brachytherapy for the treatment of lung cancer have been performed. Results indicate that early clinical applications of RFA and XRT appear to be safe. Integration with radiation is practical. Further evaluation is underway.

Image-guided Therapeutic Surgical Interventions for Screen-detected Lung Lesions [[presentation slides](#)]

Surgery for early stage lung cancer remains the first line of therapy, but few patients are surgical candidates at presentation. Solitary pulmonary nodules can be evaluated by traditional surgical techniques (lobectomy, removal of lobe segment, or wedge resection), surgical RFA, or cyberknife. The lung cancer surgical mortality rate is three percent, with survival dependent upon tumor size. Surgical RFA is being evaluated to determine safety, tumor ablation, growth, and histology. Cyberknife, similar to a gammaknife with robotics, has improved survival in non-small cell lung cancer. Ongoing major surgical trials were discussed. Biomarker research continues to expand, and randomized trials are needed to determine if early intervention is warranted. Image guidance is crucial for the evolution of therapeutic surgical interventions.

Technology Assessment Issues Raised by Image-guided Diagnosis and Therapy [[presentation slides](#)]

The four stages of developmental procedure (discovery, introductory, mature, dissemination) were presented. Accuracy and diagnostic performance must be evaluated at every stage because technology varies at every stage. Process of care is a useful endpoint after the discovery stage, while patient outcomes are useful as the technology goes into the mature stage. Given the enormous rates of positive screens obtained in high risk populations, the future of lung cancer screening depends crucially on the successful development of accurate and cost-effective diagnostic workup protocols. What is it that we're looking for? How will we obtain gold standard information on this? Ideally, randomized studies would be necessary to compare with standard therapies in terms of patient outcomes. A significant potential exists for high rates of cross-over between study arms. This would present a major problem for a comparative study. The potential for bias exists in diagnostic performance evaluations and randomization helps to avoid the effects of selection biases in comparative studies. Randomized studies are costly to perform. Modeling may offer a realistic option to randomized studies.

Discussion - Key Points

- Industry is developing software packages to combat difficulties with reading scans.
- The demand for hardware innovations for patient comfort is rising since CT is being used for procedures in which the patient is expected to lie down for an extended period of time.
- Is screening cost effective? Cost effectiveness generates information for society to use in making that decision.
- The 'moving target' will continue to pose problems as CT technology continues to evolve. A variety of platforms from different manufacturers are being used in the [NLST](#).
- Modeling will be an important tool to find parameters for algorithms as CAD technology advances.
- How can industry help disseminate CAD to help perform nodule characterization? Disparate platforms currently exist. How do we disseminate CAD methods across platforms?

Coalition and Review of Proposed 2004 Forum Topic

The Biomedical Interagency Imaging Coordinating Group held a planning meeting during this Forum to discuss proposed topics for the next Forum, tentatively scheduled for January or February 2004. Among the topics that are being considered include combination products, information integration, display and information, e.g. CAD, public-private partnerships and education patterns.