Comments

MEETING SUMMARY

NATIONAL CANCER INSTITUTE-INDUSTRY FORUM AND WORKSHOP ON BIOMEDICAL IMAGING IN ONCOLOGY

September 1-2, 1999

Washington, D.C.

The first National Cancer Institute (NCI)-Industry Forum and Workshop on Biomedical Imaging in Oncology convened in response to the rapid pace of innovation, discovery, and new developments in cancer research, basic science, and imaging technology. Participants represented many facets of industry, government, research, academia, and medicine. They were invited to help form a new synergy to create and adapt advances in basic science and imaging technology to oncology. While imaging has been essential in progress against cancer to date, it is already being used in new ways. Several speakers described these new uses of imaging technology as well as some of the remaining challenges in oncology research, treatment, and diagnosis. Representatives of industry described the challenges they face, while government representatives discussed regulatory and reimbursement policy. Two panel discussions highlighted the challenges of diagnosing and treating prostate cancer using case histories, and the role of positron emission tomography (PET) in medicine and cancer treatment today. Thereafter, the participants divided into four smaller groups to discuss biomedical opportunities and challenges, technology development and challenges, regulatory concerns, and reimbursement issues.

OPENING WELCOME, PURPOSE OF FORUM
Dr. Ellen Feigal, Deputy Director, Division of Cancer Treatment and Diagnosis (DCTD), NCI

In opening the first NCI-Industry Forum on Biomedical Imaging in Oncology, Dr. Ellen Feigal indicated that:

- The participants are engaged in efforts that have the potential to revolutionize medical practice and significantly improve the detection, diagnosis, prevention, and treatment of cancer patients.
- The idea for the meeting came about when NCI asked the National Electrical Manufacturers' Association (NEMA), trade organization for more than 600 companies, how the NCI could partner with industry to promote research development and testing of biomedical imaging in oncology. Representatives from NCI, NEMA, the Food and Drug Administration (FDA), and the Health Care Financing Administration (HCFA) were instrumental in the organization of the meeting.
- The meeting had four goals: (1) To bring together the people who fund and conduct the research, regulate products of the research and reimburse the use of the products; (2) To expand the role of anatomic, functional, and molecular imaging in detecting, diagnosing and treating cancer; (3) To develop strategies to apply advances in imaging to unmet clinical challenges in cancer; (4) To better understand processes related to the following: how organizations involved or interested in imaging make decisions; how NCI identifies scientific opportunities; how industry develops and commercializes technology; how the FDA conducts its regulatory process; and how

HCFA conducts and decides on reimbursement.

- The meeting is expected to be the first of many forums.

OPENING WELCOME
Mr. Morgan Nields, Chairman and CEO, Fischer Imaging Corporation

Key Points

- NEMA has 600 member companies with revenues of around $100 billion annually from products that include generation equipment, switches, wire and cable, insulation, factory automation, and medical imaging systems.
- One of NEMA's nine major divisions is diagnostic imaging and therapy systems, made up of 60 diagnostic medical equipment manufacturers with revenues of about $5 billion in the United States alone.
- Barriers existing primarily in regulatory and reimbursement areas hinder manufacturers in development of new diagnostic imaging and therapy products.
- The barriers cool investor interest with the result that promising new products stay on the drawing board
- The NCI-Industry Forum is a milestone that could help bring down barriers and accelerate development of technology.

VISION OF CANCER FROM A MOLECULAR CELL BIOLOGY PERSPECTIVE: INTEGRATION WITH IMAGING
Richard Klausner, M.D., Director, NCI

Key Points

- NCI has identified imaging as one of four extraordinary opportunities for new investment.
- New imaging techniques are providing information about cellular, molecular, and biochemical processes in unprecedented detail.
- Oncology research has achieved revolutionary progress in understanding of cancer on cellular, molecular, and biochemical levels.
- Advances in both areas, imaging and oncology research, can be combined to bring even more progress and a wealth of new information to cancer research, diagnosis, and treatment.
- Imaging, used most often to pinpoint lesion location, can now also be used to provide detailed information about the cellular and molecular processes of cancer.
- Imaging may be used to identify pre-cancerous lesions.
- It is possible now to think of going beyond image-guided therapy to image-determined therapy. That is, information gained during imaging can help determine treatment type, performance, and potential toxicology.
- NCI has increased funding for imaging research and is thinking about new funding mechanisms for technology development.
- NCI recognizes that imaging is a cross-disciplinary science and is beginning to work with representatives of the fields involved, including materials science, physics, mathematics, and others.
- NCI is discussing with NASA the adaptation of remote sensing technology to imaging of the body on the molecular level.

- NCI is examining its clinical trials procedures to accommodate a new emphasis on imaging

CLINICAL OVERVIEW: TYPES OF SCIENTIFIC QUESTIONS, OPPORTUNITIES, AND CHALLENGES THAT MIGHT BENEFIT FROM INTERACTION WITH NON-INVASIVE IMAGING

Robert Wittes, M.D., Deputy Director, Extramural Sciences and Director, DCTD, NCI

Key Points

- A scientific revolution is taking place in medicine, but the pace and impact are more apparent in science -- biology, applied physics and engineering -- than they are in medicine itself.
- Research has developed new ways of analyzing the expression of mammalian genes and achieved quantum-level advances in structural biology. For example, for the first time, it is possible to take a picture of a bacterial ribosome at 5 angstrom resolution.
- Soon, researchers will be able to see and understand the cell's entire architectural blueprint and its wiring diagrams, as well as the multitude of pathways in mammalian cells and how they function.
- Cancer has been diagnosed for decades by looking in a microscope and describing visual patterns. It will soon be possible to make diagnosis more rational, rather than purely descriptive, by applying new biological information the process.
- When biological pathways are defined, new targets for drug development will emerge. Imaging will be essential to help validate the targets and the drugs, as well as characterizing the drugs' action.
- Imaging of such factors as tumor markers may also improve the ability to develop prognoses, an underdeveloped area in oncology.
- The new biology will allow the development of treatments tailored to the individual.
- Technology and research are producing mind-boggling amounts of biological data. The challenge will be to apply the new methods to oncology so the data become useable information.
- There are still tremendous difficulties in applying scientific developments for practical purposes. Overcoming them may require the kind of multi-disciplinary alignment not seen since World War II.
- Some of the non-scientific challenges are as follows:
  - How to achieve interdisciplinary team science within traditional academic cultures, where division is maintained and promotion and tenure policies do not reward team science
  - How industry can best allocate its resources and assess risk
  - How are public funds best spent in imaging development and research
  - What role can the pharmaceutical industry play
  - How payers and providers can participate in the research process

TECHNOLOGY ADVANCES AND FUTURE DIRECTIONS

Imaging, already an indispensable part of oncology research and practice, is changing. Technological innovation and new precision are making it possible to produce images and data that were not possible even a decade ago. It is clear this abundance holds great potential to help the field of oncology. But as the field develops, technology-related questions and challenges are arising. For instance, researchers and clinicians seek to image with increased accuracy and precision, but what exactly do they wish to image? Oncologists seek more knowledge of how cells transform to become cancerous, but what is an altered cell? What if the cell is altered? Can imaging be used to identify and characterize micro-metastases? If researchers wish to image genes, what about the genes do they

wish to know? Can imaging be used to observe pharmacokinetics? Speakers in this portion of the workshop addressed some of these issues.

NCI Initiatives in Imaging
Daniel Sullivan, Associate Director, Diagnostic Imaging Program (DIP), DCTD, NCI

NCI has many initiatives and cooperative relationships with industry in the area of imaging. Some brief descriptions are provided here for those who are interested in participating or who seek further details.

- For questions about general relationships between industry and the NCI, contact:Carol Dahl and Leslie Alexander, NCI Office of Technology and Industry Relations. Larry Clark, Office of Imaging Technology Development, DIP, DCTD, NCI. www.nci.nih.gov/dip, a web site that provides information about some of the DIP's initiativesSome of the available mechanisms are as follows:
- NCI's exploratory development grants program provides funding for feasibility trials of ideas relating to imaging technology development.
- A mechanism called "A Molecular Analysis of Cancer" is available to small businesses, academia, and industry.
- The SBIR program is available for small businesses.
- An expanding program will promote development of diagnostic probes.
- Small Animal Imaging Research Programs combine funding for technology development for small animal imaging, and for oncology research using small animal imaging.
- The Diagnostic Imaging Cooperative Group provides a mechanism for researchers to work with industry to develop clinical trials and test the feasibility of new diagnostic imaging technologies.
- DIP has initial funding for planning and development of In Vivo Cellular and Molecular Imaging Centers. These will encourage development of infrastructures necessary to bring about multi-disciplinary teams needed to study molecular biology. Institutions that have already been engaged in development of such centers are encouraged to apply for a P-50 center grant.
- Bioengineering research grants and Bioengineering Research Partnerships support teams of researchers focused on bioengineering development.
- A new training mechanism called the R-25 encourages multi-disciplinary curriculum development and training programs.

Therapy: Challenges for Imaging Sciences
Dr. Thomas Brady, Professor of Radiology, Massachusetts General Hospital

Key Points

- The Center for Innovative Minimally Invasive Therapy (CIMTT) is a novel group in the Boston area that works with industry to develop new medical procedures quickly and translate them into patient care. Its members include Massachusetts General Hospital, and Brigham and Women's Hospital, and Draper Laboratory. A current challenge is to bring high-tech imaging equipment close to the patient, whether in the patient's room or in the hospital emergency room. Less expensive, more efficient systems are also needed.

- Techniques for quick, early assessment of hemorrhage are also sought. These would be important for stroke patients, because 10 to 15 percent of them experience hemorrhage and cannot tolerate thrombolytic therapy.
- CIMTT is developing a portable optical diffuse tomography technique that uses near-infrared light in a system that can be placed at the bedside or in an ambulance, and may be adapted for continuous monitoring. The device sends light into tissues, where it scatters and is then received by a detector. The system is expected to be inexpensive, costing $30,000 to $50,000. Tests indicate the system can image brain function activity and measure blood flow, as well as structures to a depth of a couple of centimeters.
- Dr. Brady and colleagues involved in the Center are working to improve resolution and depth penetration.
- Dr. Brady and colleagues are developing smart optical contrast agents to use with the system; they are also designing systems that can be used in pediatric studies, intensive care, and emergency rooms.
- CIMTT is also looking at image-guided therapy and the use of imaging techniques in presurgical planning and intraoperative visualization.
- Working with Johns Hopkins, CIMTT is looking at image-assisted robotic surgery in a program funded by the National Science Foundation and the National Institutes of Health.
- The team is working with Shady Dale Hospital in Pittsburgh and the Brigham and Women's Hospital in Boston. The goal is to develop and apply data to make it possible to visualize a tumor with the patient on the operating table, and then use robotic capabilities to guide the surgeon in treatment.
- Several centers are working on image-guided, focused ultrasound. These techniques are being used to ablate tumors and thrombosis, and to deliver drugs through the blood/brain barrier.
- Systems that decrease treatment time are needed.
- Currently, treatments are done with MR guidance. Other techniques are needed.
- Some of the challenges facing those who work with imaging and imaging research are as follows:
    - Imaging companies are going from two-dimensional data sets to three-dimensional data sets. It will be a challenge to interpret the overwhelming amounts of data expected.
    - How can systems be integrated? How can medicine and industry develop procedure rooms or operating rooms of the future,and how can the medical community manage the information that will flow to and from them to patient records and other facets of health care? Medicine needs a better understanding of whom to treat and why.
    - It is desirable to image with greater sensitivity and treat lesions with larger ablation.
    - The health care community needs to examine ways the cost, benefit, and efficacy of these new techniques can be balanced and assessed.

Functional Imaging
Dr. Thomas Budinger, Chairman for Bioengineering, University of California at Berkeley and Head, Center for Functional Imaging, Lawrence Berkeley National Laboratory

Key Points

- Among the malignancies oncology researchers seek to understand is brain cancer, which claims more than 13,000 lives annually. Glioblastoma is one form of brain cancer
- A review of the literature reveals that many imaging agents are used in brain tumors. Most of the agents take advantage of a primary feature of glioblastoma: the blood/brain barrier does not exist as it does for the surrounding tissue. Therefore, any agent used will enter the tumor. For this reason, rubidium-82 is useful in this form of cancer. Like potassium, this agent doesn't cross the blood/brain barrier, but it will

enter glioblastoma. The same is true for selenomethionine.

- If there is a blood/brain barrier, or if there are microfocimetastases that have a barrier or are too small for resolution, FDG accumulation can be imaged. FDG with PET is a good prognostic indicator that has helped many patients.
- Questions remain about the use of tracers and their interaction with cells in the presence of a blood/brain barrier or without such a barrier. With many tracers, it cannot be easily determined whether something is inside the cell or on a cell's receptor surface. Dr. Budinger and colleagues are solving that with the observation of molecular specificity in agents such as anexin. Carbon-11 methionine is an effective agent for the study of brain tumors. But most of the methionine that goes into cells becomes involved in methyl turnover, leaving the question: To what extent is this blood/brain barrier disruption or actual metabolism? In one study of a tumor, Dr. Budinger and colleagues imaged low uptake of FDG, high uptake of methionine and high uptake of floraldopa. The team wondered if this had to do with the fact that there was a blood/brain barrier disruption here or no blood/brain barrier because there was no metabolism?
- MR has moved to the evaluation of brain tumors and the efficacy of therapy. MR has taken over evaluation of recurrent tumor. Dr. Budinger and colleagues have combined three MR techniques with processing techniques to show the volume of rectal carcinoma and its decrease under therapy. This is a fantastic help to the patients.
- Dr. Budinger and colleagues hope to move up to a higher field to be able to see compounds such as sodium, which is abnormally abundant in tumors, using endogenous carbon-13 or agents such as injected carbon-13. At the current level of 1.5 tesla measurement is not possible; beyond a level of 4, it is.
- In breast cancer, the combination of nuclear techniques and ultrasound techniques may be valuable for the evaluation of tumors. Dr. Budinger's team did so in a study of 32 patients, of whom 50 percent had new information and 25 percent had a change in therapy as a result of undergoing the combined techniques. The procedure currently takes 1.5 hours and costs $2,000. Dr. Budinger believes these figures can be reduced to $1,000 and 15 minutes per patient without new technology.
- Dr. Budinger's team is developing a device that will have 1.7 millimeter resolution for evaluation of axillary nodes. The cost of the instrument will be 10 times slower than standard PET. It will have four times lower dead time, twice the resolution and 30 times higher sensitivity, which means that a lower dose will be necessary for the patient. The device will be the size of a lap-top computer that can be put into any position, allowing the technician to get closer to the tumor with high sensitivity and improved resolution.
- New tracers are under development. One, the aptomere for thrombin, is already developed. The team is developing techniques of labeling DNA saptomeres can be used as PET tracers. This will open up the whole area of protein-specific tracers.
- The potential of using ultrasound to modify and burst liposomes or change liposome position in cells and tissues is an exciting area. It will require a change in the power for ultrasound devices.
- Dr. Budinger's team is investigating the attachment of fluorane-18 on a choline analog to use in detection of the increased choline signal present in prostate cancer.
- The team is also working on a low-cost prostate imager. The device is placed in the rectum for five minutes, where it takes data. It is then removed and plugged into a laptop computer. It could be changed to monitor the cervix.

Imaging at the Molecular Level
Dr. Thomas Meade, Director, Program for Bioinorganic Drug Design and Discovery, California Institute of Technology

Key Points

- The Program is studying whether imaging modalities can penetrate the cellular level to provide information about the molecular level.
- One of the challenges is that the typical clinical resolution of MRI is in the millimeters. To image on the molecular level requires micron-level resolution, a drop of nine orders of magnitude.
- The Program has built a machine that has achieved resolution of 35 to 40 microns in images of a live mousepup. The team has produced images of a dwarf mouse lemur, an animal whose head is about the size of an adult's thumb, at about 22 micron resolution.
- The team has designed and synthesized enzymatically activated MR contrast agents. These agents provide physiological information in the form of gene expression, and ultimately in function of cells. The preliminary version of such an agent made with amelanthenide gadolinium ion and used with MRI produced images of a tadpole at about 25 micron resolution.
- The Program has created synthesized classes of calcium contrast agents to be used to detect disease states and map brain function in the form of an MRI image at the level of microns. The researchers' goal was to make an agent that changed in equilibrium with the metabolite they were trying to track. The team made such an agent that is sensitive to the concentrations of calcium found in vivo.
- A higher magnetic field is needed to create this kind of resolution. Whether there are any toxicological effects in humans from that high a field is an unanswered question at this point. Scientists working with NEMA and the FDA have been doing evaluations to slightly beyond 4 tesla. There is no reason to believe that there is any physiologically damaging effect even at 10 teslas.

PET Imaging in Oncology
Dr. R. Edward Coleman, Director of Nuclear Medicine and Vice Chairman, Department of Radiology, Duke University

Key points

- PET scanning is an important part of clinical practice. It plays a major role in diagnosing and staging several types of cancer.
- Glucose metabolism, blood flow, oxygen metabolism, blood volume, myocardial perfusion, and amino acid distribution can be imaged with PET with a resolution of about 5 millimeters.
- PET can determine the degree of malignancy in cancers. For example, in brain tumors and sarcomas, the higher the glucose metabolic rate, the more malignant the tumor.
- PET also differentiates tumor from fibrosis or scars after therapy.
- PET can identify sites of malignancy with rising serum markers. PET has been shown to be able to characterize the site or the origin of rising CEA, and it identifies sites of primary tumor and metastatic disease.
- The technology is very accurate at showing a tumor in the head, neck, and throat area and often alleviates the need for a patient to go through multiple blind biopsies in a search for tumor location.
- In a summary of 20 studies from the literature about the use of PET scanning to characterize solitary indeterminate lung nodules or lesions among 873 patients, PET demonstrated a mean sensitivity of 96 percent and specificity of 85 percent. In its own study, Duke imaged nodules down to 6 millimeters. In that study there were two false positives; each had active tuberculosis, which shows up hot on the PET

scan. Other inflammatory conditions such as histoplasmosis, coccidial mycosis, and lipoid pneumonia will also accumulate FDG. The Duke team is now attempting to characterize nodules smaller than that. The researchers see and can detect some nodules at 3 to 4 millimeters and determine if they are malignant.

- The Duke team has investigated the ability of FDG to demonstrate biology. In one study examining the doubling time of lesions, the researchers found that the more glucoseutilized, the shorter the doubling time, whether the lesion was benign or malignant.
- Recognizing that standard mediastinoscopy has unsatisfactory sensitivity and specificity, the team has looked at PET's utility in staging the mediastinum. In 15 studies with a total of about 500 patients, sensitivity and specificity were in the high 80s, and accuracy was superior to CT.
- PET is also accurate in staging metastatic disease and characterizing adrenal lesions. These lesions are common in the normal population, and differentiating benign from malignant lesions becomes problematic in patients with lung cancer because lung cancer commonly spreads to the adrenal glands. In the team's analysis of 33 indeterminate masses, PET had a sensitivity of 100 percent and specificity of 80 percent in characterizing adrenal lesions.
- Comparing PET to conventional imaging in whole-body scans, the Duke team reported PET was correct 91 percent of the time, compared to 80 percent of the time for conventional imaging.
- In a study of patients who presented with indeterminant pulmonary nodules, the Duke team looked at prognosis related to the standardized uptake ratio SUR. If their SUR was greater than 10, their survival time was shorter than those with a lower SUR. If they had a nodule of less than 3 centimeters in size, they had a better chance of survival. Those with smaller nodules and lower SURs combined had an even higher survival rate.
- PET is also usefully in colorectal cancer, melanoma, and lymphoma. The team's one caveat is that PET is not as accurate as MRI in detection of small brain metastases at the time of presentation.

Biomedical Imaging
Dr. Michael Phelps, Chair, Molecular and Medical Pharmacology, Director, Crump Institute for Biological Imaging, and Associate Director, Laboratory of Structural Biology and Molecular Medicine, University of California, Los Angeles

Key Points

- PET is a biological imaging technology that uses molecular probes to identify and elucidate biological processes. In PET, molecules form the images.
- Dr. Phelps's team and other scientists have used PET to identify abnormal biological changes in pre-symptomatic stages of neurological diseases.
- In a 15-year study by Dr. Phelps and colleagues, children of Huntington's disease patients were tested repeatedly to determine if they had developed symptoms of the condition. Some of them, however, had metabolic deficits in the caudate and putamen. Follow-up of patients who went on to develop symptoms, plus analysis of genetic markers, indicated that the team had identified the metabolic deficiencies seven years before symptoms appeared.
- Studies by other researchers of familial Alzheimer's disease identified metabolic deficits in the parietal cortex. The projection was that based on these alterations the disease can be identified five years before symptoms originate.
- Another study demonstrated that PET has greater than 90 percent accuracy in identifying Alzheimer's

three years before clinical diagnosis can be established.
- A team at the University of Washington is using PET to look at DNA synthetic rates of cell proliferation, which play critical roles not only in the characteristics of neoplasms but in therapies directed at modifying cell replication.
- The team has used FLT, an analog of thymidine and of AZT.
- Studies of non-small cell lung carcinoma have shown the agent successfully indicates areas of high cell replication suggestive of malignancy.
- A number of institutions are performing micro-imaging studies of a variety of organ systems and tissues in mice. Dr. Phelps's team has gotten good delineation of the glucose metabolism in the brain of a rat, whose weight is 1 gram, and of a mouse brain weighing only 15 milligrams. The team can identify structures in images of the brain of a baby monkey, which weighs 25 grams. The team is developing systems with small resolution specifically for micro-imaging. Technology development in this area will benefit diagnosis in human studies.
- Dr. Phelps and colleagues are also working on ways to image gene expression in vivo.
- Dr. Phelps's group has developed agents using short modified oligomers labeled with fluorane-18. With the elegant coding of nucleic acids, they can be bound to the specific messenger RNA that is the target.
- The group has also used a PET reporter gene approach taken from basic biology.
- In tests with mice, Dr. Phelps and team placed a reporter gene and therapy gene into an adenovirus that localizes to the liver. The combination was injected into the tail vein. In one test, the reporter gene codes for herpes simplex virus thymidine kinase. F-18 labeled fluorogancyclovir was injected and, in the animals given the PET reporter probe, showed where gene expression was occurring. Excellent correlation was seen with use of the D-2 receptor gene as reporter. The product of the gene was D-2 receptor protein, and the probe was fluorethylspiferone, a potent C-2 antagonist.
- Antibodies are also under investigation as imaging agents. Antibodies have been difficult to use diagnostically and therapeutically because they are large and are broken down by the immune and enzyme systems. Researchers are cloning or synthesizing the active end of antibodies into small molecules that retain the affinity and mimic the activity of the whole antibody.
- Researchers at UCLA have labeled a "minibody" with copper-64, a long-lived positron-emitting isotope, for experiments targeting CEA in breast cancer. In a mouse model, CEA lesions are well-visualized.
- PET programs are working with the pharmaceutical industry. Dr. Phelps and colleagues have been working with Monsant to develop an imaging probe for COX-2. They have identified the molecule, labeled it, and have shown it is an excellent imaging molecule for imaging processes.
- The team is combining micro PET, micro MR, micro CTs, and fluorescent and optical imaging techniques to look at mouse models as avenues to treatment of human disease.

Image Guided Diagnosis and Therapy: Future Directions
Dr. James Anderson, Director of Radiology Research, Johns Hopkins School of Medicine

Key Points

- The impact of computer-integrated surgical and therapeutic systems and technology on medical care over the next 20 years will be just as great, if not greater, than the impact of computer-integrated manufacturing systems and technology on industry production over the past two decades.
- Dr. Anderson and colleagues began to assemble a multi-disciplinary group to work on image-guided projects about 12 years ago. The group sought to bring together university clinicians and basic scientists,

engineers, computer scientists, and industry.

- The Center received funding for an engineering research center for computer-integrated surgery systems and technology. Dr. Anderson and colleagues included in the process a graduate student teaching program to train engineers in image-guided therapy. They believe that graduate education is crucial for the long-term survival of a clinical department. The team's partners are the Massachusetts Institute of Technology, Brigham and Women's Hospital, Carnegie Mellon University, and Shady Side Hospital in Pittsburgh.
- The Center has developed a sort of medical CADCAM, or computer-aided therapy design, which the researchers are translating into computer-aided therapy practice.
- Test the idea, the center is building basic research teams to work on specific, clinically-relevant problems. Each team includes researchers, surgeons, industry, a clinician, an engineer, and students.
- Currently, research is taking place in three areas:
- Modeling and analysis - Development of technologies or devices that provide an interface between the virtual reality world created with the models and the practical world of the operating room, e.g., robotic components.
- System integration - The Center is focusing on development of generic technologies so that any innovation can be applied to multiple areas. For example, the teams are interested in translating techniques useful in brachytherapy for the prostate, head and neck, and areas in the liver. The challenge is to create a patient-specific model. The center's goal is to make it possible for a patient to come in during the morning for a non-invasive study and provide the physician that evening with a three-dimensional reconstruction of the crucial anatomy and practice a simulation approach. The next day, when the patient comes back for therapy, the physician will be able to use the model to guide the therapeutic approach.The center has two different simulation systems. One under development is a cardiovascular interventional system, and the other is a neurosurgical system that has already had some clinical evaluation in surgical separation of Siamese twins.
- Surgical robots - Starting with the basic design of RoboDoc, the center has developed five different components.
    - One RoboDoc device is used for orthopedic surgery. The goal is to be able to use CT images to outline the optimal size of the opening that has to be made in the femur for the fitting of the prosthetic device.
    - Much of that same technology is translated into a smaller robotic device called Steady Hands Surgery. This device, an engineering system to reduce the tremor associated with hand motion, is used ophthalmology and microvascular surgery. Using the device, the team has been able to reduce the tremor from about 80 microns down to about 20.
    - Another device currently being evaluated clinically in initial stages is a small PACI system, or a percutaneous entry device, that allows for precise needle placement using fluoroscopy guidance. This has been used successfully to access renal calyx, and now it is being extended into the biliary system for interventional techniques here. This robotic device has a remote center of motion.
    - The Center is also developing new miniature MR probes. These are transcatheter-type coil devices, to allow the researchers to begin seeing from within the body and guide external devices, whether they be percutaneous or transcutaneous, more accurately. The devices are being used in the vascular system, and are under development for the urogenital system. They are under consideration for the prostate.

CASE STUDIES

Case studies addressed critical medical problems and technology challenge. After each medical case presentation, panelists representing expertise from imaging, clinical oncology, FDA, HCFA, and NEMA discussed their approaches and perspectives. In the technology section, panelists discussed what they saw as the critical issues in imaging, regulatory areas, and reimbursement and coverage for PET and other techniques.

Case Study #1
Pre-Invasive and Invasive Prostate Cancer
Moderator: Dr. Peter Scardino, Chief, Urology Service, and Head, Prostate Cancer Program, Memorial Sloan-Kettering Cancer Center

Panelists: Dr. Susan Alpert, Director of Device Evaluation, Center for Devices and Radiological Health, FDA; Dr. Grant Bagley, Director of Coverage and Analysis Group, Office of Clinical Standards and Quality, HCFA; Dr. Anthony D'Amico, Assistant Professor of Radiation Oncology, Harvard Medical School; Dr. Bruce Hillman, Professor and Chair of Radiology, University of Virginia; Dr. Patrick Loehrer, Professor of Medicine, University of Indiana; Dr. Patricia Love, Director, Division of Medical Imaging and Radiopharmaceutical Drug Products, Center for Drug Evaluation and Research, FDA; Mr. Thomas Miller, President and CEO, Carl Zeiss, Inc.; Dr. Sarah Nelson, Associate Professor of Radiology and Engineering, University of California-San Francisco; Dr. Derek Raghavan, Professor of Medicine, University of Southern California

Key Points

- An American man age 75 has a 42 percent chance of having cancer cells in his prostate. The lifetime risk of developing the disease is around 10 percent, and the lifetime risk of dying of the disease is about 3 percent. The risk for African-American men is higher than for Caucasians
- Useful tools exist to increase the precision of diagnosis. These include the PSA test, biopsy, the Gleason grade measure of tumor development, and description of the clinical stage, or size, of the tumor.
- Still, prostate cancer presents the clinician with quandaries. One of the biggest challenges is that neither rising PSA, the presence of cancer cells on biopsy nor Gleason grade may indicate definitively the presence of lethal disease. Imaging, while an important technique when combined with the others, may not clearly define areas of malignancy.
- Given the uncertainties in current approaches to prostate cancer, the panel's comments indicate that the clinician's training and judgment, combined with test results, are perhaps the most important contributors to a diagnosis and selection of treatment. Similarly, the type of treatment a patient receives may depend on which institution treats him and the expertise and preferences of the clinicians there.
- One challenge in diagnosis is the fact that rising PSAs are common, but only one of four patients biopsied receives results that are positive for presence of cancerous cells. Therefore, a significant question for urologists is how to treat men who have elevated PSAs, but negative biopsies. Intense monitoring of all such patients nationwide may be economically undesirable. Many patients' PSA may rise significantly, perhaps from 23 to 300, yet they will remain asymptomatic, have a normal bone scan and not die, and lead happy, productive lives. Rising PSA following successful radical prostatectomy is a common occurrence.
- Another challenge is that cancerous cells found on biopsy may indicate the presence of clinically insignificant disease, but also may represent a small cancer that has the properties that will

eventually kill the patient.

- Some patients have a superb technical pelvic dissection, with clear margins, no extension, no nodal involvement, and still develop disseminated disease in a relatively short period of time.
- If a cancer of sufficient size exists, each biopsy session has about a 70 percent chance of identifying it. However, for prostate cancers in general, biopsies miss tumors at a rate estimated as high as 50 percent.
- Randomized trials have shown unequivocally that mammography saves lives, but that has not been shown in any randomized trials for prostate screening. Also, there are no data that show that early intervention with cytotoxic chemotherapy or PSA decreases in response to early chemotherapy confer a survival benefit.
- Nevertheless, trends in the literature are providing a more definitive picture of the factors that may lead to better diagnosis, treatment, and prognosis. Volume is significant. Several retrospective studies in the literature suggest that large prostate gland volumes are a favorable prognostic factor when and if you find or diagnose a prostate cancer. Several studies indicate PSA may rise about 0.7 millimeters per year in the presence of benign prostatic hyperplasia without malignancy. A slow-rising PSA suggests that, if cancer is present, it may be slow-growing enough so the patient will die with the disease, rather than of it, decades after the first tests take place. Spectroscopy significantly improves the diagnosis of extracapsular extension by MRI. It is important to know the status of lymph nodes before management is planned. One major prognostic factor is the PSA level at the time of treatment. The higher that PSA is, the less likely one is to sustain an undetectable PSA beyond five years from radiation treatment. Studies demonstrate that there is high variability in how clinicians interpret the significance of extracapsular extension.
- Development of optical imaging to aid prostate diagnosis is desirable and possible.
- Prostate surgery holds the potential for damaging nerve tissue and compromising a patient's chances of recovering sexual function. Thus, imaging is needed that will determine not only where the tumor is, but exactly where the patient's normal structures are.
- Over-testing can create anxious patients.
- The American College of Radiology Imaging Network (ACRIN), a NCI clinical trials cooperative group is sponsoring studies of old and new technology. The network is interested in studies that aim to assess efficacy and safety and well as appropriateness for payment.

Case Study #2
Positron Emission Tomography in the Staging of Cancer
Moderator: Dr. E. James Potchen, Chairperson, Department of Radiology, Michigan State University

Panelists: Dr. Susan Alpert, Director of Device Evaluation, Center for Devices and Radiological Health, FDA; Dr. Jane Axelrad, Associate Director for Policy, Center for Drugs, FDA; Dr. R. Edward Coleman, Director of Nuclear Medicine, Vice Chairman, Department of Radiology, Duke University; Dr. Jeffrey Kang, Director of Clinical Standards and Quality, HCFA; Dr. Patricia Love, Director of Medical Imaging, FDA; Dr. W. Fred Lucas, President, Lucas Medical Associates, Inc.; Dr. Michael Phelps, Chair of Molecular and Medical Pharmacology, Director, Crump Institute for Biological Imaging, Associate Director, Laboratory of Structural Biology and Molecular Medicine, University of California, Los Angeles; Dr. Barry Siegel, Director of Nuclear Medicine, Mallinckrodt Institute of Radiology

Key Points

- Society has yet to decide what insurers', industry's or payers' responsibilities are towards clinical research and the diffusion of technology. The Medicare program was constructed 30 years ago as a way of paying for delivery of services. Should HCFA pay for the development and subsequent diffusion of technology? Can HCFA more easily accommodate "exceptions" to its reimbursement rules?
- Although the idea has been proposed that reimbursing agencies determine how much they might pay should a certain technology be developed, assigning dollar values to innovation and outcomes is troubling from a public policy standpoint. It is difficult to do because it may pose a threat to income. Panelists agree, however, it is important to have clear criteria for coverage.
- In the case of PET, the technology was developed at the time skepticism was appearing in the literature about the value of MRI. Thus, PET was held to a higher standard. It lacked a well-defined sponsor, having been developed as a research tool in university settings, and lacked data that could quickly show safety and effectiveness. Panelists commented that promising technologies need strong sponsors early in their development.
- Reimbursing agencies are interested in the incremental value a technology might add. When MRI came along, it was compared to plain film. Because PET was a late entrant, it faced the question of what its incremental value was over CT and/or MRI. If PET had come along 10 or 15 years ago before CT or MRI, the comparison would have been reversed. Thus, the timing of technology development is important and separate from the issue of science.
- Every imaging company in nuclear medicine has a PET program now. The number of these companies has grown from about four six years ago to 17.
- Even though sales have increased, at best this year there will probably be 100,000 studies done in PET worldwide. That compares to 100 million diagnostic imaging studies worldwide.
- New probes are needed. However, companies are fearful about investing in the development of probes for many reasons, including concern about long-term prospects for any such product and current preferences among some clinicians for FDG.
- If imaging technology is to advance, all the stakeholders must participate in the process.

SUMMARY/DISCUSSION OF FORUM ISSUES
Dr. Michael Vannier, Professor and Chair of Radiology, University of Iowa
Dr. R. Edward Coleman, Director of Nuclear Medicine and Vice Chairman, Department of Radiology, Duke
University

Key Points

- Imaging has the potential to revolutionize cancer medicine. However, imaging today has some important limitations.
- It lacks sufficient precision, detail, and accuracy to deliver on its promises.
- A number of barriers exist. These are in areas of regulation and reimbursement; they also result from limitations of investment capital and access to capital. Another major barrier is in the area of risk. Industry manages and balances risk with potential reward in a variety of ways; however, sometimes the balance is unfavorable. High-risk ventures are still possible, but they will need external stimulus to take place.

- The flow of funds that industry receives through the medical imaging market that delivers services to patients is highly influenced by HCFA.
- Early CT and MR product development was done offshore because the U.S. environment was less conducive to the work. The introduction of new modalities is perhaps even less attractive today. Anything new must surpass existing technologies, and many of the existing modalities are very good. The Balanced Budget Act has put many academic medical centers into financial crisis.
- The National Institute of Science and Technology, which is part of the Department of Commerce, has an advanced technology program that funds only high-risk projects.
- The FDA's approach to development and approval of orphan products may be adaptable to imaging for certain technologies. The FDA's orphan drugs program has had a tremendous positive effect in making products and drugs available for diseases and conditions which otherwise would not have treatments available because of the unfavorable economics.

WORKSHOP SESSION SUMMARIES

- Workshop participants broke into four groups to discuss biomedical opportunities/challenges, technology development/ challenges, regulatory concerns, and reimbursement issues. One goal the discussants had was to define areas their own organizations could help to influence. Another was to consider ways to align priorities among the various entities that must come together to advance the development and application of new imaging technologies in oncology.
- For Groups 1 and 2 (biomedical and technology), questions to consider included how opportunities and challenges are identified; what the strengths and weaknesses are in the current process of identification; how the process might be improved; and what the opportunities and challenges are to date.
- For Groups 3 and 4 (regulation and reimbursement), the questions to consider included what the process for making decisions is; what the critical issues are; whether the process is clear to outside players; what the strengths and weaknesses of the process are; and how the process might be improved.
- Each of the groups was also asked to consider issues of integration and how to create a continuum for the entire process.

Group 1: Biomedical Opportunities/Challenges
Chairs: Richard Wahl, M.D., Professor of Internal Medicine and Radiology, University of Michigan
Gerald Knudson, President and CEO, eRAD

Panelists: Susan Arbuck, NCI; Philip Drew, Concord Consulting Group; David Goldenberg, Garden State Cancer Center; Bruce Hillman, University of Richmond Health Sciences Center; John Hoffman, NCI; W. Fred Lucas, Lucas Medical Associates, Inc.; Thomas Meade, California Institute of Technology; Anne Menkens, NCI; Nakissa Sandrich, NCI

The group agreed that imaging has many potential uses in cancer research as well as diagnosis and treatment, and that improvement is needed in cancer therapy. Members developed recommendations that could help lay the groundwork for new discussions and research projects in the field of imaging.

Observations

Imaging could address many questions in oncology. These include:

- Whether cancer or pre-cancerous lesions are present.
- Whether cancer is localized or disseminated.
- What is the stage of the cancer?
- What do researchers want to image? At what resolution?
- How can imaging therapy be used to predict a response to treatment? To predict treatment pharmacokinetics? Potential toxicity?
- Can imaging agents be developed that target well enough to localize the tumors and can be used to treat the tumors at higher doses? (Agents to explore include targeted radionuclides as well as non-radiopharmaceutical approaches)
- What techniques and imaging agents would be most useable for detection of smaller lesions? For deep viewing or superficial structures? Is the NIH set up to review imaging studies?
- How can NIH, including NCI, FDA, and HCFA work in a more coordinated way?

Biomedical Recommendations

- An ongoing interaction between cell biologists, oncologists, and imaging specialists to identify and agree upon targets to be assessed, as well as imaging agents appropriate for specific situations.
- More interactions between imaging scientists and cell biologists in developing research and clinical implementation programs.
- Conduct more evaluation of existing technologies, such as PET. Conduct further research to determine more fully the meaning of data and signals from these technologies.
- Include imaging studies in the development of new cancer therapies.
- Continuing feedback to ensure what's being measured is important and that it is relevant to treating and predicting outcome.
- An NCI publication to disseminate findings on such issues as response criteria.

Policy Recommendations

- Consider changing regulations to allow for Phase I trials of agents not intended for pharmaceutical use and even at lower doses than drugs for treatment. Determine if the toxicological approach to evaluation of new chemical entities is appropriate (many in group feel barriers still too high).
- At NIH, inter-disciplinary review and a greater cancer focus in imaging study sections might be appropriate.

Biomedical and Policy Recommendations

- Regular follow-up to ensure progress towards goals is achieved.
- Evaluate institutional reward systems: Will they allow those within to break down barriers to communication and alignment of goals?
- Agency sections should prioritize their most important goals and projects.
- Thinking in a more long-term way.

- Include physicians and surgeons in the discussion/education process.
- Encourage development of consensus on use of imaging methods in clinical practice and in research

Group 2: Technology Development/Challenges
Chairs: James E. Potchen, M.D., Department of Radiology, Michigan State University
Claude Benchimol, General Manager, Global X-Ray Engineering, General Electric Medical Systems

Panelists: Thomas Budinger, University of California at Berkeley; Laurence Clarke, NCI; Carol Dahl, NCI; Brian Harvey, FDA; Horace Hines, ADAC Laboratories; Leon Kaufman, Toshiba America MRI, Inc.; R.K. Leedham, FDA; Patricia Love, FDA; Sarah Nelson, University of California at San Francisco; Timothy Ochran, US Oncology; Alan Penn, Alan Penn & Associates; Mike Tesic, Fischer Imaging; Kirby Vosburgh, G.E. Research and Development Center; Irving Weinberg, PEM Technologies Inc.

The working group reviewed issues that will be crucial as medicine, government, and industry interact to expand the field of imaging. Members recognized that technology development is a complex process. Recommendations suggest that discussions about technology development include diverse representatives.

Observations

- Technology development is driven by "pull" and "push" processes: Pull when there is a medical need, push when entrepreneurial thinkers have an idea and develop it. Each converge toward same goal and outcome--bringing technology to market--but in early stages they are different and may need to be treated differently.
- No one group has critical mass in resources, coordination, and information.

Recommendations

- NCI should be a catalyst for change by facilitating a process to integrate all stakeholders, government institutions, academia, and industry. NCI could also help develop a process through which new ideas would be validated as worth pursuing.
- Consider more teams in which people from diverse communities and multi-disciplinary groups work together to build more out of the parts they contribute than would come from individual grants.
- Consider naming a primary contractor to serve as program manager of all the institutions contributing to imaging research and discussions.
- Support FDA in its consideration of a program for new technology development. FDA could adapt some of the ideas that already exist in the orphan drug program.
- Encourage HCFA to think of itself as an investment organization as well as reimbursement agency.
- Promote continuing education. All levels of continuing education need to be kept up to speed with technological advances.
- Focus on ways to attract people to careers in technology.
- Communicate with payers, providers, and employers to encourage them to support research.

GROUP 3: REGULATORY CONCERNS

Chairs: Susan Alpert, M.D., Director of Device Evaluations, Center for Devices and Radiological Health, FDA

Mr. Morgan Nields, Chairman and CEO, Fischer Imaging Corporation

Panelists: Jane Axelrad, FDA; Michael Barber, G.E. Medical Systems; Anna Chacko, Brooke Army Medical Center; Barbara Croft, NCI; Florence Houn, FDA; Jennifer Keppler, ICP; Martin Lipton, University of Chicago; Thomas Miller, Carl Zeiss, Inc.; Judith Murphy, Nycomed Amersham; Robert Samec, Vital Images; Judith Murphy, Nycomed Amersham; Robert Samec, Vital Images, Inc.; Barry Siegel, Washington University; Michael Vannier, University of Iowa College of Medicine

The working group reviewed current regulatory processes and developed recommendations for better interaction between medicine, government, and industry. Members recognized a need to look into regulatory and business climates in other countries.

Observations

- The FDA process is working reasonably well. The area of difficulty is in the area of innovative drugs and devices.
- The politics affect the process.
- Initially, some meeting participants believed that research and development work was going offshore because the U.S. FDA process is too difficult. However, there may be a number of reasons. One may be that the European model focuses on safety, rather than on safety and effectiveness as in the U.S. Another may involve various advantages to doing particular sets of business in different environments, including Japan.

Recommendations

- Look into reasons for offshore research and development.
- Create a scientific body to work with regulatory agencies early to define regulatory pathways new devices or drugs may follow when NCI is requesting studies on them. Also, scientific involvement early in the process may help the FDA move products through pipeline to advisory panel level.
- More workshops and discussions are needed. Include agency representatives in these.
- A better understanding of the potential for reimbursement might encourage product innovation. Government agencies need to stay educated on technology developments.
- Explore opportunities to include U.S. and European third parties in research and development.
- Consider assessing risk differently for different populations depending on their disease status and the duration of an imaging agent's use; consider assessing risk differently for agents used in less-than-pharmaceutical doses.
- Include venture capital community in the discussion; show potential backers the opportunity for investment.

GROUP 4: REIMBURSEMENT ISSUES

Chairs: Jeffrey Kang, M.D., Director of Clinical Standards and Quality, HCFA
Mr. Stephen Whisenhut, Global Sales Manager, Oncology, Picker International, Inc.

Panelists: Leslie Alexandre, NCI; Robert Bree, University of Michigan Medical Center; Mitchell Burken, HCFA; R. Edward Coleman, Duke University; Terry Douglass, CTI, Inc.; David Feigal, FDA; Norman LaFrance, Bracco and Princeton; Richard Levy, Varian Medical Systems, Inc.; Mary McCabe, NCI; Michael Phelps, University of California at Los Angeles; Barry Siegel, Mallinckrodt Institute of Radiology; Ruth Tesar, PET Net and Institute Clin PET Peter Valk, Northern California PET Imaging Center

The working group reviewed the critical issues in reimbursement from medical, business, and government perspectives. Members agreed that clarification of HCFA's reimbursement and approval process procedures is needed. HCFA is exploring the idea of conditional coverage.

Observations

- HCFA is working with FDA so that trial design can include requirements of both organizations when necessary.
- HCFA is considering the idea of conditional coverage as a way to reach a binding agreement with stakeholders that a product will be covered if it meets certain endpoints.
- HCFA recognizes the need to be explicit about expectations.
- The agency suggests that the earlier stakeholders work together in a development process, the sooner coverage decisions can be made. In the case of the decision last fall to cover transmyocardial revascularization using laser, HCFA's decision came only 30 days after FDA approval.

Recommendations

- HCFA provide explicit coverage criteria to industry and the clinical community.
- Consider a two-tiered system, with new product development as one tier and standard approval process the other. In the development process, consider allowing industry and investors to have a greater proportion of control over what gets into pipeline.
- Explore further the idea of conditional coverage.
- Clarify the issue of national versus local coverage; sometimes when something approved nationally, there is dispute at local levels over whether it should be reimbursed.
- Further explore the possibility of combining FDA and HCFA procedures in certain cases to expedite decision process.
- In discussions, include everybody at the table, including private organizations.

Floaters: Robert Britain, NEMA; Ellen Feigal, NCI; Richard Klausner, NCI; Edward Staab, NCI; Daniel Sullivan, NCI; Robert Wittes, NCI

SUMMARY
Michael Vannier, M.D., Professor and Chair, Radiology, University of Iowa
R. Edward Coleman, M.D., Director of Nuclear Medicine and Vice Chairman, Department of Radiology, Duke
University

Key Points

- The existing technology development system begins with scientific advances, adds government support, attracts investment capital, and delivers new technologies that can be applied to cancer.
- No one body "owns" the process. But, if all parties worked together they would have enough impact to surmount problems that delay development and delivery of innovation.
- Emphasis should be placed on interfaces between entities interested in imaging and communications among them.

CLOSING REMARKS
Robert Wittes, M.D., Director, DCTD and Deputy Director for Extramural Sciences, NCI

Key Points

- Participants in the conference agreed a highly interactive process is needed, one that will include the major stakeholders and allow them to interact in a way that they have never interacted before.
- Stakeholders need to decide what to do when a promising new technology comes along that the nation needs, and no one group can develop it alone. One question is how companies participating in such an effort might share pre-competitive information freely and function interactively when they might be competitors in other areas.
- NCI has a history of relationships with pharmaceutical and device companies that can help in any sharing necessary.
- NCI can play an important coordinating role in the advancement of imaging not only through research but by serving as a convener and as an organizer. NCI can work with industry through trade associations. NCI is committed to these roles.

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