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**Abbreviations:**

BIROW = Biomedical Imaging  
 Research Opportunities Workshop  
 FDA = Food and Drug  
 Administration  
 IGI = image-guided intervention  
 IRB = institutional review board

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## Biomedical Imaging Research Opportunities Workshop: Report and Recommendations<sup>1</sup>

*Editor's Note: The following report consists of summaries of four topical sessions and breakout group discussions conducted during the first Biomedical Imaging Research Opportunities Workshop. To reach the widest audience, the workshop organizers have asked the editors of several journals, including Radiology, to publish the report.*

### OVERVIEW OF THE WORKSHOP

The first annual Biomedical Imaging Research Opportunities Workshop (BIROW I) was held January 31–February 1, 2003 in Bethesda, Maryland. This workshop was initiated by medical, scientific, and engineering researchers and societies to identify and explore opportunities for basic science research and engineering development in biomedical imaging. This grass-roots effort sought new ideas and syntheses from leading scientists and engineers, as well as from clinicians and those involved in government funding for medical imaging. BIROW I was sponsored by ARR (Academy of Radiology Research), AAPM (American Association of Physicists in Medicine), BMES (Biomedical Engineering Society), and RSNA (Radiological Society of North America) along with thirteen other participating societies—allowing for unique interactions among investigators from various aspects of biomedical imaging research.

In addition to providing information and ideas for new, as well as experienced, investigators, the workshop aimed to support accelerated development of biomedical imaging as a scientific discipline and facilitate coordinated imaging research. The workshop included invited speakers on selected topics, breakout groups, discussion with invited government representatives, and focused white papers from the breakout sessions' recommendations. The four selected topics for BIROW I included: 1) example of imaging solutions to a multi-disease biological challenge—imaging of hypoxia; 2) extending imaging methodologies and systems across spatial scales; 3) assessment and validation of imaging methods and technologies; and 4) image-guided therapy. Additional information on the first workshop and current planning for the second workshop are posted at the website (<http://www.birow.org/>).

BIROW I consisted of plenary sessions on each of the four topics addressed, followed by two sessions of breakout groups on each of the topics. In plenary sessions, responses and comments were made by leaders in government funding agencies and, finally, recommendations of the breakout groups were reported and discussed. A most riveting discussion was led by the dinner speaker, Elias Zerhouni, MD, Director of the National Institutes of Health. Dr. Zerhouni challenged the participants to approach problems using the concept of team science indicating the benefits of cross talk between the disciplines. One example given was that of the use of CT in the microscopic imaging of tissue—using similar theory and techniques developed for CT in the imaging of human anatomy.

During the day, poster sessions were offered on each of the four topics, as well as on research that might suggest topics for the next BIROW. Inclusion of posters was undertaken to provide a vehicle for young investigators and others to explain their ideas in some detail. It was hoped and later felt that this would aid the search for new ideas and improve dissemination of the workshop discussions and consensuses to new investigators who might profit most from them. Abstracts of those posters are being published in *Academic Radiology*.

During and immediately after the meeting, topical session chairs and breakout group leaders drafted white papers to summarize the state of the art and research opportunities

on their topics. It was planned that development, evaluation and wide dissemination of white papers for each of the topic areas would provide an unusual opportunity to stimulate thought and activity in a wide segment of medical imaging and related communities. Those white papers follow this introduction.

There have been numerous recent meetings and plenary lectures at major medical imaging meetings about progress, challenges, and funding opportunities in medical imaging, or a related specialty area. Similarly there have been several NIH workshops and meetings on opportunities and priorities, usually in some specific area of problem or opportunity that is believed to deserve special attention and research. BIROW was designed to focus groups of experts on several moderately specific research topics, much as in a grouping of NIH workshops. Several topics were covered in breakout groups with experts on those topics, and the topics were introduced and results summarized and discussed among all participants, informing and drawing from experts on the various topics.

In each of the initial topical plenary sessions, three invited leaders in that field summarized the state of the art, as well as their thoughts on outstanding research opportunities. The topics, session chairs, speakers and breakout group leaders were as follows:

Topic I: Example of Imaging Solutions to Multi-Disease Biological Challenge—Imaging of Hypoxia. Session Chair: Michael J. Welch, PhD, Washington University; Breakout Group Leader: Howard Halpern, MD, PhD, University of Chicago. Speakers: 1. Mark Dewhirst, DVM, PhD, Duke Univ Medical Center, Why Is Hypoxia Important? 2. Michael Welch, Techniques to Image Hypoxia; 3. Janet Eary, MD, University of Washington, Clinical Applications of Hypoxia Imaging.

Topic II: Extending Imaging Methodologies and Systems across Spatial Scales. Session Chair: Jeffrey L. Evelhoch, PhD, Pharmacia Corporation; Breakout Group Leader: Michael Vannier, MD, PhD, University of Iowa. Speakers: 1. Thomas Budinger, MD, PhD, University of California, Berkeley, Overview; 2. R. Mark Henkelman, PhD, University of Toronto, MRI; 3. Bruce Tromberg, PhD, University of California—Irvine, Optical

Topic III: Assessment and Validation of Imaging Methods and Technologies. Session Chairs: Steven E. Seltzer, MD, Philip Judy, PhD, Brigham & Women's Hospital; Breakout Group Leader: G. Scott Ga-

zelle, MD, MPH, PhD, Harvard Medical School. Speakers: 1. Kyle Myers, PhD, Department of Heath and Human Services, FSA, Quantitative System Evaluation and Optimization; 2. Bruce J. Hillman, MD, University of Virginia, Imaging Clinical Trials: Evidence Based Radiology; 3. Alicia Y. Toledano, ScD, Brown University, Objective Assessment of Imaging Methods.

Topic IV: Image-Guided Therapy. Session Chair: J. Daniel Bourland, PhD, North Carolina Baptist Hospital; Breakout Group Leader: William R. Hendee, PhD, Medical College of Wisconsin. Speakers: 1. Charles Pelizzari, PhD, University of Chicago, Image-Guided Therapy Overview; 2. Clifford Ling, PhD, Memorial Sloan-Kettering Cancer Center, Biological Imaging; 3. Krishna Kandarpa, MD, PhD, Catheter-Based Intervention

The four topics were chosen to interest a diverse range of specialists in medical imaging. Topic I was chosen as an example of potential imaging developments that target a specific molecular process, or small set thereof, which is relevant to multiple diseases. This choice was meant to focus discussion on those developments in hypoxia imaging and opportunities therein. The three presentations in plenary session made an excellent start to the entire workshop, raising awareness of the tremendous potential power of modern molecular imaging targeted at a specific physiologic process, i.e., hypoxia. It was judged that while imaging of hypoxia has been studied with radionuclide tracer techniques for many years, the goal is worthy of renewed effort because of the large potential revealed by achievements in recent years. These advances included imaging of a variety of different indicators of hypoxia using various modalities with different strengths and weaknesses. The breakout group directed the majority of its attention identifying and addressing problems that restrict advances in imaging a variety of the molecular processes which can be targeted for treatment, including not only hypoxia, but also intracellular pH, thiol level, angiogenesis, apoptosis, and various antigen concentrations, gene expressions, receptor and enzyme concentrations. Key challenges identified included lack of biological target/process validation, need for improved quantification of imaging parameters, limited understanding of interrelationships of multiple biologic parameters, need for validation of image fusion techniques, inappropriate and perhaps inadequate IRB and FDA approval processes for new imaging devices

and biologic probes, inadequate manpower, need for resources and priorities in translational research, and need for hypothesis-driven preclinical and clinical studies. Five practical recommendations were made, e.g., establishment of standard testing paradigms for multidisease biological problems and establishment of a central repository of imaging data.

"Imaging Modalities across Spatial Scales" was chosen as the second topic as a means of stimulating exploration of the generalization of the advances resulting from recent developments of mouse imaging for basic biology studies, as well as diagnosis and assessment of therapies, all using genetic and other molecular probes and agents. The stimulating exercise of translating the great advances made over the past decades in human organ imaging to the scale of the mouse has helped reveal new creative avenues for present and future medical imaging. Working changes in scale in the other direction, e.g., adapting optical (microscopy) imaging to the *in vivo* mouse, has demonstrated great possibilities for minimally invasive imaging in the human. Methods and examples for generalizations across changes in scale have been developed in several branches of engineering and science. Directions for such generalizations in medical imaging were outlined by the breakout group. Scale was taken to refer not only to spatial scale, but also ranges of many other parameters such as temporal resolution and biological, chemical, diagnostic, and therapeutic science and applications. Organized classification of the ranges of multidimensional scales over which various individual modalities and combinations thereof can contribute as well as ranges of needs and possible developments might be a particularly inviting initial goal.

By far the greatest cost of medical imaging science and technology is in assessment of clinical efficacy and cost effectiveness. The finding of scientifically meaningful and efficient methods of validating imaging equipment prior to and during animal and clinical trials is thus an extremely high priority and was BIROW Topic III. "Technology assessment" was perceived differently by various researchers depending on the stage in the development chain. Thus, a systems approach to this most multidisciplinary undertaking was addressed quite productively. While the determination of physical image quality indices is well studied, the relationships of such indices to ultimate performance and outcome are unclear

and challenging. The need for development and wide dissemination of analytic methods specific to the assessment and validation of imaging technologies—both at the early phase and the clinical trial phase—was noted. In addition, the breakout group noted a need to identify and validate surrogate endpoints to help to improve assessment efforts and make trials more efficient. The role and importance of modeling and simulation were also discussed as means to identify critical information to be acquired in future trials as well as identify potential performance targets or short-term outcomes. The need for understanding the correct requirements for assessment of imaging systems, as distinct from such requirements for assessing drugs and other treatments, was stressed here as in most of the other topic discussions. Lastly, the importance of training investigators in techniques for conducting rigorous assessments of imaging technologies—both at the early validation stage as well as the clinical stage—is crucial. One suggested approach included the involvement of clinical investigators and imaging experts in the process of setting priorities for research funding and program development as they relate to medical imaging and its assessment.

It was believed by the BIROW organizers that image-guided therapy would be the area of medical imaging in which the exciting developments of highly specific microscopic and molecular imaging would be realized most strongly and rapidly. The treatment of this issue as BIROW Topic IV met the high expectations. Image-guided interventions (IGIs) include imaging of the medical problem, delivery and/or activation of the treatment, and monitoring of the treatment. A systems approach to the design, development, evaluation, and implementation of techniques for image-guided intervention was outlined. This system approach would involve a team of scientists, engineers, and physicians as well as preclinical studies with animal models. The identification and verification of the treatment region (i.e., the target and its relevant boundaries) is a large challenge for various image-guided interventions leading to the need for improved methods such as those for pathological verification, the fusion of anatomic and functional images, and the assessment of tissue response. Image-guided robotic methods and advanced percutaneous catheter-directed procedures are only a few challenges for IGI.

Similarities among the four breakout

groups' recommendations included the need for better education and training as well as a need for improved methods for technology and performance assessment, resources for infrastructure, and data sharing.

The four topics and other issues were discussed by government representatives, including: Roderic I. Pettigrew, MD, PhD (Director, NIBIB), Daniel C. Sullivan, MD (Associate Director, Diagnostic Imaging Program, DCTD, NCI) Richard Swaja, PhD (NIBIB, Senior Advisor for Biomedical Engineering), Col Kenneth Bertram, MD, PhD (Director, Congressionally Directed Medical Research Programs, DOD), Peter T. Kirchner, MD (for Medical Science Division, DOE [temporarily at NIBIB]). Dr. Pettigrew chaired the session. Dr. Sullivan outlined the large range of funding mechanisms and initiatives available in biomedical imaging from NCI, with emphasis on newer initiatives. Under his direction, NCI's Biomedical Imaging Program has become the largest and most diverse source of imaging research support at NIH. NCI will still remain a leading developer and supporter of biomedical imaging research, but imaging research that is not directed to a specific disease or body part will typically be directed toward the new NIBIB. Dr. Swaja, outlined the very rapid development of imaging research at NIBIB, including development of several significant workshops and initiatives, some in the areas of this workshop. Research training grants will be a significant activity for some time, as requested by all of the breakout groups. Col. Bertram noted that CDMRP, DOD is focused more on a cure than on general science and the funding mechanisms include an unusual but generally successful, strong involvement of consumer advocates. The surprisingly large support of biomedical imaging science by the Department of Energy was reviewed by Dr. Kirchner. Emphasis was initially on peacetime uses of atomic energy and has continued to evolve, often with support of efforts much larger than typical NIH ROI awards.

The four BIROW topics were chosen to bring together researchers in medical imaging, including basic scientists, engineers and physicians. Assuming BIROW continues as a series of annual workshops for more than a few years, the topics in any workshop might well be narrowed and, perhaps, chosen to be more closely related to allow for further scientific depth as well as input from outside the medical imaging community.

The organization of BIROW by a wide consortium of medical, scientific and engineering societies strongly involved in medical imaging should help assure its continuation as a dynamic undertaking. The workshops should offer insights from a wide range of the best minds available, including, but not limited to the most recognized NIH advisors. The organization consists of a representative group of sponsoring societies to direct the workshop planning and meeting arrangements. A larger group of societies provided members of the program committee as well as a number of key workshop participants and announcement of the meetings and their results. Strong input and support is provided by representatives from NIH and other government agencies with particular contributions to and support of medical imaging research. The workshop was supported financially in part by grant 1 R13 EB000859-01 from the National Institute of Biomedical Imaging and Bioengineering (NIBIB) with contributions from the National Institute of Child Health and Human Development. The American Association of Physicists in Medicine and the Radiological Society of North America assumed the main financial support and responsibility, and the participating societies committed financial support to their representatives' travel.

Speaking for the BIROW I Executive Committee and sponsoring organizations were: Paul L. Carson, PhD, AAPM, Executive Committee Chair; Maryellen Giger, PhD, Program Committee Chair; C. Leon Partain, MD, PhD, RSNA; N. Reed Dunnick, MD, ARR; John Linehan, PhD, BMES; Philip Alderson, MD, ARR.

BIROW I Program Committee Members were: Maryellen Giger, PhD, AAPM, 2003 Program Committee Chair; G. Scott Gazelle, MD, PhD, RSNA, 2004 Program Committee Chair.

Members of the Executive Committee (one representative from each additional participating society and NIH Institute) were: John Boone, PhD, SPIE; Dan Bourland, PhD; Laurence Clarke, PhD, NCI; Robert Edelman, MD, ISMRM; Jeffrey L. Evelhoch, PhD, ISMRM; Isaac Francis, MD, ARRS; Gary Fullerton, PhD; Philip F. Judy, PhD, MIPS; Krishna Kandarpa, MD, PhD, SIR; Etta Pisano, MD, AUR; Richard Swaja, PhD, NIBIB; Michael Vannier, MD, IEEE; Michael J. Welch, PhD, SNM.

The steady management of BIROW I by Angela Keyser and her AAPM staff, was critical to the success of this first intersociety workshop. Contributions

from the RSNA staff also were essential. BIROW II will be managed by the RSNA with support from the AAPM and the other sponsoring societies. BIROW II will be organized by C. Leon Partain, MD, PhD, and Program Chairman, G. Scott Gazelle, MD, PhD. It is planned that BIROW III will be organized by the Biomedical Engineering Society.

**EXAMPLE OF IMAGING SOLUTIONS TO MULTI-DISEASE BIOLOGICAL CHALLENGE—IMAGING OF HYPOXIA: MICHAEL J. WELCH, HOWARD HALPERN, KAREN KURDZIEL**

**Background**

In recent years the number of methods of treating disease that targets specific molecular processes increased significantly. As a result, the need to evaluate response to these treatments is also increasing. Imaging technologies can meet this need by providing an *in vivo* window into the cellular and subcellular mechanisms involved. Many targets have been identified that are important in many diseases. These targets include, but are not limited to: imaging hypoxia, imaging intracellular pH, imaging thiol level, imaging angiogenesis, imaging apoptosis, imaging gene expression, imaging various levels of receptor concentration and enzyme concentration as well as other parameters such as antigen concentration. Various imaging techniques have been evaluated to image these parameters including: MRI, MRS, Electron Paramagnetic Resonance Imaging (EPRI), nuclear (both single photon and positron emitters) and optical techniques. Hypoxia was presented as an example of an imaging target. The relevance of hypoxia in various diseases including: cancer, heart disease, stroke, diabetes and infection was presented.

**Key Challenges in Imaging Complex Biological Systems**

**1. Lack of biological target/process validation.** Several different methods may be used to target a single biological process, but the resultant parameters are not always equivalent. More simply, we do not always know that we are imaging the process we think we are imaging. For example, an  $O_2$ -sensitive electrode gives an actual  $pO_2$  reading, whereas PET imaging of CuATSM retention reflects the number of reductions of  $Cu^{2+}$  to  $Cu^{1+}$  in the tissue. While this parameter is related to  $pO_2$  it may be affected by other mech-

anisms/interactions within the system. Other techniques are being developed to image hypoxia. These include MRI, EPRI and optical techniques among others. For example, quantitative EPRI provides an image of actual  $pO_2$  values. This, in turn can be checked against localized electrode measurements. It is important to evaluate these various techniques in a well-controlled model. Therefore, the hypoxia image by PET Cu-ATSM may differ from a quantitative  $pO_2$  image. In order to understand a biological process, the processes affecting the measured parameters must be understood, as well as quantified.

**2. Need for quantitative approaches to imaging parameters.** Although some imaging modalities produce quantitative data, data that can be calibrated, others provide relative or descriptive data. Parameters that cannot be compared between imaging sessions and among subjects are of limited value for interrogating complex systems. New modalities that provide quantitative data are needed. Where quantitative data are available, new mathematical approaches to modeling the complex biological systems in terms of these parameters must be developed.

**3. Lack of understanding of the interrelationships of multiple biologic parameters.** Each imaging method/probe contributes unique data describing the biological system. While there may be some overlap of information, many times the data will be complementary. Expanding on the quantitative approaches developed in number 2 above, there is a need to identify and describe the interrelationships among the parameters obtained (i.e., the effect of hypoxia, metabolism and perfusion on expression of multidrug resistance, the effect of hypoxia and pH on wound healing, etc.).

**4. Need for validation of image fusion techniques for different modalities.** Versatile, robust registration software algorithms that give predictable, consistent results are needed to provide accurate spatial fusion between images that may not share a significant amount of mutual pixel information. The anatomical resolution of imaging methods varies greatly, making image fusion challenging. In general, "intensity/counts-based" modalities (PET, SPECT. . .) show significant "bleeding" of pixel information when counts in an area are high; areas of activity can appear larger than the anatomical area that is represented. Conversely anatomical regions that are smaller than the resolution of the imag-

ing method may be represented by less intensity than is actually present due to partial volume averaging. Various different techniques may be useful for imaging the same parameter. For example, a region of hypoxia could be identified utilizing PET, SPECT, MRI or EPRI and changes over a short time frame monitored by optical techniques. It is, therefore, important to have validated fusion techniques for these various technologies.

**5. Institutional review board (IRB) and the Food and Drug Administration (FDA) approval of new biologic probes and devices is complex and slow.** Currently, the FDA approval process for new imaging agents is similar to that for new therapeutic agents. Therapeutic agents are commonly administered at concentrations just below their maximum tolerated dose (MTD) in order to achieve optimal effects, whereas the optimal concentration of an imaging agent is defined by optimizing image contrast or target-to-background ratios. This difference is particularly problematic with imaging probes that are administered at tracer concentrations (ng or  $\mu$ g). The synthesis of sufficient quantities of tracer to determine an MTD can cost several hundred thousand dollars. In addition, the endpoints for imaging clinical trials differ from traditional therapeutic trials. Most IRBs treat imaging trials as if they were therapeutic trials and do not understand that the endpoints are not how many complete, partial and non-responders there are, but the ability of the imaging method to predict these numbers.

**6. Inadequate manpower and resources to develop and evaluate new agents and imaging techniques.** In the last decade, significant advances in our understanding of the molecular basis of disease have been made. The development of target specific imaging methods/probes is essential for real-time visualization of complex biological systems. Due to this rapid expansion of the field, the number of trained individuals to design new imaging agents to evaluate these agents in cellular and animal models as well as to translate the laboratory discoveries to patient population is highly limited. Trained individuals in all of these areas are needed.

**7. Need for resources and priorities for translational research.** The number of centers with the equipment and resources to develop and evaluate molecular imaging agents is few. Resources are

needed to expand the opportunities in this area.

The clinical application of basic science advances is slow. Due to regulatory and intellectual property issues, as well as the small potential market for new imaging agents, there are too few investigators working to translate imaging probes and methods to the clinics. There are too few investigators that have the training to bridge the gap between basic science and clinical medicine.

**8. Need for hypothesis driven pre-clinical and clinical studies.** Currently, new imaging methods (MR sequences, dynamic imaging) on conventional imaging equipment are used clinically despite the fact that no pre-clinical or clinical studies of efficacy were performed. FDA approval of an imaging modality says nothing about clinical efficacy. In order to provide the best clinical care for our patients, new imaging methods/probes should undergo pre-clinical and clinical studies to demonstrate that they are valid and efficacious.

### Recommendations for Addressing the Issues

**A. Establish standard testing paradigms for the major complex multidisease biological problems (i.e., hypoxia, multidrug resistance, angiogenesis, apoptosis, proliferation).** This step would support growth in imaging research and set the stage for understanding the interrelationships of multiple biological parameters. One example is the development of a well characterized mouse model (known genotype/phenotype). This model, for example might develop tumors in which the level of hypoxia is proportional to a measurable parameter (e.g., tumor size). The change in either oxygenation or the volume of hypoxia might be reproducible in the face of a defined perturbation (e.g., carbogen breathing or administration of a vasoconstrictive substance) and in which other related measurable parameters (i.e., blood flow, genetic expression of hypoxia/angiogenic markers, necrotic/apoptotic fraction) have been characterized. Key here is the assignment of a set of specific animal models and measurement conditions which researchers would use for cross validation.

Another standard testing paradigm that would advance the development and translation of new imaging probes is a standard "interspecies metabolism comparison" model. This model may be composed of a combination of *in vitro*, *in*

*in vivo*, and mathematical modeling that results in the accurate prediction of the distribution and target affinity of an agent in various species. This would allow early identification, based on data from mouse models, of imaging agents that would have an unacceptable distribution in humans.

**B. Establish a central repository of imaging data.** This concept is a unique and essential component of our recommendations. A central repository of imaging data will allow for assessment of physiological and method variability as well as provide a means to assess the variability among different imaging methods/probes and facilitate the discovery of interactions, show gaps, and promote collaboration among investigators.

Once the models described in (A) above have been developed, they should be held by NIH (to prevent intellectual property issues) and made available to researchers to be used in the evaluation of new imaging methods/probe on the condition that the data (once peer reviewed) be submitted to an NIH-established imaging parameter database. The information in this database would likewise be available to researchers, thus forming the platform on which a study of the interrelationships of imaging parameters is made.

The NCI currently gives investigators access to various mouse models through the Mouse Modelers of Human Cancer Consortium (MMHCC) mouse repository (<http://web.ncifcrf.gov/researchresources/mmhcc/default.asp>). The National Center for Research Resources has a similar resource The Mutant Mouse Regional Resource Center (MMRRC) (<http://www.ncrr.nih.gov/ncrrprog/cmpdir/RODENT.asp#mut>). However, these resources need to be expanded to include models of multi-disease complex biological challenges with complete physiologic characterization.

To utilize such a resource fully, we recommend the formation of collaborative groups to encourage comparison of imaging agents and methods aimed at the same biological targets. The success of imaging research will depend on the formation of interdisciplinary teams focused on a variety of projects: developing new instrumentation, improving existing instrumentation, designing new imaging probes, establishing and characterizing animal models, quantifying imaging parameters, validating biological targets/processes, modeling biological systems using the imaging parameters, integrating parameters and validating

the models, and finally, using these imaging parameters to improve patient care.

**C. Make basic, translational and clinical imaging research an NIH wide priority and emphasize the need to integrate of state-of-the-art imaging in areas of basic, translational and clinical research.** The NIH needs to increase funding for research in biomaterials and bioengineering to improve existing imaging technologies. The NIH needs to increase funding to develop new imaging methods/modalities/probes focusing on those that provide quantitative images of parameters that can be calibrated. Once validated, the imaging methods/probes need to be translated into clinical use. Although the FDA and IRB are part of the problem, NIH should make translational research a priority and increase funding for it. Optimizing imaging parameters is costly as well as time consuming, since research time on clinical equipment can be much longer than a standard clinical imaging slot. The data analysis often includes consideration for metabolites, probe uptake time, blood pool clearance, receptor binding/saturation, and other patient-related factors. Once some clinical efficacy is demonstrated, hypothesis-driven clinical trials need to be performed, so increased funding for clinical trials of imaging methods/probes is also needed.

**D. Promote training for new researchers and cross-disciplinary training for both new and established investigators.** At present, many training awards provide less funding than typical postdoctorate/residency salaries. The stipends on new training awards must be competitive. Imaging science has progressed to a point where interdisciplinary teams are essential, and researchers with a basic understanding of more than one of the major fields involved (medicine, biology, physics, engineering, chemistry, computer science, informatics, statistics) would be well prepared to coordinate such efforts.

**E. Work with the FDA to establish reasonable guidelines for imaging methods/probes.** Independent investigators and industry are not equipped to work with the FDA to resolve regulatory concerns. While patient safety and quality state-of-the-art medical practices are desired by all involved, many outdated and inappropriate regulations are applied to the approval process and review of studies for new imaging methods/probes. Although the FDA drafted guidelines for the development of medical imaging drugs and biological products in 2000

(see <http://www.fda.gov/cder/guidance/3646dft.pdf>), no final recommendation or implementation of these guidelines has yet been made. The NIH needs to work with the FDA to establish guidelines relevant to the potential risks and benefits of new imaging methods/probes in a timely fashion. Additionally, the NIH should provide guidelines (perhaps on a website) to which IRBs can refer when evaluating imaging protocols. The NCI has established a program, Development of Clinical Imaging Drug and Enhancers (DCIDE), that makes pre-clinical development resources available to help promising agents achieve FDA investigational new drug (IND) status. The NIH needs to make deliverables of this program available for the development of devices and non-cancer related agents. The NCI is also developing a searchable database of potentially useful imaging agents (described in the peer-reviewed literature) with information on synthesis methods, IND status, and known biological targets. Extension of this promising resource to include non-cancer related agents is recommended.

### The Future

Soon imaging will not simply provide insight into the past or present state of a biological process—imaging will predict its future state. To accomplish this, a focus on training and establishment multidisciplinary teams is required. Breakthroughs in the development of new imaging methods/probes are critical, as is the development of a quantitative groundwork for understanding the interrelationships of the physiological parameters measured. In order to implement what is learned, help with regulatory issues and increased funding and priority for translational research are needed. Imaging is no longer bound by space and time. It is evolving to an  $n$ -dimensional field and will soon provide an interactive roadmap for medical research.

### IMAGING MODALITIES ACROSS SPATIAL SCALES: MICHAEL VANNIER, JEFFREY L. EVELHOCH

Biological systems and organisms possess structure at all degrees of magnification—from molecular to whole organism and even population levels. Imaging has contributed to understanding biology using instruments based on modalities, such as x-ray, optical, radionuclides and others, that typically operate at a single

resolution or within a relatively narrow range. To delineate the current status and predict where future discoveries might be made using new imaging instruments, BIROW evaluated the state-of-the-art and defined the issues and opportunities for imaging modalities across spatial scales.

### State-of-the-Art Summary

A state-of-the-art summary of the field was given in three parts by Tom Budinger from the University of California Berkeley (overview of multiscale medical imaging), Mark Henkelman from the University of Toronto (mouse imaging), and Bruce Tromberg from the University of California Irvine (optical imaging at multiple scales).

**Multiscale Medical Imaging.** Current imaging modalities include *Magnetic Resonance Imaging (MRI)*, *Positron Emission Tomography (PET)*, *Single Photon Emission Computed Tomography (SPECT)*, *X-ray Transmission, X-ray Computed Tomography (x-ray CT)*, *Ultrasound*, *Electrical Impedance Tomography (EIT)*, *Electrical Source Imaging (ESI)*, *Magnetic Source Imaging (MSI)*, and *Laser Optical Imaging*. Each can contribute a piece from a complex puzzle, and, in general, there is little expectation that any modality will completely replace any other. Synergies are possible, and multimodality imaging has been developed in a few specific areas, most notably PET-CT. However, optimization of individual modalities has progress far more than multimodality instrumentation and methods to date.

**Mouse Imaging.** Imaging the common lab mouse motivated building the Mouse Imaging Center for Canada at the University of Toronto. This facility includes Magnetic Resonance Imaging (MRI) systems which monitor models of human disease discovered in mice, including transgenic knock-in and knock-out gene manipulated strains. Modern imaging, appropriately scaled in size, is an ideal means to characterize disease, even in mice. Osteoporosis, cancer and cardiovascular disease are targeted for early study. Since medical imaging (MRI, computer tomography and ultrasound) is by nature non-invasive, the process was scaled for mice and for some modalities (notably NOT x-ray CT) can be harmless to the mice, enabling longitudinal studies.

The results of transgenic and gene-targeting experiments are mainly analyzed using postmortem two-dimensional histological methods, making it difficult to understand underlying dynamic pro-

cesses. High-throughput phenotyping assays are an important component of detecting anomalous traits while allowing further characterization. The Mouse Imaging Centre (MICE) is a multimodality imaging resource for the characterization of mouse development and pathologies. In addition to providing high throughput phenotypic screens for targeted and random mutations, MICE has facilities for longitudinal anatomical and functional surveys at all stages of development using ultrasound biomicroscopy (UBM), magnetic resonance imaging (MRI), micro-computed tomography (micro-CT) and laser scanning confocal microscope with multiphoton excitation capability. The strategy for applying these new micro-imaging methods to elucidate structure-function relationships in mouse mutants will be presented. Future optical imaging will include multi-photon excitation microscopy, with time lapse imaging of fetuses in vitro. Small animal physiologic support and monitoring crucial to the maintenance of animal models is also being optimized for each modality to facilitate high throughput phenotyping.

**Biomedical Optics.** In this broad overview, biomedical optics was defined as the ability to develop technologies to view gene expression in single cells, use light to view remitted light signals that travel through several-centimeters-thick tissue, do high-resolution imaging of endogenous structures without exogenous probes, and add new contrast elements. Biomedical optics is both a diagnostic and a therapeutic field; diagnostics require light absorption or scattering, while therapy requires only light absorption in the tissue. Biomedical optics are effective because of fundamental light/tissue interactions, which are due, perhaps, to the unique spatial, spectral, and temporal properties of lasers (e.g., lasers beams are capable of focusing high over small spaces, and can launch light through relatively thick tissues). Translational applications of optical imaging in the brain are relatively new. One application is in using optical coherence tomography to image the three-dimensional structure of the cortex. In addition to specific applications biomedical optics allow for sophisticated probe designs, by modifying surgical instruments. Barriers to translational research include energy, distance between laboratories, and lack of funding.

The development and application of novel optical techniques for non-invasive monitoring and imaging of physiological processes in tissues and cells is

important. Photon migration, which can be used to measure the magnitude of light scattering and absorption in thick tissues at depths of several centimeters, is applied to in vivo functional imaging of breast, cervix and uterine physiology in humans. Optical microscopy can generate functional maps of molecular events in living cells, and this can be extended to in vivo applications enabled by progress in the development of smaller, more penetrable probes for biological imaging. Combining laser micro-irradiation and microscopy technologies allows one to simultaneously visualize and perturb cell physiology. This work should lead to a better understanding of the relationship between gene activation and light-induced oxidative, thermal, and mechanical stresses in cells.

### Extension across Spatial Scales

There are many levels of scale in biology: molecular, micro, organ, organism, population, where imaging can make a contribution. Spatial scales are a special case of multiscale biological phenomena that encompass molecules, single cells, tissue (histology) as observed with a surgical microscope, intensity modulated radiation therapy (IMRT) and image-guided surgery, gross anatomy of individuals, and extension to population atlases representing arbitrarily large groups of individuals.

To meet the requirements of multiple scales, new instruments and methods are needed to collect more and better data, often by applying specific molecular agents (drugs). The integration of imaging systems that accommodate multiple modalities, cooperative development of instruments with the drugs or agents that can be optimized for specific tasks, with validation of these elements early in the development phase are needed.

Given that imaging systems (instruments and drugs/agents) are available, post-processing software tools for registration and segmentation, establishment of image databases, and image analysis tools are required.

The users of multiscale imaging systems are researchers such as biologists, biomedical engineers, industry, and ultimately clinicians—internists, surgeons, oncologists (radiation, surgical, medical), radiologists, and others. The product of a multiscale imaging system may be a modality (one or a combination), a protocol, an image, a parameter (predictor, for example), a decision, a therapy or interven-

tion, but most generally a parametric map.

### State-of-the-Art

In our assessment of the imaging multiscale state-of-the-art, we encounter important questions: 1) How can we best characterize imaging modalities and methods? 2) How do we identify the imaging modality and/or method (including exogenous agents) that answers a specific biological or clinical question?

The answers to these questions are open and merit attention from developers in the field who can guide the application of multiscale imaging by a multidisciplinary team approach.

### Breakout Group Questions

This breakout group addressed two questions: 1. What are issues and challenges in biomedical imaging? 2. Which ones have highest priority? What should be done in near term and long term (5–10 years).

The groups met over 2 days and formulated a response to the questions, culminating in a set of prioritized short-term and long-term recommendations.

### Requirements—Across Spatial Scales.

Multiscale imaging is defined by its technology and range of applications, encompassing trans-species studies using multiple modalities that overcome limitations of any single modality. The principal focus is cellular and tissue microenvironments which are manifested as whole organism effects that may extend to entire populations. The structure-function relationship is investigated in the presence of biological complexity and heterogeneity. Gene and protein expression are reflected in the imaging phenotype, and linkage of corresponding changes at the molecular level to phenotypic and physiological state is fundamental to multiscale imaging. The focus of investigation may be a local phenomenon (biopsy) or extend to the whole genome using transgenic, knock-in, and knock-out constructs.

How can we translate multiscale imaging developments into practice? The strategy would be to adapt technology from medical imaging (and other disciplines) to microscopy and vice versa, further emphasizing the need for multidisciplinary teams.

The utility of multiscale imaging is as expansive as its scope, for basic science—

understanding disease mechanisms; cell biology; to clinical diagnosis & staging for selecting, tailoring and monitoring therapy.

One system—one scale is common today, where imaging instrument developers define a field-of-view as a design parameter. This imposes a limitation on the instrument's ultimate range of application in multiscale studies. An operating room microscope integrated with CT/MRI/PET scans in neurosurgery is a typical example. The surgeon works at the micro scale guided by information at that level, as well as at macro levels provided by clinical scans. There is often a need to translate from one imaging system (at one scale) to another (at another scale) so image registration across scale—in real time is required.

For any intended application, multimodality systems need optimization—and this has NOT been done to date in a rigorous manner. Multiscale systems may be useful in planning, simulating, designing and interpreting clinical trials, for example by modeling imaging system and observer performance, e.g., CT scanner population study simulation to achieve spiral CT dose, resolution, noise estimates, and sample size effects.

Sharing images and related data opens new opportunities for post-processing tool development. Nanoscale technology, including multifunctional agents (and multimodality agents) are potentially synergistic with imaging instruments, including micromachines.

Synergistic technologies for <image>: <image> registration (fusion), visualization, integration (with gene/protein expression data, pharmacodynamic, pharmacokinetic, and pharmacogenetic databases) across modalities & scales are needed. Extended software tools capable of relating individual images with populations (e.g., atlases) and comparing populations with spatial statistics are potential areas for fruitful development of new technology.

### How Are Discoveries Facilitated?

Motivation to pursue multiscale imaging is provided by clinical needs, unaddressed with current methodology—allowing investigation in vivo that correspond with underlying mechanisms in vitro. Imaging may not provide the initial discovery, but can reduce time from concept to verification. Imaging may be essential to discovery phase for identification of new chemical entities or lead compounds.

New contrast agent/radiopharmaceutical/optical probe development is essential for multiscale targeting and verification (related to mechanism of action). This complements the notion of body region optical imaging coupled to safe agents that provide new tracers for in vivo use. New image contrast mechanisms (imaging physics; biophysics; biomechanical properties) can provide tools that enable discoveries where quantitative imaging is especially valuable as metric. 2D/3D/4D data acquisition, management, analysis are important across spatial and time scales, coupled to the requisite information infrastructure.

### How Do You Measure Progress?

The impact of multiscale imaging research will be seen in pharmaceuticals—as more and better agents, reduced time to market, reduced clinical trial sample size & time requirements—and potentially a new framework for evaluating agents taking them from the laboratory through preclinical and ultimately to clinical trials. New agents for research can aid imaging, as contrast agents or labeled radiotracers, as well as for individualization of therapy. There are important potential benefits to patients: better quality of life, lower cost for medical treatment; and more therapeutic options for a broader spectrum of diseases.

The caveat to these claims is that long term support will be required to be fully realize benefits that produce a measurable impact in outcomes.

### Support Mechanisms

BIROW identified many sources of support, including traditional R01 grants that include biomedical research partnership (BRP) and biomedical engineering (BME) awards. In the recent past, the R21/R33 phased innovation award for technology development was established, with a very enthusiastic response from the imaging community.

Larger awards for Research Resources which include 5 major elements: technology research and development, collaboration, service, training, and administration have been extremely valuable for the biomedical research community, especially for unique imaging resources. Other large awards include Centers of Excellence (P20/P50), small animal imaging research program (SAIRP) and In Vivo Cellular Molecular Imaging Center (ICMIC) awards.

Other mechanisms for multi-institu-

tion network/consortia agreements, program project grants (typically for a single institution) are useful for focused collaborations.

Training awards (individual/institutional) are essential for progress in multiscale imaging. There is a need for a “New Investigator Award” tailored to attract and engage scientific societies as partners. Major professional societies can identify candidates and provide partial support for their development. However, few societies could fully equip and staff a new imaging lab for an aspiring young investigator, no matter how meritorious their work and potential.

Teams of investigators should qualify for major and minor instrumentation awards, especially to acquire unique large instruments. It is clear that state-of-the-art imaging instruments require up-front investment not otherwise available. These specialized instruments are essential for formation of interdisciplinary imaging teams needed for future science.

### Near-term Recommendations

There is a critical and immediate need to provide support to new investigators in the post-Whitaker Foundation world of biomedical imaging. That is to say, the Whitaker Foundation has lead the development of biomedical engineering training and funded the startup of new investigators, many of whom work on biomedical imaging, but this will cease in 2003 after the last round of applications is reviewed.

This field will be led by centers that can afford large equipment and instrument development costs, but without external support from government agencies and private foundations, there will be few of these essential resources. And, importantly there is a need for assistance to move investigatory drugs (imaging contrast agents and radiotracers) through FDA processes for use in a research setting.

A need for multidisciplinary cross-training is required for success in multiscale imaging, since the practical and experimental demands cross all related scientific and technical boundaries of traditional research organizations. The coalescence of multidisciplinary teams is needed, and there is strong interest in establishment of Glue grants (<http://www.nigms.nih.gov/funding/gluegrants.html>) in imaging. This mechanism is intended to provide the “glue” to bring the investigators together and to allow them to work in an interactive fashion.

### Long-term Recommendations

There will be a continuing interest and long term benefits from development of new instruments, probes, and related technologies to solve current problems and resolve important questions, e.g., islet imaging.

The imaging information infrastructure must be in place to accommodate and effectively manage increasing amounts of diverse data, supported by the development of interchange standards for data and shared open-source software tools for analysis.

Networks of experts empowered with advanced unique instruments and methods will conduct scientific investigations by forming ad hoc multidisciplinary problem-solving teams—using support provided to build infrastructure PRIOR to formulation of hypotheses. This extends the notion of glue grants a step further in response to anticipated opportunities that emerge and attract the attention of expert teams without the impediment of incremental funding and at a pace out-of-sync with traditional funding cycles.

## ASSESSMENT AND VALIDATION OF IMAGING METHODS AND TECHNOLOGIES: G. SCOTT GAZELLE, STEVEN E. SELTZER, PHILIP JUDY

### Introduction

Assessment and validation of imaging methods and technologies include activities which range from early validation and technical assessment studies (generally conducted early in the development process) to large scale, multi-institutional clinical outcome studies. The breakout session included individuals whose interests spanned the gamut of these activities. Discussion focused on summarizing the extent of the field, identifying challenges facing investigators and needs for the future, and formulating recommendations for specific initiatives which might advance the field. Additional thoughts regarding challenges and opportunities were also solicited from session attendees and are included in this summary.

### Overview

The phrase “technology assessment” clearly has very different meanings to different individuals. Many in the group came to the breakout session interested primarily in the specifics of how new technologies are initially validated, spe-

cifically in issues related to how best to set parameters for acceptable precision/variability prior to moving forward with clinical trials. Others focused more on later stage assessments, and were concerned more about supporting the development of an infrastructure to support large, rapidly conducted multicenter clinical trials of new technologies. It was agreed that assessment and validation of imaging methods and technologies includes a continuum of activities. The group tried to include both ends of this continuum in its discussions and recommendations.

### Challenges and Needs

The group identified a number of specific challenges facing investigators and needs for the future. At the most general level, it was agreed that needs could be divided into three types: 1) *expertise* in study design and analytic methods; 2) *infrastructure* to support the conduct of assessment studies, particularly large, later stage clinical trials; and 3) *funding* to support these activities and encourage investigators to participate. It was furthermore agreed that the availability of funding could facilitate the development of expertise and infrastructure. However, participants recognized that there is neither a sufficient number of appropriately qualified investigators, nor an adequate infrastructure to support the number and complexity of assessments that need to be conducted.

More specifically, the group recognized that there is a pressing need for the *development* of analytic methods specific to the assessment and validation of imaging methods and technologies, and that—if at all possible—every effort should be made to ensure that these analytic methods are widely *disseminated* as they are developed. Reference was made to the ROC analysis software developed by Charles Metz, which can be downloaded from the internet and is widely used to conduct analysis of diagnostic test performance. However, it was felt that in most cases, analytic approaches and models developed by individual investigators generally remain proprietary and are not made available to others. In some cases, such as with a complex decision analytic disease model that took years to develop and might lead to a series of grants and/or publication, it was recognized that investigators would be unlikely to be willing to share their work. However, it was felt that in other cases, appropriate incentives could promote

sharing of analytic approaches and models.

Beyond the specific challenges described above, perhaps the greatest challenge which faces the field today is the need to effect a change in the culture of radiology. With respect to the session topic, it was felt that there is a great need to foster an appreciation of the value of participating in diagnostic technology assessments, and more generally, of the value of these studies. The group recognized that appropriate incentives (including better recognition by promotion committees) could help to effect this culture change, and that radiology could perhaps learn from other specialties, where greater exposure to academic activities in general, and clinical research in particular, is included as part of the residency and fellowship training experience. However, given the manpower shortage facing the field today and the economic realities facing many trainees, effecting a meaningful change in culture will be a difficult task.

### Recommendations

The group identified a number of specific recommendations which it felt could have an important effect on the field. These included: 1) that integration across the entire continuum of assessment and validation activities, and communication among the many participating disciplines, is essential; 2) that there is a need to support methods development for all stages of assessment and validation activities; 3) that identification and validation of surrogate endpoints could help to improve assessment efforts and make trials more efficient; and 4) that modeling and simulation could have a very important role in diagnostic technology assessment.

Integration and communication are essential in order to make sure that appropriate methods are utilized at the appropriate stage in the assessment of each new technology. Ideally, validation studies in the lab should be conducted with an eye toward the eventual plan for animal and clinical assessment studies. By beginning to formulate tentative plans for later stage assessments early in the development process, critical performance data can be accumulated early and more efficient trials designed and conducted. Furthermore organized surveillance and early engagement of promising new technologies can help to target resources available for later assessment studies to those candidate technologies

likely to have the greatest impact on health outcomes.

As described above (challenges and needs), there is considerable room for the development of analytic methods relevant to the assessment and validation of imaging technologies. The group recommended that resources be devoted to the development of biostatistical tools, approaches to understanding and incorporating the role of human observers in the assessment process, and the development of additional meaningful study endpoints. With respect to study endpoints, it was recognized that these must match the purpose of the study being conducted, but that they should ideally capture the effect of the imaging technology on patient outcomes such as length and quality of life.

Considerable discussion was devoted to the topic of surrogate endpoints. These are intermediate endpoints that have been validated as having a definite and predictable relationship with patient outcomes of concern. For example, reduction in tumor size or number of metastases, if shown to be predictive of patient survival or quality of life, could be useful surrogate endpoints for the evaluation of targeted therapies. The identification and validation of surrogate endpoints for a variety of diseases could help to expedite clinical trials, which could then be designed to capture data regarding the surrogate endpoints rather than patient outcomes that occur farther in the future.

The potential role and importance of modeling and simulation was also discussed. Modeling can help identify critical information to acquire in future trials. Modeling can be used to identify performance (or cost) targets which a new technology must meet in order to be an attractive alternative to existing technologies, or to identify critical information to acquire in future trials. Modeling can also be used to determine the effect of new technologies on patient outcomes based on shorter term, or surrogate, endpoints derived from clinical trials. In a modeling study, the short-term outcomes of concern (generally the probability of particular events) are defined in advance; the model is used to predict long-term outcomes and thus extends available trial results. Existing trial results are then used to verify and calibrate the model, and model results can be used to refine the design of later trials. A modeling approach also offers more flexibility than randomized trials. For example, it is possible to compare more interventions and follow-up protocols than are practi-

cal in a trial. One can also simulate patient populations that did not participate in randomized trials, or evaluate potential improvements in test performance or advances in therapies. Lastly, the results of modeling studies are generally available more rapidly than clinical trials, and at a much lower cost.

### Additional Thoughts

A number of additional points were raised by the group. To begin with, it was recognized that education is absolutely essential if the field is to move forward. Clearly, there is a great need to educate trainees concerning the need and techniques for conducting rigorous assessments of imaging technologies. Better education of our trainees can also help to achieve the much needed "culture change" mentioned above. In addition, it is essential for radiologists and other imaging scientists to educate investigators working in other disciplines about the capabilities of imaging technologies, and the challenges we face in evaluating their performance. Reviewers, be they study section members or journal reviewers and editors, also need to be better educated regarding these issues. Lastly, through ongoing dialog, it is critical to continue to raise the awareness of the NIH and other funding agencies about the challenges and opportunities related to diagnostic imaging and its assessment.

The group also suggested that NIH extramural staff should make an effort to engage clinical investigators and imaging experts in the process of setting priorities for research funding and program development. Only by working together, can the highest priority issues be identified and addressed. In addition, it was felt that imaging scientists should make a greater effort to coordinate our research activities with investigators in other specialties so that research was focused on the topics of greatest clinical importance. All agreed that it is important that our research remains relevant to clinical problems.

Finally, the group agreed that industry, payers, and regulatory agencies were critical partners in the assessment and validation process. Industry and payers have important needs to understand the benefits and appropriate role of imaging technologies in medical care. They stand to benefit from the results of any assessment studies performed, and should share in the support of those studies. Regulatory and reimbursement agencies represent an important part of the overall

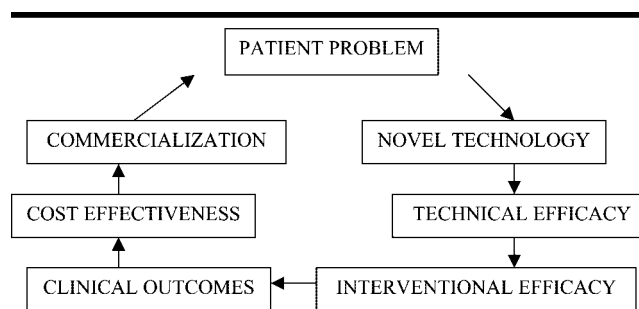


Figure 1. Systems approach to design, development, deployment, and evaluation of medical interventional techniques.

process which ultimately controls the diffusion of new medical technologies (assessment is part of this process). It was felt that greater collaboration and transparency in these processes was needed. Specific examples offered included the need for regulatory agencies to work with investigators to validate and then accept surrogate endpoints, which would then be accepted by them in considering approval of new imaging technologies.

### Summary

In summary, the group identified many challenges and opportunities facing those wishing to conduct rigorous assessment and validation of imaging technologies. Specific needs and recommendations were outlined by the group. Overall, it was felt that the field has made great progress in the past several years, and that the future is promising.

### IMAGE-GUIDED INTERVENTION: WILLIAM R. HENDEE, PHD, J. DANIEL BOURLAND, PHD

#### Introduction

The workshop described in this white paper occurred as part of meeting on Biomedical Imaging Research Opportunities held in Bethesda, Maryland, on January 31–February 1, 2003. The meeting was convened by the American Association of Physicists in Medicine and cosponsored by the Radiological Society of North America, the Biomedical Engineering Society and the Academy of Radiology Research. Thirteen other scientific organizations served as cooperating societies for the meeting.

The workshop was initially entitled Image-Guided Therapy. This title was changed by the workshop participants to Image-Guided Intervention (IGI) to reflect broader applications of image-guided techniques (biopsy, surgery, ra-

diation therapy, chemotherapy, etc). It was also suggested by some participants that the expression "Information-Guided Intervention" is preferable to Image-Guided Intervention, because not all of the information used to guide interventional procedures is in the form of images.

The workshop discussion ranged over a wide range of topics during two sessions, one in the evening of the first day and the second in the morning of the second day of the meeting. This white paper attempts to crystallize these topics into challenges and opportunities in five subject areas. Each of these subject areas, listed in the Subject Content section below, is considered separately in the paper. It should be emphasized, however, that the subject areas overlap considerably. In many cases there are substantial opportunities and challenges at the overlapping interfaces between the subject areas. In some instances, certain technologies or approaches are mentioned specifically. In general, these technologies and approaches cut across all 5 subject areas.

#### Subject Content

Systems Development, Systems Model for IGI Technology Development, Pre-clinical Studies of IGI Systems, Identification of the Interventional Target, Image Challenges/Opportunities in IGI, Education, Training and Skill Development

#### Systems Development

Image-guided interventional techniques are well served by a systems approach to their design, development, deployment and evaluation. This approach is illustrated in Figure 1. In a systems approach, a clinical need (patient problem) is identified that is amenable to a technology solution. In response, a novel technology is designed to solve the clinical need. When this happens, the tech-

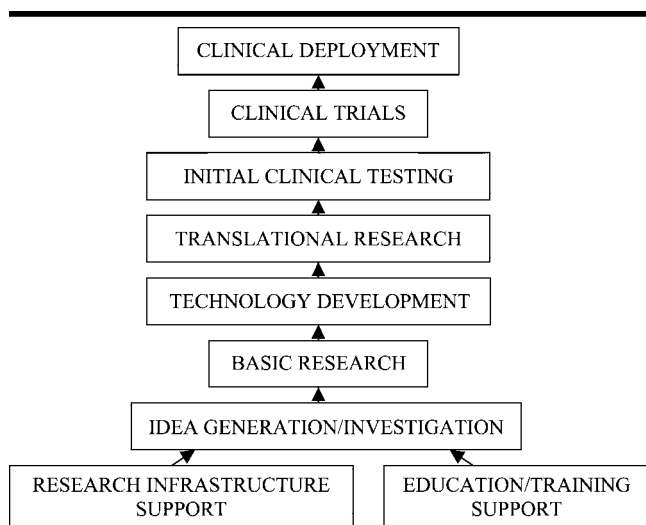


Figure 2. Funding strategy in support of research.

nology is said to be responding to a “clinical pull.” Frequently, a novel technology is designed or adopted from existing technology without a specific clinical problem in mind. A first step for the technology is then to identify an applicable clinical need. This approach to technology development is referred to as “technology push.”

Once a technology has been developed, it is evaluated from an engineering perspective (technical efficacy) to ensure that it has potential to satisfy the clinical need as described in terms of technical (engineering) specifications. Once this criterion is satisfied, the technology is used in patient volunteers under controlled conditions to evaluate its usefulness in the clinical setting. Initially the interventional efficacy may be evaluated by intermediate measures of usefulness, but ultimately the usefulness will be judged on the basis of clinical outcomes related to patient well-being.

In parallel with clinical outcomes, the technology will be assessed in terms of its cost-effectiveness compared with alternate interventional strategies that may provide similar clinical outcomes. A frequent rule of thumb in this stage of evaluation is that the novel technology must satisfy at least two of the following criteria: Faster, Better, Cheaper. If the clinical outcomes and cost-effectiveness are favorable, the technology may enter commercial production. It is through commercial production and marketing that the technology is made available to many patients who may benefit from its use.

The systems approach to technology design, development, deployment and

evaluation requires a continuous funding strategy in support of research. This strategy is outlined in Figure 2. It is only through a research funding strategy that provides support across all stages of technology development and evaluation that novel technologies can be developed to improve the health and healthcare of patients.

### Systems Model for IGI Technology Development

Workshop participants emphasized the need for a systems model for development of image-guided navigational and interventional strategies. This systems model includes the following elements:

1. Team approach to development that includes scientists, (physicists, computer scientists, and pharmacologists) engineers and physicians
2. Endorsement by the institution and funding sources for novel technology development
3. Support of funding sources for high risk, high impact ideas
4. Realistic estimates of costs and development time for novel technologies
5. Recognition that a systems model encompasses both evolutionary (incremental) and revolutionary (quantum leap) pathways, and that both are essential to technology development
6. Approaches to technology evaluation that are agreed upon by consensus building
7. Three necessary evaluation steps: validation, efficacy and efficiency
8. Validation should occur at both the engineering and the clinical phase—and

should acknowledge that these phases interact in iterative fashion in the evolution of a technology

9. Evaluation criteria: is a new technology Faster, Better, Cheaper—at least two should be satisfied for a technology to be clinically/commercially viable

10. Final and intermediate engineering and clinical end-points are agreed upon

11. An excessive regulatory burden (OHRP, FDA, HIPAA, ORI, etc) chills clinically-focused research, and impedes technology development

12. Continued growth in receptivity and funding is needed at NIH with regard to technology-driven, as well as hypothesis-driven, research

### Preclinical Studies of IGI Systems

In the development of new IGI approaches, preclinical studies are needed. These studies should include applications to animal models, with recognition that not all applications scale to the level of rodents, and larger animals may be needed. For example, a non-primate model for ischemia is needed. Attributes of animal models and their use include:

1. Small and large animal models are needed with specific diseases and injuries
2. Animal models and intervention endpoints should scale to humans, and vice versa
3. Animal models are needed that reflect target and normal tissue responses similar to humans
4. Agreed-upon methods are necessary for pre-clinical evaluation of interventional techniques for specific disease processes

### Identification of the Interventional Target

Identification and verification of the specific target and its boundaries (ie the specific tissue volume to “treat”) is a never-ending challenge for many applications of image-guided intervention. This topic raises the following issues:

1. Pathological verification of diseased tissue—but how does the pathology specimen relate geometrically to the treatment volume?
2. Improved methods are needed for combining anatomic and functional images from multiple modalities
3. Improved methods are required for image segmentation, registration and spatial and temporal fusion
4. Methods for in vivo pathological analyses are needed
5. Are target boundaries a macroscopic

or a microscopic challenge in specific IGI applications?

6. Can images enable a “biologically correct” intervention?

7. Target volumes change from moment-to-moment; real-time methods for data acquisition/display/analysis are needed

8. Tissue response is important not only in the target, but in the target environs (i.e., nearby normal or “critical” tissues)

9. The variable response of patients to specific interventions may be predictable through molecular genetics.

### Imaging Challenges/Opportunities in IGI

Image-guided interventions impose special demands on the medical imaging process. These demands extend beyond the normal imaging requirements of acceptable image quality at reasonable cost. The additional demands include:

1. Image and resource sharing—a need for accessible atlases of images

2. Data libraries, algorithms and software sharing should be encouraged and facilitated

3. Resource/data sharing permits the reuse of information gathered by others

4. Image/data transfer protocols must be agreed-upon by industry and the profession

5. Validation and quality assurance procedures for IGI images should be agreed upon

6. Image software and hardware limitations must be recognized and accommodated

7. Images must be adequate “to do the job”—they do not have to be perfect, just matched well to the clinical requirements

8. 3D imaging will prove especially useful in IGI

9. 3D images require new detector arrays, 3D display methods, and in-depth training of physicians in new ways of seeing. When 3D arrays of image data are collected, the display, interpretation and evaluation methods are often 2D.

10. Image-guided intervention may include: (a) imaging of the problem, (b) delivery/activation of the treatment, (c) evaluation of the treatment

11. Image-guided robotic methods of treatment delivery promise to have applications in (a) the operating room, (b) remote use (military, rural areas)

12. Percutaneous catheter-directed procedures are powerful techniques yet underdeveloped compared with traditional external image-guided interventions. They hold promise for in situ therapy in many organ systems through: (a) delivery of lytic, embolization, anti-inflammatory, and anti-neoplastic agents (e.g., drugs and other materials) and therapy devices (e.g., stents); (b) in-catheter MR, US, and optical imaging for diagnosis and therapy monitoring

13. New catheter materials and interventional techniques are required for IGI in deformable tissues and in the peripheral vasculature

### Education, Training and Skill Development

IGI is substantially different from the normal practice of the medical imaging specialist, and places new demands on the education, training and skills of its practitioners. Among these demands are:

1. Substantial manual dexterity for some applications of IGI

2. Close oversight by a mentor for skill development during training

3. A challenge for the engineer/physicist is to reduce the manual dexterity requirement through remote controls and automation

4. Another challenge is to integrate multi-modality information in real time to facilitate IGI practice

5. IGI improvements require collaboration among scientists, engineers and physicians from the outset

6. Collaboration is facilitated by bringing scientists, engineers and physicians together early in their education (e.g., combined graduate/medical student classes)

7. Departments can encourage collaboration by providing an exploratory cul-

ture that encompasses both engineering and medicine

8. Scientist/engineer/physician collaboration in IGI development is acknowledged by funding agencies through recognition of co-principal investigators (scientist, physician and engineer)

9. Segmented education (set-asides of specific time for research during medical education) is less productive than an integrative culture that encourages continuous involvement in research

10. Competitive research requires specialized training (eg postdoctoral experience) and a dedication to research

### Summary Statement

The emerging theme from this workshop is the need for a systems approach to design, development, deployment and evaluation of new methods, devices and procedures for Image-Guided Intervention. The approach should rely strongly on a clinical pull (i.e., response to identified clinical needs) as well as on a technology push (i.e., search for clinical applications of potential technologies). This dual nature of technology development in IGI requires a close working relationship among engineers, scientists and physicians, so that clinical needs can be identified and matched with the possibilities and limitations of emerging technologies. This potential match is continuously shifting as additional clinical needs arise and as emerging technologies evolve.

A productive working relationship among individuals with different backgrounds and interests is best facilitated by educational programs in which the individuals study together, followed by work environments that encourage collaboration across disciplines. This is the culture that will most likely provide both incremental and breakthrough advances in Image-Guided Intervention. Creation and sustenance of this culture is probably the greatest challenge, and the greatest opportunity, facing the Image-Guided Intervention community.