

MEETING SUMMARY

SECOND NATIONAL FORUM AND WORKSHOP ON BIOMEDICAL IMAGING IN ONCOLOGY

September 14-15, 2000

Alexandria, Virginia

The Second National Forum and Workshop on Biomedical Imaging in Oncology convened imaging technology developers in academia and industry and key government agencies involved in funding, regulating, or reimbursing technology. They were invited to continue to develop a synergy created at last year's meeting to adapt advances in basic science and imaging technology to oncology. Speakers focused on the topics of molecular probes and imaging agents, new imaging technologies for the detection of lung cancer and breast cancer, and challenges for investment in such technologies.

OPENING WELCOME, PURPOSE OF FORUM, INTERVAL UPDATE ON ACTION ITEMS FROM FIRST NATIONAL FORUM AND WORKSHOP ON BIOMEDICAL IMAGING IN ONCOLOGY

Ellen Feigal, M.D., Deputy Director, Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI)

In opening the Second National Forum on Biomedical Imaging in Oncology, Dr. Ellen Feigal indicated that:

- The forum is part of an ongoing process with the theme of sharing perspectives, working collaboratively across disciplines, and across agencies to bring emerging technologies from discovery to the marketplace.
- The translation of the scientific and technology revolution into medical practice requires active collaboration across multiple disciplines and active coordination between multiple agencies.
- Science is advancing at a very rapid pace and we are discovering underlying biologic, physiologic, and molecular processes in cancer development and in metastasis. How can imaging extract this functional information at the cellular level?
- Some of the issues raised at the Forum last year included: how can we align technology development decisions with clinical and biomedical needs and opportunity? Can we clarify the product development pathways? How can we reduce and share the business risks? How do we achieve real alignment of priorities and decision making processes by the major participants and players in imaging technology development?
- What have we done about these issues? As a result of the First Forum, the Interagency Council on Biomedical Imaging in Oncology (ICBIO), a multi-agency group designed to serve as a sounding board for investigators and manufacturers attempting to take emerging medical imaging technology to the marketplace, was created. The ICBIO meetings are confidential, and include

staff from the National Cancer Institute (NCI), the Food and Drug Administration (FDA) and the Health Care Financing Administration (HCFA). Eighteen proposals were received and three companies presented at the July 20, 2000 ICBIO meeting. The next due date for proposals is October 9, 2000 for the second ICBIO meeting on November 20, 2000. We expect to hold 3 to 4 meetings per year.

- The second action taken was the creation of the Development of Clinical Imaging Drugs and Enhancers (DCIDE) program to expedite and facilitate the development of promising imaging enhancers and molecular probes and their translation from the lab to proof of principle clinical trials. The first proposals to utilize the NCI program's resources arrived this month.
- The third action taken, although started well before the first meeting, was the release of the FDA's Guidance for Developing Medical Imaging Drugs and Biological Products in June with the comment period ending September 29, 2000.
- The NCI has worked on the fourth issue, the development of a rigorously designed digital mammography screening trial with the NCI-supported American College of Radiology Imaging Network, four competing device manufacturers, the Center for Devices and Radiological Health at the FDA, and HCFA. The trial is slated to begin in the fall.
- The FDA and NCI are working together with the NCI-funded Breast Cancer Surveillance Consortium investigators to evaluate new technology and provide population based information on the performance of breast cancer screening in the community.
- The sixth issue that investigators, the NCI, and FDA are developing together is a clinical trial evaluating spiral CT in lung cancer screening. The trial is expected to begin within the coming year.

FUTURE DIRECTIONS IN IMAGING

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

Key Points

- The NCI is increasingly interested in the problem of how one goes from knowledge to products. The products are broadly defined as biological advances to benefit people.
- Since the 1950s, the NCI has moved the treatment and prevention of cancer in people ahead by funding drug discovery and development. Over the last few years, imaging has become a special area that we think can revolutionize the practice of cancer medicine. How can we help make this a reality?
- Up until recently, investigators have evaluated tumor markers one at a time. Microarrays enable scientists to analyze the expression of thousands of genes in tumors and in normal tissues thereby opening a new vision for what a molecular marker is. There is reason to believe that most of the important things that one wants to know as a clinician about the behavior of a tumor is encoded in the information from microarrays.
- Within the next 10 to 20 years we can imagine using the radiology suite in clinical facilities to read this information to improve patient care and clinical decision making.
- It is possible to imagine a new way of discovering, developing, and clinically testing

interventions, delineating pathways, and identifying targets, but it is impossible to examine how this can happen in the best way without molecular imaging technology.

- Molecular imaging would improve knowledge about drug access to tumor cells, optimal dose selection, tumor characterization, and the effect of drugs on a tumor.
- Currently, the results of the interventions of a phase III randomized , controlled clinical trial have an uncertain extrapolation to populations and an even more uncertain extrapolation to the individual since eligibility is determined in broad terms and usually without much reference to tumor characteristics. When physicians are confronted by a patient about whether he or she may benefit from a trial, a physician tries to match the patient's criteria with the eligibility criteria in the trial and provides a probabilistic estimate that he or she will respond or not. Our hope is that molecular imaging will improve our ability to more precisely estimate which patients will respond or not.
- Phase III trials are conducted fairly late in drug development, but what about the initial testing of interventions in people? The assessment of target modulation in early clinical trials is important to the NCI. Relevant questions to be considered include: is the target inhibited by an agent that has been selected against a target? is the target inhibited? and does the affect on the target correlate with physiological effects on the cancer? is the target therapeutic or preventive? We're currently limited by the lack of appropriate assays, and by the need to do invasive biopsies when the assays are available. Our hope is that molecular imaging will circumvent these limitations, and the implications for clinical medicine are enormous.
- What is needed to put all this in place? We need drug discovery against credentialed targets, better animal models to work these drugs up and a more expeditious development of lead components to the clinic to ask questions related to the tumor, not merely the host. We need in vivo cellular and molecular imaging to image these processes in vivo and in real time.
- The creation of imaging probe libraries and restructuring of early clinical trials are keys to improving in vivo cellular and molecular imaging.
- The non-scientific issues of long range goals, market size, and the question of transdisciplinary discovery and development and alignment of priorities among the partners (academia, industry, funding agencies, regulatory agencies, healthcare providers, payers and consumers) need to be discussed at this meeting as well.
- Funding agencies such as the NCI are looking to reduce risks for high impact areas of very high risks and support technology with high impact.
- The big question today is can we align our various priorities in a manner that would really expedite the flow of new imaging technology into the research and clinical arenas?

NCI INITIATIVES

Daniel Sullivan, M.D., Associate Director, Biomedical Imaging Program (BIP), DCTD, NCI

Key Points

NCI has a long range interest in molecular imaging, but remains interested in morphologic imaging, in image-guided procedures and therapy, and in informatics and interpretation of images. We have many

initiatives and cooperative relationships with industry in the area of imaging..

For questions about general relationships between industry and the NCI, contact: Drs. Carol Dahl and Leslie Alexander, NCI Office of Technology and Industry Relations, <http://otir.nci.nih.gov/otir/> or Dr. Larry Clark, Biomedical Imaging Program, DCTD, NCI, <http://cancer.gov/bip/> .

Some 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 [<http://cancer.gov/bip/NCI-DIPinisumm.htm#a13>].
- A program announcement entitled "Innovative Technologies for the Molecular Analysis of Cancer: Phase Innovation Award" is available to small businesses, academia, and industry [<http://cancer.gov/bip/NIH-NCIinisumm.htm#a1>].
- A program announcement entitled Development of Novel Imaging Technologies (Phased Innovation Award is available to small businesses, academia, and industry [<http://www.nci.nih.gov/bip/NCI-DIPinisumm.htm#a12>].
- The Small Business Innovative Research (SBIR) program is available for small businesses [<http://cancer.gov/bip/industry.htm>].
- Development of Clinical Imaging Drugs and Enhancers (DCIDE) - A competitive program to expedite and facilitate the development of promising investigational imaging enhancers (contrast agents) or molecular probes from the laboratory to IND status [<http://cancer.gov/bip/dcide.htm>].
- Small Animal Imaging Research Programs combine funding for technology development for small animal imaging, and for oncology research using small animal imaging [<http://cancer.gov/bip/sairp.htm>].
- In vivo Cellular and Molecular Imaging Centers - The ICMIC grants will facilitate interaction among scientists from a variety of fields to conduct multidisciplinary research on cellular and molecular imaging related to cancer [<http://cancer.gov/bip/ICMICs.htm>].
- American College of Radiology Imaging Network (ACRIN) is an NCI-sponsored Cooperative Group that was established to perform multi-institutional clinical trials in diagnostic imaging related to cancer [<http://www.acrin.org>].
- Bioengineering research grants and Bioengineering Research Partnerships support teams of researchers focused on bioengineering development [<http://cancer.gov/bip/NCI-DIPini.htm#indus>].

OVERVIEW OF MOLECULAR PROBES AND IMAGING AGENTS

Ralph Weissleder, M.D., Ph.D., Associate Professor of Radiology, Harvard Medical School, Massachusetts General Hospital

Key Points

- In traditional anatomic imaging, the imaging information relies on physical parameters - on absorptions, scattering, and magnetic properties of tissues. In molecular imaging, the information resides in the specific molecules being imaged.
- Molecular imaging allows us to assess signaling pathways important in tumor development. Imaging may allow us to detect these pathways, before we are able to detect the tumor mass, and also allow us to assess during treatment whether specific therapeutic drugs attack their intended signaling pathways.
- How will we look at these pathways? We'll need chemistry to make the probes and drugs, and we'll require novel imaging sensing systems. We'll need to make a paradigm shift in our thinking for what is required for conventional non-specific contrast agents that we currently use in magnetic resonance imaging and computerized tomography (CT) to what is required for molecular imaging, otherwise known as the smart or the sensing agents.
- The fundamental difference between molecular imaging agents and the conventional ones are that the molecular imaging agents change their properties when they hit a target or sense a target.
- NCI is funding research on molecular imaging agents, and Dr. Weissleder noted a few examples.. The research involved protease sensitive near infrared fluorescence imaging probes. Initially this contrast agent is invisible until it interacts with its target and becomes fluorescent. Animal studies reveal that this Cathepsin B specific agent can detect tumors as small as two micrometers.
- Another NCI-funded research project involved a probe that is sensitive for Cathepsin D, another class of protease. The protease was cleaved specifically by one tumor, and allowed investigators to read out a protease profile within a tumor. The first matrix metalloproteinase (MMP) sensitive imaging probe gets activated by MMPs implicated in angiogenesis and tumor formation of metastases. The animal studies in fibrosarcomas, which are highly MMP-2 expressing tumors, showed nearly complete suppression of enzyme activity within two days of treatment with an MMP-2 inhibitor. This enzyme suppression occurs months before actual tumor shrinkage.
- These molecular probes can image other disease processes, such as rheumatoid arthritis.
- The utilization of libraries and library technologies for developing imaging agents are fundamental in the development of novel molecular probes.
- The imaging community needs to rethink the way imaging drugs are developed since there are currently 10,000 targets that can potentially be read out on a lympho chip or on other gene expression arrays and it could potentially take ten years for ten targets to develop imaging drugs.
- As an example, Dr. Weissleder noted that they have on average developed one or two magnetic drugs per year, but within the past few months have generated a library of 104,000 compounds, 40 of which are undergoing further testing. New imaging and detection tools are required, and there is particular interest in the area of optical imaging technologies.
- The driving forces of development of molecular imaging are the need for early detection of disease and the need for biomarkers for objective treatment assessment and determining whether a given target is present in a heterogenous patient population even before you initiate treatment.
- The imaging agent community and industry, including the device industry, which have typically operated in separate fields, must work together in order to move molecular probes and contrast agents into the clinic.

TUMOR ANGIOGENESIS OVERVIEW AND MANDATES FOR IMAGING

William Li, M.D., President and Medical Director, The Angiogenesis Foundation

Key Points

- Solid tumors must recruit their own private blood supply to grow beyond a few millimeters in diameter. Angiogenesis is the growth of new blood vessels. Anti-angiogenic therapy is an emerging new strategy to treat cancer, not by destroying cancer cells directly, but rather by attacking the blood supply of tumors and depriving their circulation.
- This new focus on tumor vasculature is leading to new paradigms for drug development in oncology and new requirements to image and evaluate tumors at the microvascular level.
- Over the past 30 years we have come to understand the molecular and cellular cascade of events involved in angiogenesis. Now, a large body of clinical evidence also exists concerning the role of angiogenesis in human cancer. For example, the density of microvessels within tumors correlates inversely to survival in patients with breast, brain, prostate, lung, colon, and other cancers.
- The first specific anti-angiogenesis agent, TNP-470, entered human clinical trials in 1992. In 1994, a case study of the first complete remission of a metastatic cancer of the cervix following 18 weeks of TNP-570 was reported in the New England Journal of Medicine. These and other types of individual responses to various anti-angiogenic agents offered an early clinical proof of concept and provoked strong interest in the biotech and pharmaceutical sectors to develop anti-angiogenic drugs for cancer.
- There are more than 200 biotechnology medical device genomics in every major pharmaceutical company around the world engaged in angiogenesis research and development.
- More than 6,000 cancer patients worldwide have been treated with one of the 52 distinct anti-angiogenesis drugs.
- Despite this momentum, major challenges exist because there are no best practices yet established for assessing efficacy of anti-angiogenesis agents and no uniformity or standards in clinical imaging protocols. The lack of imaging standards is especially concerning as all players are confronting new paradigm shifts associated with anti-angiogenic and cytostatic therapies.
- Oncology care for the past 30 years has focused on cytotoxic therapy, in which one looks for a direct attack of the drug on the tumor, and hence, a decrease in tumor size. In contrast, anti-angiogenesis and cytostatic therapies attack vascular endothelial cells, and restrict tumor growth. The therapy may stabilize disease, suppress residual tumor and metastases and/or be combined with standard chemotherapy and radiation. There is potential for the patient to be on chronic, lifelong anti-angiogenic therapy to suppress recurrence and metastases. Imaging the tumor mass alone is insufficient for evaluating the effects of these agents.
- Can we image specific features of angiogenesis? Investigators at an NCI-sponsored angiogenesis workshop concluded that the microcirculation of tumors and the effect of anti-vascular agents may be assessed through imaging by a number of key parameters such as microvessel density, tissue metabolism, tumor blood flow or velocity, vascular permeability, and tumor blood volume. Additionally there are a number of molecular targets such as endothelial cell receptors,, cell surface markers, growth factors, gene expression, and other molecular determinants paving the

way for specific imaging of angiogenesis.

- These experts also concluded that MRI, CT, ultrasound, positron emission tomography (PET), and optical imaging modalities are capable, with refinement of technique, of capturing specific parameters of tumor angiogenesis.
- Angiogenesis imaging impacts on entire oncology therapy pathway, including endpoint selection, surrogate markers, and monitoring activity/response. Discoveries that have led cancer biologists to think about tumor blood vessels as a new control point and treatment are now leading the imaging community towards critical new opportunities to detect, image, and evaluate angiogenesis for drug development and monitoring in a highly promising new era of cancer therapies.

COMPUTERIZED TOMOGRAPHY/MAGNETIC RESONANCE IMAGING

King Li, M.D. Associate Professor of Radiology, Stanford University School of Medicine

Key points

- Can CT or MRI actually assess angiogenesis in vivo? The technique of dynamic contrast enhanced CT involves injecting a contrast material and then following tissue and vascular contrast enhancement over time, developing mathematical models for the contrast enhancement and trying to develop measurable parameters.
- CT quantification can be derived using semi quantitative parameters (peak tissue enhancement, enhancement rate, time-to-peak tissue enhancement, area of tissue enhancement curve) and absolute physiologic parameters (perfusion, blood volume, mean transit time, and capillary permeability)
- There are no published studies directly correlating CT measurements with accepted "indicators" of angiogenesis or assessing the changes in CT measurements following anti-angiogenesis therapy.
- Magnetic Resonance Imaging (MRI) is a more versatile technique than CT
- Overall, results so far with MRI have been inconclusive.
- Before incorporating imaging tests into clinical trials, pre-clinical validation is needed. with the imaging modality proposed for the clinical trials.
- Molecular MRI contrast agents add increased capability for MRI, and should be rapidly advanced to approval for clinical use.

ULTRASOUND

Samuel A. Wickline, M.D., Professor of Medicine, Adjunct Professor of Physics and Biomedical Engineering, Co-Director, Cardiovascular Division, Co-Director, Cardiovascular Engineering Graduate Program of the Institute of Biological and Medical Engineering, Washington University School of Medicine

Key Points

- A dramatic explosion in ultrasound technologies has occurred over the past five years in relationship to the development of proprietary micro bubble contrast agents for ultrasound imaging, e.g. harmonic, pulse inversion, power Doppler harmonic, and intermittent pulsing with bubble destruction and refilling. LevovistT, OptisonT, DefinityT, and SonovueT are contrast agents currently in the market.
- Imaging derived parameters from contrast ultrasound involve the intra-tumoral and feeder vessel morphology as well as the regional parametric distribution of velocity, relative blood volume, and relative volume flow.
- Advantages of bubble contrast ultrasound include the fact that it is inexpensive and can be easily incorporated into clinical management with real time results. Disadvantages are that you can't use it in lung, brain, GI tract and bone, areas that ultrasound can't image well. Microbubbles have questionable utility for specific epitope targeting, but studies are in place to overcome this limitation using nongaseous a nanoparticle emulsion. This is a two-phase system containing a perfluorocarbon in the middle wrapped up in a lipid membrane, which can conjugate a variety of binding ligands.
- Specific targeting of fibrin imaging and tissue factor are examples of 'molecular imaging' without ultrasound that provide proof of concept for angiogenesis imaging by targeting epitopes such as vascular cell integrins.

NUCLEAR MEDICINE/POSITRON EMISSION TOMOGRAPHY

Francis Blankenberg, M.D., Assistant Professor of Radiology and Pediatrics, Department of Pediatric Radiology, Stanford University Medical Center

Key Points

- When one talks about the revolution in biology, one is talking about molecules and receptors. Nuclear medicine and PET scanning can exploit the role of receptor imaging for anti-angiogenesis therapies. Receptor imaging is an extremely powerful technique, and one that is also safe and flexible. There are physical attributes that receptors need to have. A large number (10,000 to 50,000 sites per cell) of high affinity (1×10^{-8} and 1×10^{-10} molar) binding sites, that are selectively expressed during the biologic process of interest and present throughout the target tissue, are necessary for receptor imaging.
- Both favorable biodistribution and radionuclide characteristics are desirable with receptor imaging.
- The use of validated tracers to image flow, metabolism, blood volume, and permeability is recommended for the short term.
- For the long term, the recommendation is to evaluate and validate new approaches to monitoring effects of anti-angiogenesis drugs. We recommend supporting the infrastructure in order to accelerate the development of Fluorine labeling of proteins for PET. An alternative approach is to increase production facilities for other positron emitters with more favorable labeling chemistries,

such as I-124, Tech-94 and C-11.

OPTICAL TECHNOLOGIES

Jerry Williams, Sc.D., Professor of Oncology - Radiological Sciences, Johns Hopkins University

Key Points

- There are multiple ways of using multiple wavelengths of the electromagnetic spectrum in optical imaging. Covered three specific examples of optical imaging using 1) passive infrared imaging illustrated with Kaposi's sarcoma, 2) semi-active infrared imaging in xenograft tumors, and 3) molecular imaging spectroscopy looking at an example of photoacoustics spectroscopy.
- Thermal emission imaging is used to evaluate lesions by displaying changes and sample radiants produced by heating or in some cases cooling the temperature of a lesion. With a very simple assay, one could compare lesions and different images to detect small changes in certain positions within the tumor.
- Semi-active infrared imaging can be used to quantify blood volume in xenograft tumors.
- Photo acoustics spectroscopy uses a light pulse with high intensity and short duration to determine the specific molecular characteristic of a target, e.g. photo acoustic spectra of hemoglobin and oxygenated hemoglobin.
- Optical imaging has the potential to complement other imaging modalities.
- The development of laparoscopic and endoscopic procedures, together with computer assisted inter-tissue robotic positioning should increase the application of optical imaging in clinical medicine.

ROUNDTABLE ON ANGIOGENESIS: CLINICAL, SCIENTIFIC, AND REGULATORY ISSUES

Chair: Adrian Nunn, Ph.D., Senior Director, Chemical and Biological Evaluation, Bracco Research, USA

Panelists: Francis Blankenberg, M.D., Assistant Professor of Radiology and Pediatrics, Department of Pediatric Radiology, Stanford University Medical Center; Patricia Keegan, Deputy Director, Division of Clinical Trial Design and Analysis, Center for Biologics Evaluation and Research, FDA; Greg Lanza, M.D., Ph.D., Professor, Cardiovascular Division, Washington University School of Medicine; King Li, M.D., Associate Professor of Radiology, Stanford University School of Medicine; Patricia Love, M.D., Director, Division of Medical Imaging and Radiopharmaceutical Products, Center for Drug Evaluation and Research (CDER), FDA; Samuel Wickline, Professor of Medicine, Washington University School of Medicine; Jerry Williams, Sc.D., Professor of Oncology - Radiological Sciences, Johns Hopkins University

Science - Perfusion

Given the fact that tumor blood flow is heterogeneous in both time and space and the fact that perfusion

imaging of pro-angiogenic therapies failed to show any changes in clinical trials, is the panel optimistic that perfusion imaging is a reasonable means of measuring the effects of angiogenesis? Are surrogate measures of perfusion such as microvessel density or vascular permeability any better?

- It is too early to make a determination. We need to look at measurable parameters, use different imaging modalities, and validate it against indicators of angiogenesis. Perhaps functional genomics should be performed to evaluate perfusion and evaluate gene patterns. There might be something missing in the correlated measures that are currently being evaluated.
- Results from studies in cardiac perfusion with ultrasound agents indicate a relative measure of flow, but whether this is indicative of what happens in tumor vasculature is unknown.
- This opens up other questions such as how many different modalities can we do in comparison? what technology best characterizes or predicts the outcome?

Since perfusion is so erratic in tumors, is a long input function (e.g., slow clearance from the blood) of a targeted imaging agent desirable to smooth out temporal variability?

- One potential advantage of targeting is that the accumulation and integration of label over time helps overcome the moment to moment fluctuations
- The accumulation of the background level of the contrast agent is not detectable since the dose is small.

Science - Animal Models

a) Angiogenesis is a result of a complex interplay between the tumor cells and the local vasculature of the 'host'. Does the panel think that targets located on the tumor cells or the host vasculature are more or less desirable and why?

b) Given the complex interactions what does the panel think of the relevance of preclinical animal models? Are human tumors in a host species relevant? Under what circumstances? What should be the role of the NCI in this regard?

- The host is as important as the tumor cells that are transplanted. Evaluating the vasculature versus evaluating the tumor does not have to be mutually exclusive, e.g. one can look at apoptosis and angiogenesis using alpha-v-beta-3 imaging at the same time. A combined approach allows one to better understand the interplay between components of the complex system.
- Well characterized animal models and reliable, well characterized ligands and probes are key to conducting this research. Spontaneous arising tumors are better animal models than an implanted tumor, and it was suggested that NCI make such animal resources available.
- NCI should help develop angiogenesis profiles.

Clinical - Patient Availability

There is strong competition for oncology clinical trial patients from the much larger pharmaceutical industry. Is there a place for testing experimental oncology imaging agents on patients also enrolled in experimental therapies? What role can the NCI play in this regard?

- Testing of therapies and imaging agents in the same clinical trial can be done if the investigators can clearly identify the different aspects and can sufficiently separate the effects of the therapy vs the agent. For example, an ideal setting is to study the therapeutic intervention aimed at interrupting angiogenesis along with the imaging agent designed to assess angiogenesis.

Regulatory - 'Normal' Tumors

The latest FDA draft 'Guidelines for Industry for Developing Medical Imaging Drugs and Biological Products' states in part that "functional, physiological, and biochemical assessments are designed to determine if the value of a measured variable is normal or abnormal" and as such effectively excludes any measurement of angiogenesis from this category. Does the panel agree with this?

- The correlates for clinical impact of angiogenesis, in either patient management or diagnosis, have not been obtained. Until knowledge is available, a clinical claim of efficacy based on angiogenesis perturbation alone is not prudent.
- The FDA remarked that the guidance allows flexibility, in the sense that should such information become available in the future, one could make a clinical claim based on functional or physiological measurements.
- The NCI can help by broadening the groundwork to determine if there commonalities across tumor types of a particular biologic process, e.g., identify which tumors can be grouped together, thus creating tumor profiles.

Clinical - Future Monitoring

If future anti-angiogenesis therapies are tumorstatic rather than tumoricidal, angiogenesis imaging may be used repeatedly in patient management. Would the panel predict what characteristics an angiogenesis imaging agent needs? What is the test/re-test variability? What sensitivity is required? What tox/path profile is acceptable? What about imaging times, set up, etc.?

- Sensitivity and specificity are each important. It is key to visualize the impact of an anti-angiogenesis agent very early, at a stage that predates the detection of the tumor using structural imaging.
- The technology should be affordable, and the imaging process itself reasonable in length of time
- In order to move the field of agent development forward, industry would like an indication from providers or payers that they will pay for the new technology.

Science - Role of NCI

The characterization of potential targets for imaging agents such as receptors is much more precise and detailed for the brain than for the vasculature in general. Is there a role for the NCI in generating, collecting, and publishing such data and in supplying materials?

- From the clinical and regulatory side, it would be helpful to have access to a database to speed up the investigational new drug development time.

Clinical - Gold Standards

Does the panel believe that there is a gold standard for angiogenesis imaging and if so what is it?

- Investigators are trying to do two things at once - appreciate the biology of anti-angiogenesis processes and validate imaging. The NCI needs to get involved and promote likely agents.
- The gold standard for using imaging to monitor the outcome of disease is the outcome of disease. How does an imaging agent become a surrogate for establishing the clinical effectiveness of another product? The gold standards will change depending upon the overall use of the product.

INNOVATIVE TECHNOLOGY: INVESTMENT AND COVERAGE ISSUES

Richard Levy, Ph.D., President and Chief Executive Officer, Varian Medical Systems, Inc.

Key Points

- The panel will address the journey from good science to commercialization, to getting the science out where it can do the most good for the most people.
- Can the golden age of radiological equipment, circa 1976, happen again?
- Changes that have taken place in the field of imaging over the past 25 years:
 - Change in competition for patients has moved from hospitals to integrated delivery networks and competition for insurers. Competition between technologies has changed to a competition between costs.
 - There is more technology now compared to 25 years ago.
 - Society has moved from fee-for-service when increased costs meant increased reimbursement to capitation where reimbursement is not increasing along with costs.
 - Today the role of the physician in making judgements on new technology is decreasing, while the role of the administrator is increasing.
 - Investments in the healthcare industry have decreased.
 - Funding for academic research institutions has decreased.
 - The time it took to complete the journey from a new intervention to a commercial success was short and predictable, whereas today factors are unpredictable.
- The panel intends to explore how various segments of the imaging industry and regulatory community react to challenges.

ROUNDTABLE: FROM DISCOVERY TO THE MARKETPLACE - INVESTMENT AND COVERAGE ISSUES

Chair: Richard Levy, Ph.D., President and Chief Executive Officer, Varian Medical Systems, Inc.

Panelists: Alan P. Carpenter, Jr., Ph.D., Vice President, Medical Imaging Research and Development, Dupont Pharmaceuticals; Mark J. Carvlin, Ph.D., General Partner, Mi3 Venture Capital; Gerald Knudson, Chairman and Chief Executive Officer, CombiMatrix Corporation; Bryan Luce, Ph.D., M.B. A., Chief Executive Officer, MEDTAP International, Inc.; Mark Rhoads, President and Chief Executive

Officer, PETNet Pharmaceutical Services, Inc.; Sean Tunis, M.D., M.Sc., Director, Coverage and Analysis Group, HCFA

The following questions were posed and the panelists provided their perspective:

- How do you deal with the regulatory environment?
- How do you prioritize/decide on investments in innovation?
- How do you prove efficacy and justify reimbursement?
- How do you secure a source of funding for investments in innovation?
- How do you speed up commercialization of new technologies?

Mark Rhoads

- PETNet has focused on the PET radiopharmaceutical supply issue. The FDG supply is now within 100 miles of approximately 50% of the US population and their intent is to increase this market reach to 100% over the next three years by increasing the number of sites.
- PETNet is undergoing the regulatory burden of filing a new drug application (NDA) with the FDA since it needs to move from working under the practice of pharmacy to good manufacturing practices (GMP) .
- A priority for PETNet is to develop new PET tracers that open up new organ systems that may be better than FDG in certain circumstances
- The PET community recently petitioned HCFA for broad-based coverage for PET.
- PETNet has aligned with several other PET related companies to approach pharmaceutical companies to bring PET to companies who are interested in accelerating the drug discovery process with PET.

Gerald Knudson

- CombiMatrix is a company that uses a semi-conductor C-moss chip with embedded electrodes and covered with a polymer which can hold 10,000 times more DNA in a square centimeter than a person in research can put on a glass slide.
- Currently the company has not dealt with FDA or other regulatory agencies because it produces a tool for the pharmaceutical industry.
- Government and regulatory bodies have changed. Technology development has become more costly. A key factor in decision making is time to market.
- Understanding the reimbursement process and getting all the players in concert to obtain regulatory approval are critical elements in moving innovative technology ahead.

Alan Carpenter

- Dupont Pharmaceuticals is involved in the development of imaging drugs and funds new research through internal investment.

- The two main issues that factor into the decision making process are the potential clinical and financial values and risks.
- The risks inherent in image product development are technical failure, increasing regulatory standards, lack of physician/specialists champions, slow technology development (vs. pharmaceuticals), lack of reimbursement, inadequate reimbursement, and lack of long term outcomes studies at time of launch.
- The consequences of financial matters include: make no-go decision early in development, do not pursue moderate sales opportunity products, support clinical studies to ensure market penetration is relatively rapid, and balance risk/reward.
- The future of diagnostic imaging is reliant upon peak sales potentials in the range of \$100 million, and identifying ways to expedite clinical development and regulatory review with the FDA.
- Mechanisms to conduct high quality clinical outcomes research in a reasonable time frame in collaboration with professional societies or agencies is required to expedite new technologies.

Bryan Luce

- MEDTAP engages in outcomes research to determine the cost effectiveness of quality of life research for industry and government.
- Technology is moving rapidly without adequate evaluation and decision making with respect to effectiveness.
- In the past, virtually all evaluations in terms of cost effectiveness and overall effectiveness were performed by the pharmaceutical industry.
- Institutionalized decision making at national and local levels is beginning to become evident, e.g. Blue Cross Blue Shield and managed care organizations.
- The National Institute for Clinical Efficacy in the United Kingdom was established to evaluate the evidence of clinical effectiveness and cost effectiveness of new technologies.
- Healthcare providers today base their decision making on evidence. The appropriate standards of evidence for diagnostic and imaging technologies has not been addressed. Are cost effectiveness models going to be acceptable?
- The FDA plays a dominant role in communicating the value between manufacturers and healthcare decision makers because the value/cost effectiveness message does not rely purely on clinical trial programs.
- The FDA does not allow the exchange of information about cost effectiveness between the manufacturer and healthcare decision maker, so promotion is not seen as cost effective.
- Industry must engage the FDA and healthcare decision makers in discussions regarding the standards of evidence for the imaging industry.

Mark Carvlin

- Venture capitalists (VC) want a return on their investments, so they are interested in the risk or uncertainty of the technology and length of time from out of pocket expenses until the returns

accrue.

- The first five years of a VC fund are investment and the next five years are nurturing and gathering returns.
- Cost and time are critical in the research and development phase.
- Providers can play a key role in reimbursement by demanding new technology for their patients; the cost of withholding reimbursement is just as dear as the cost of granting reimbursement.

Sean Tunis

- HCFA determines whether technology is reasonable and necessary for Medicare coverage.
- HCFA recently conducted a town hall meeting to discuss the newest rendition of the definitions for reasonable and necessary.
- Gold standard criteria for clinical effectiveness of diagnostic technologies have evolved over the past ten years.
- The key challenges for moving technologies from discovery to the marketplace are to reduce the time from FDA approval (sensitivity, specificity, +/- clinical effects) to HCFA approval (proven clinical effectiveness) and to broaden market presence.

Discussion

- Many companies are introducing technology overseas before bringing it to market in the United States (US) because of the rigorous regulatory process in the US.
- Reimbursement is considered in the research and development process, e.g. if reimbursement is not considered worthwhile, companies will decide to stop technology development in the beginning.
- A link with imaging probes and therapeutics increases the probability of success in sharing clinical value; a reduction in use of therapeutic drug is assumed when used.
- Imaging can play a major role in using healthcare resources judiciously in the future.
- Publishing reimbursement criteria is difficult because there are competing fundamental values.
- When asked why it is so difficult for HCFA to publish criteria, Dr. Tunis replied that there are many fundamental competing social values that all seem to become enmeshed in where the cut-off is set for pay or no pay. The decision is based on how much innovation is wanted and how much will be paid for what incremental improvement.

OVERVIEW ON SCREENING

Anthony Miller, M.D., Director, Clinical Epidemiology, German Cancer Research Center

Key points

- Requirements for effective screening programs include the following: valid and acceptable screening test, earlier and efficient diagnosis of the disease, minimal diagnosis of nonprogressive

disease, effective treatment of detected disease and compliance with therapy.

- Developers of screening tests try to identify the interval closest to the actual onset of detectable cancer. This may increase the likelihood of picking up very early tumors which under normal circumstances would have regressed if left undetected. Is there any evidence for this concern? A study from British Columbia strongly suggests a regression of carcinoma in situ for cervical cancer. Given this data, chances are very high that regression occurs even more for the earlier lesions that are now being detected and treated.
- If early lesions are included in analyses, sensitivity is increased and specificity is decreased. This results in a much higher proportion of disease that would have regressed in the absence of this detection.
- The Canadian National Breast Cancer Screening found that more cancer was diagnosed as a result of mammography. There was little over diagnosis, but vast early detection. Screening did not result in reduction of breast cancer mortality, but resulted in more biopsies and longer followup time.
- Improved treatment may compete with the potential benefits of screening that might occur in the absence of such treatment.
- Screening cannot solve the problem of cancer mortality and is an expensive use of healthcare resources. Its efficacy depends on the efficacy of treatment.

ROUNDTABLE: SPIRAL COMPUTERIZED TOMOGRAPHY

Chairs: William Black, Professor of Radiology and Community and Family Medicine, Dartmouth-Hitchcock Medical Center; Claudia Henschke, M.D., Ph.D., Professor of Radiology, Weill Medical College of Cornell University

Panelists: Marjorie Bowman, M.D., Chair, Department of Family Practice and Community Medicine, University of Pennsylvania Medical Center; James Cooper, M.D., Senior Geriatrics Advisor, Office of Clinical Standards and Quality, HCFA; Stanley Fox, Ph.D., General Electric; Susan Honig, M.D., Medical Reviewer, Division of Oncology Products, CDER, FDA; Edward F. Patz, Jr., M.D., Professor of Radiology, Duke University; Daniel Schultz, M.D., Director, Division of Reproductive, Abdominal, Ear, Nose and Throat and Radiological Devices, FDA

Claudia Henschke

- Lung cancer is a commonly diagnosed cancer and has a poor outcome.
- Dr. Henschke's study evaluated the value of spiral CT as a screen in detecting lung cancer in individuals at high risk to develop cancer. All subjects were screened at baseline and annually. At baseline, 23% had an abnormal CT and 12% of those were malignant. 82% of the malignancies were in stage one lung cancer. At annual repeat, 1.5 % had abnormalities on their CT which did not resolve within one month. 41% of them were malignant and 83% of the malignancies were stage 1A non-small cell carcinoma. This compares to 7% in this stage in the SEER data. Data on baseline were published and annual repeat CT screening results have been submitted for publication.

- Is screening cost effective? Preliminary analysis reveals that baseline screening costs \$2000 and is highly cost effective when compared to the standard \$50,000 per life year saved. This study did not have mortality data, and data on cure rates by stage and size will be available with further follow-up.

The following questions were posed and each panelist provided his or her perspective:

How should the cost effectiveness of screening for lung cancer with spiral CT be determined?

- Answers varied: conduct randomized, controlled trial, with the outcomes defined as reducing deaths, decreasing morbidity, improving function.
- Most of the panel felt that a controlled clinical trial with mortality as the end point was the only way to really know if a screening method was effective. However a minority of the panel strongly believes that as desirable as a controlled clinical trial may be it is not feasible. In the present climate, too many members of the control group would cross over to the readily available spiral CT. Therefore other types of studies and methods for analysis should be seriously considered.
- We cannot rely on randomized clinical trials to answer all questions related to screening, but we should use them to evaluate new and major interventions, such as screening for lung cancer with spiral CT.

Who should be targeted for screening, assuming that screening either works or we are at a point where we will eventually accept the evidence that it does?

- The role of the FDA is to determine safety and effectiveness, not the target population.
- Persons who are at highest risk for dying from lung cancer should be targeted. Where do you draw the line at risk factors?
- Another way would be to look at the people who benefit and determine their characteristics.
- Some make decisions based on the US Preventive Services Group Task Force who offer conservative, evidence based recommendations.
- A published survey of HMO medical directors revealed their decisions were based on a number of determinants, such as evidence and political factors.
- The long term payoff is for doctors to encourage behavior modifications in patients rather than to figure out how to get patients screened.
- Cost effectiveness varies among the age of the population, e.g. screening in persons 50 year old appears cost effective.

Who should perform the screening? How should the quality of screening be assessed?

- From a primary care physician perspective, screening should be widely available at a reasonable costs.
- HCFA realizes that if they decide to pay for a procedure and the profit margin is reasonable, the

procedure will become widely available, perhaps to a broader population than would truly benefit from the screen.

- The screening tests should be done at the lowest dose possible.
- Screening should take place in a multidisciplinary setting with quality standards, e.g. American College of Radiology standards.
- Screening is a complex process, one must be clear on how to perform the exam, how to interpret it, and how to manage patients with various findings

How should we inform persons or eligible people in the population about options for screening lung cancer?

- Once the FDA approves a device, it requires that the device be labeled to accurately and adequately provide the data upon which that claim was made. In some cases only the practitioner is privy to that information, but sometimes the FDA will mandate patient labeling which is written in lay terms so the patient can understand and participate in that decision as well.
- The public should be informed of the positive and negative aspects of a screening procedure.
- Physicians should be aware of existing data and know the best way to communicate, in a culturally competent way, that information to patients so options can be provided.
- The approach should be a combination of public and physician education as well as doctor/patient, verbal, and written communication.

Do you endorse CT screening outside the research setting?

- No, there is concern about incidental abnormalities with spiral CT of the chest.
- No, not until it is endorsed by the US Preventive Services Task Force.
- No, a randomized clinical trial with mortality reduction is the endpoint.
- No, data cannot be supported.
- No, no one has approached the FDA for the claim.
- Yes, overall cohort studies and case controls give more consistent results than randomized trials.
- No, further data showing mortality reduction and cost effectiveness is warranted.

Discussion

- Dr. Miller commented that a study endpoint could be obtained within five years if the trial was large and well organized since the majority of lung cancer cases die quickly, as opposed to the 15 years stated earlier by Dr. Henschke.
- Dr. Henschke was asked to comment on why the screening tests in her study were not able to detect the squamous and small cell lung cancers, those which largely result in lung cancer death. She remarked that they were not detected as prevalent cases in the initial screening tests, but were detected as incident cases in subsequent exams.. Dr. Henschke has submitted the data on incident cases for publication.

ROUNDTABLE: DIGITAL MAMMOGRAPHY

Chair: Etta Pisano, M.D., Professor of Radiology and Chief of Breast Imaging Department of Radiology, University of North Carolina, School of Medicine

Panelists: Marjorie Bowman, M.D., Chair, Department of Family Practice and Community Medicine, University of Pennsylvania Medical Center; Ronald Castellino, M.D., Chief Medical Officer, R2 Technology; Emily Conant, M.D., Associate Professor of Radiology, Hospital of the University of Pennsylvania; James Cooper, M.D., Senior Geriatrics Advisor, Office of Clinical Standards and Quality, HCFA; Susan Honig, M.D., Medical Reviewer, Division of Oncology Products, CDER, FDA; Terrence Kay, Director, Division of Practitioner and Ambulatory Care, Center for Health Plans and Providers, HCFA; Morgan Nields, Chairman and CEO, Fischer Imaging Corporation; Frederic Pla, Ph.D., Manager of Global X Ray Research, General Electric; Daniel Schultz, M.D., Director, Division of Reproductive, Abdominal, Ear, Nose and Throat and Radiological Devices, FDA

Etta Pisano

- Digital mammography has better image contrast than film screen mammography, enables the manipulation of the contrast, allows for the addition of computer aided detection, and makes transmission and retrieval easier. Digital mammography looks similar to film screen.
- The General Electric (GE) digital mammography system recently received FDA approval for hard copy display only. Fischer Imaging, Fuji Medical, and Trex Medical Systems are conducting clinical trials while Siemens and Schick have units in development.
- A Department of Defense (DOD)-funded study evaluated GE detectors in approximately 5,000 women who underwent digital and film screen mammography and resulted in equal sensitivity (but this was not statistically significant) and improved specificity (which was statistically significant) for digital mammography.
- Currently the DOD is conducting a trial in 1000 women that expands upon the results of a smaller pilot study conducted by the Office of Women's Health with 200 women who were biopsied based on mammographic or physical findings. The results showed that machine type, lesion type, and image processing method affected sensitivity.
- A screening trial funded by the NCI under the auspices of American College of Radiology Imaging Network (ACRIN) is in the final planning stages. The trial will involve 49,500 women at 20 centers who will undergo screen film and digital mammography with systems from either GE, Fuji Medical, Fischer or Trex Medical. They will evaluate effectiveness by comparing accuracy and the area under the ROC curve for digital mammography versus screen film mammography. The study will also evaluate cost effectiveness and patient outcomes.

Morgan Nields

- Digital mammography will impact on screening and diagnostic studies in rural populations and overcome some of the technical limitations because there is better image quality, film processing is not involved, and results can be transmitted to a specialist center via telemammography.

- The DOD funded a 600 patient study with two year follow-up to evaluate film screen and digital mammography in a tele mammography setting. Interim results reveal that digital had better accuracy, sensitivity, and specificity when compared to film screen.

Frederic Pla

- Digital mammography is not a technology fixed in time. Real time imaging, teleradiology, and multimodality imaging are future advanced applications of digital detected technology.
- Digital detectors offers the ability to resolve contrast to better visualize a dense breast or tissue near the skin line.
- Filmsynthesis takes a series of shots at various angles with equivalent doses as one mammogram and produces a three-dimensional image to evaluate the depth of the breast.
- Contrast medium mammography is being clinically evaluated at three centers.
- Trends in breast disease management encompass detection, characterization, and treatment, and the advanced applications can effect all three.

Ronald Castellino

- Computer aided detection (CAD) searches for features on a mammogram, such as microcalcifications or masses as evidence of cancer.
- Only one CAD system has been approved through the pre-market approval process by the FDA. Algorithms were run on 1000 screening mammograms from biopsy proven cancer cases. CAD was successful in correctly marking the location of microcalcification 99% of the time and 75% for mass lesions, yielding an overall detection rate of 84%.
- A retrospective study was conducted to evaluate false positives by collecting the results of the performance of the radiologists on the number of cases they interpreted and their recall rates in a historical fashion in 24,000 cases. A 99% detection rate for microcalcification and 86% for the detection of masses resulted in a 90% overall detection rate. As compared to the previous study, sensitivity increased and the number of false positives for examination decreased by a factor of two.
- A study of 13,000 consecutive screening mammograms over a one year period were evaluated with CAD. Detection without the input of CAD was 3.2 cancers per 1,000 patients screened and the contribution with CAD detected 3.8 cancers per 1,000 patients screened.
- The utilization of CAD in digital mammography will facilitate the implementation of full field digital mammography since information is presented in a more interpretable fashion to the radiologist.
- Approximately 800,000 women in the US have had their mammograms interpreted with assistance of CAD, which has no reimbursement.
- For every 100,000 cancer detected by screening mammography, the use of CAD could detect an additional 20,500 breast cancers.

Roundtable

- Dr. Schultz from the FDA was asked to comment on the FDA approval process, PMA vs 510K and where we stand with digital mammography. Dr. Schultz remarked that the PMA process allows manufacturers to submit their data to the FDA, to have it reviewed for safety and effectiveness in a timely fashion, and to adequately label the device so people understand the data upon which the approval was based. Given the problems with evaluating digital mammography, it was deemed that the PMA process and the latitude that it gives the FDA in terms of allowing for a claim of safety and effectiveness, as opposed to substantial equivalence, seems to be the straightest approach. With the PMA process, the FDA can evaluate each manufacturer on an individual basis. The 510K is not an option since non-substantial equivalents for a manufacturer have been determined.
- Dr. Schultz was asked to comment on soft copy and PMA. Dr. Schultz stated that the FDA envisions soft copy coming in as a supplement to the original PMA. The FDA does not see the need for large reader studies to determine whether soft copy devices can be used with digital mammography.
- Dr. Charles Finder from the FDA was asked to comment from the audience about the development of Mammography Quality Standards Act (MQSA) regulations for digital mammography. Dr. Finder revealed that there are certain regulations for initial training before using the machines. Facilities will have to follow the manufacturers' manuals in terms of the quality control they were recommending. The FDA continues to work with manufacturers during the approval process to ensure their manuals are comparable to what is already required for film screening.
- How can reimbursement get addressed for both standard and digital mammography so that costs are met?
Mr. Kay, HCFA - Congress approved coverage for screening mammography and established the payment mechanism and payment ceiling. Diagnostic mammograms fall under a different methodology and fee schedule.
- How can we afford the technology described by Mr. Nields and Dr. Pla?
Mr. Kay, HCFA - Legislation can be enacted to increase reimbursement for mammograms. It is likely that the Medicare population is a significant fraction of the mammogram patients. Payers often rely on national Medicare physician fee schedules to establish their own fee schedules. It would be helpful to obtain information on reasons for extra cost, the extra benefits, and the implications to justify increased reimbursement.
- How good does digital mammography have to be to justify increased costs?
Dr. Honig - It is important to identify the risks, benefits, and value.
Dr. Conant - Specificity is extremely important given the additional imaging, high anxiety, and false positive biopsies that women undergo. Reproducibility and networking to share images for education and consultations are other benefits not previously mentioned. Dr. Pisano noted that five centers in the US and Canada are being funded by the National Library of Medicine to participate in and develop a system for storing digital mammography images in a central facility.
Dr. Bowman - Cost should be analyzed in terms of better specificity.

Final Comments

- Dr. Pla - Reimbursement is an issue for manufacturers in addition to physicians. If we believe that new technology will benefit patients by offering increased sensitivity and specificity, then the payment system should be evaluated.
- Dr. Schultz - The FDA agrees with inherent benefits mentioned by the panelists. The FDA considers the fact that mammography plays a critical role in the healthcare of millions of US women and feel very strongly that in order to be able to bring this new technology to the market safely, critical data needs to be provided before approval can be granted.
- Nields - The big issue is that we have technology that has been proven to save lives, but we are not willing to pay for it.
- Mr. Kay - HCFA wants to assess new technology and new services as appropriate for Medicare beneficiaries. HCFA looks at cost data, sources of cost, and market availability when figuring a reasonable amount for reimbursement
- Dr. Honig - There are a number of potential benefits to digital mammography that benefit women and help physicians take better care of their patients. Data obtained from clinical trials is critical in deciding how to best use the technology to benefit the most people
- Dr. Conant - She is ready to use soft copy. The cost of the machine and lack of reimbursement inhibit her institution from purchasing the machine
- Dr. Bowman - Some screening technologies that come along are immediately taken up partially because of their major advantages. Screening technology must be widely available or it may as well not exist.
- Dr. Castellino - Early communication with the FDA during product development is essential to the PMA approval process. Today administrators base decisions on cost and whether technology will be reimbursed. Acquisition of technology today is based on cost and reimbursement and not on benefits to patient care.
- Dr. Pisano - Digital mammography is comparable to the fiberoptic scope, but will not be as popular due to reimbursement issues. The bottom line is if we don't reimburse appropriately, we will not be able to afford the technology. Digital mammography will ultimately be proven better, but problems need to be addressed now so the technology can be utilized.

WORKSHOP SESSION SUMMARIES

Workshop participants broke into three groups to discuss issues related to molecular probes and imaging agents, moving discoveries to the marketplace, and screening/detection. One goal the discussants had was to define areas their own organizations could help to influence.

Group 1: Molecular Probes, Imaging Agents

Chairs: Adrian Nunn, Ph.D., Senior Director, Chemical and Biological Evaluation, Bracco Research, USA; Ralph Weissleder, M.D., Ph.D., Associate Professor of Radiology, Harvard Medical School, Massachusetts General Hospital

Panelists: Kim Adcock, M.D., Colorado Permanente Medical Group; Francis Blankenberg, M.D., Stanford University Medical Center; Houston Baker, Ph.D., NCI; Carol Dahl, Ph.D., NCI; Gerhart Graupner, San Diego State University; Robert Hoffman, Ph.D., AntiCancer, Inc.; Richard Levenson, M.D., CRI, Inc.; King Li, M.D., Stanford University; William Li, M.D., Angiogenesis Foundation; Patricia Love, M.D., FDA; Lawrence Schott, M.D., HCFA; Vilim Simcic, Ph.D., Siemens Medical Systems; Robert Sutherland, Ph.D., Varian Biosynergy, Inc.; David Thomasson, Ph.D., Siemens Medical Systems; Samuel Wickline, Washington University School of Medicine

Observations

- Three phases of imaging exist and are categorized by increasing information, difficulty and risk. The first phase is anatomic imaging and involves tumor shrinkage. The second phase is physiologic imaging, e.g. blood pool agents. The third phase is molecular imaging which incorporates novel technologies.
- Adding an imaging arm to ongoing biological studies would lead to a better understanding of the utility of imaging.
- The Developmental Therapeutics Program at the NCI has an angiogenesis resource center on their website at <http://dtp.nci.nih.gov/>.

Clinical Recommendations

- The approval for intravascular MRI and CT contrast agents for phenotypic imaging should be encouraged.
- Manufacturers should develop validated software for phenotypic imaging.
- The NCI should act as a broker between imagers, academia, industry, and therapeutic drug sponsors in both the animal and clinical research setting.

Scientific Recommendations

- Centralized databases are key to advancing science in this field.
- The NCI should work with the FDA to develop validated model systems, both *in vitro* and *in vivo*, for angiogenesis imaging. The NCI should publicize the availability of these systems.
- The NCI should add imaging to the ongoing broad attempts to collect biological data (Director's Challenge) to allow for correlation between genomics, proteomics, histology, and imaging.

Regulatory Recommendations

- The FDA should spend more time educating academia about the regulatory process.
- The FDA needs to better publicize their guidance documents.

Group 2: Moving Discoveries to the Marketplace

Chairs: William D. McPhee, L.L.B, Managing General Partner, Medical Imaging Innovation and Investments L.P.; Sean Tunis, M.D., M.Sc., Director, Coverage and Analysis Group, HCFA (HCFA)

Panelists: Leslie Alexandre, Dr. P.H., NCI; Richard Bird, M.A., Medical Optical Imaging, Inc.; Alan Carpenter, Ph.D., DuPont Pharmaceuticals; Laurence Clarke, Ph.D., NCI; David Feigal, FDA; Jeff Garwin, M.D, Ph.D., UltraTouch Corporation; Arve Gillette, Oncology and Hematology Associates, Inc.; Melvyn Greberman, FDA; Nancy Hykel-Malone, Independence Blue Cross; Patricia Keegan, M. D., FDA; Gerald Knudson, CombiMatrix Corp.; Gregory Lanza, M.D., Ph.D., Washington University School of Medicine; R.K. Leedham, R.Ph, M.S., B.C.N.P., FDA; Richard Levy, Ph.D., Varian Medical Systems, Inc.; Carol Lowery, D.C.R.T., D.M.U., Siemens Medical Systems; Bryan Luce, Ph.D., M.B.A., MEDTAP International, Inc.; Mark Rhoads, P.E.T.Net Pharmaceutical Services, Inc.; Lawrence Schott, M.D., HCFA; Johnnie Smith, NCI; Victor Villagra, M.D., CIGNA HealthCare; Kirby Vosburgh, Ph.D., CIMIT and General Electric

The working group reviewed issues that will be crucial as technology moves from discovery to the marketplace . Members recognized that technology development is a complex process. Recommendations suggest that discussions about technology development include diverse representatives.

Observations

- The return on investment is a function of : 1) the characteristics of disease including, but not limited to prevalence and natural history, 2) features of the proposed technology in terms of benefits and risks, 3) nature of FDA requirements, 4) criteria that HCFA and other payers use to determine reimbursement and 5) a myriad of other factors such as clinician or patient demand. Another factor involved in all of these is time as it relates to technology, disease, and both FDA and HCFA approval. The greater uncertainty in all factors, the greater the uncertainty of predicted return of investment.
- When investigators move from initial research into development, launch, growth and maturity, they tend to consider FDA and HCFA implications when budgeting capital for trials. HCFA reimbursement is often times a major determinant in the viability of any return on investment and therefore any investment decision
- Information on HCFA, the Medical Coverage Advisory Committee, and Interim Guidelines on Evaluating Effectiveness, the gold standard for evaluating evidence to support a determination of clinical effectiveness, can be obtained from the HCFA website at <http://hcfa.gov> .
- Technology moves from evolution through revolution. What is the scope of change that the proposed technology or pharmaceutical is going to impose on the system?

Recommendations

- HCFA should provide explicit, detailed criteria for coverage and reimbursement. All stakeholders (patients, payers, practitioners, industry) should play a role in developing this criteria.

- Revolutionary technology needs a de novo assessment that is more difficult than assessing incremental changes in technology. Revolutionary technology, if it is to move forward, needs to have the business risks shared
- The NCI, FDA, and HCFA should come together earlier regarding the expectations and criteria for new technology and begin to integrate their approaches so the imaging community is not dealing with different paradigms.
- Industry and government should be involved in the process of determining the value of new technology. What is acceptable value for the money charged? What models do you use? Who decides?
- Joint meetings with government agencies should be held to provide information to investigators and educate the agencies on each other's procedures.

GROUP 3: Screening/Detection

Chairs: Morgan Nields, Chairman and CEO, Fischer Imaging Corporation; Etta Pisano, M.D., Professor of Radiology and Chief of Breast Imaging Department of Radiology, University of North Carolina, School of Medicine

Panelists: William Black, M.D., Dartmouth-Hitchcock Medical Center; Marjorie Bowman, M.D., University of Pennsylvania Medical Ctr.; Ronald Castellino, M.D., R2 Technology; Emily Conant, Hospital of the University of Pennsylvania; Barbara Croft, Ph.D., NCI; Sabine Duffy Siemens Medical Systems; Charles Finder, FDA; Stanley Fox, Ph.D., General Electric Medical Systems; Leonard Glassman, M.D., Washington Radiology Association P.C.; Claudia Henschke, M.D., Ph.D., Weill Medical College of Cornell University; Marek Kimmel, Rice University; Anthony Miller, M.D., German Cancer Research Center; Richard Miller, Ph.D., Radiological Society of North America; Alan Penn, Ph.D., Alan Penn and Associates, Inc; Robert Phillips, M.D., FDA; Frederic Pla, Ph.D., General Electric Medical Systems; Patrick Quarles, CombiMatrix, Inc.; Jaime Quinn, M.P.H., NCI; Joanne Scott-Santos, Siemens Medical Systems; Robert Philips, FDA

Observations

- The number of radiologists in the breast imaging field is decreasing while the volume of work is expected to increase. A survey of radiology department chairs about costs and salary concluded that a negative \$100,000 existed per 1 FTE radiologist involved in breast imaging.
- The costs for screening mammography today are not being met. Is the solution decreasing the costs per study or increasing reimbursement?
- Improved reimbursement is probably a better approach than increasing radiologist salaries to meet true costs.
- Predictions are that access to breast imaging will decline and mammography services will decrease.
- Digital mammography may increase the caseload, but not decrease the work burden for radiologists.
- The rate of false positives increases when films are viewed longer.
- With the objective of improving digital film interpretation, the Biomedical Imaging Program

(BIP) at the NCI recently released a program announcement on digital mammography display.

- Various study designs for screening exist, however methodologic flaws exist for most of them.
- Molecular genetic findings should be considered in our screening approaches
- There is room for methodological research in screening. ACRIN is sponsoring methodological research by trying to replicate results achieved through large trials through reader studies
- Delving into HCFA coverage issues with CT colonography may provide a better understanding of the HCFA approval process for screening/detection technology.
- Screening should focus on who is at higher risk to begin with and who has the most potential value.
- The NCI has biological samples readily available for research, ie: Breast Cancer SPORES.
- The loss of insurance coverage, unemployment, and imposed burden of a pre-existing condition may occur when persons are labeled as high risk.
- The risks to industry are high in the breast imaging field and perhaps only large companies will be the ones to get involved in future.
- The incentive for manufacturers to invest in screening/detection technology is to provide better care at the same or decreased cost.

Recommendations

- New methodology, other than huge randomized trials, for evaluating technology is warranted. Government agencies should fund research in this area.
- Funding should be increased for cost effectiveness and patient outcomes research.
- Studies should be designed to obtain information on who is at increased risk and how the technology can be used specifically for those individuals instead of studies being designed for the general population.
- The NCI should continue to fund biological specimen banks to assist with the assessment of risk and perhaps targeted screening.
- ACRIN trials should include a tissue banking component.
- The legislators and lawmakers who determine whether screening is a benefit to society, should be informed about issues related to imaging.

[2000 National Forum and Workshop on Biomedical Imaging Homepage](http://www.cancer.gov/dctd/forum/summary00)