

C. Leon Partain, MD, PhD
 Heang-Ping Chan, PhD
 Juri G. Gelovani, MD
 Maryellen L. Giger, PhD
 Joseph A. Izatt, PhD
 Ferenc A. Jolesz, MD
 Krishna Kandarpa, MD, PhD
 King C. P. Li, MD, MBA
 Michael McNitt-Gray, PhD
 Sandy Napel, PhD
 Ronald M. Summers, MD,
 PhD
 G. Scott Gazelle, MD, MPH,
 PhD

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Abbreviations:

BIROW = Biomedical Imaging
 Research Opportunities Workshop
 CAD = computer-aided detection
 CADx = computer-aided diagnosis
 FDA = Food and Drug
 Administration
 MIC = molecular imaging center
 NIBIB = National Institute of
 Biomedical Imaging and
 Bioengineering
 NIH = National Institutes of Health
 ROC = receiver operating
 characteristic
 RSNA = Radiological Society of
 North America

¹ From the Dept of Radiology, Vanderbilt Univ Medical Ctr, RR-1223, MCN, 1161 21st Ave South, Nashville, TN 37232-2675 (C.L.P.); Dept of Radiology, Univ of Michigan Health Systems, Ann Arbor (H.P.C.); Dept of Radiology, Univ of Texas M.D. Anderson Cancer Ctr, Houston (J.G.G.); Dept of Radiology, Univ of Chicago, Ill (M.L.G.); Dept of Radiology, Duke Univ Medical Ctr, Durham, NC (J.A.I.); Dept of Radiology, Brigham and Women's Hosp, Harvard Medical School, Boston, Mass (F.A.J.); Dept of Radiology, Univ of Massachusetts Medical School, Worcester (K.K.); Imaging Sciences Program, NIH, Bethesda, Md (K.C.P.L.); Dept of Radiology, David Geffen School of Medicine at UCLA, Los Angeles, Calif (M.M.G.); Dept of Radiology, Stanford Univ School of Medicine, Calif (S.N.); Diagnostic Radiology Dept, NIH, Bethesda, Md (R.M.S.); and Inst for Technology Assessment and Dept of Radiology, Massachusetts General Hosp, Harvard Medical School, Boston, and Dept of Health Policy and Management, Harvard School of Public Health, Boston, Mass (G.S.G.). Supported in part by grants from NIBIB (1 R13 EB003553-01) and the Whitaker Foundation. Received Nov 4, 2004; revision requested Dec 13; revision received Jan 23, 2005; accepted Feb 1. **Address correspondence to** C.L.P. (e-mail: leon.partain@vanderbilt.edu).

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Biomedical Imaging Research Opportunities Workshop II: Report and Recommendations¹

The second annual Biomedical Imaging Research Opportunities Workshop (BIROW), or BIROW II, was held February 25–26, 2004, in Bethesda, Maryland. The workshop was a continuation of the first BIROW and was initiated again by medical, scientific, and engineering researchers and societies to identify and explore opportunities for basic science research and engineering development in biomedical imaging (1). This broad-based multiple-disciplinary effort sought new ideas in synthesis from leading scientists and engineers, as well as from clinicians and those involved in government funding for medical imaging. BIROW II was sponsored by the Academy of Radiology Research, the American Association of Physicists in Medicine, the American Institute for Medical and Biological Engineering, the Biomedical Engineering Society, and the Radiological Society of North America (RSNA), along with 15 other participating specialty societies.

OVERVIEW OF THE WORKSHOP: C. LEON PARTAIN AND G. SCOTT GAZELLE

The four selected topics for BIROW II included (*a*) optical imaging, (*b*) computerized image analysis, (*c*) imaging of gene expression, and (*d*) image-guided vascular interventions. Note that information on the workshop and the current planning for the third workshop are posted on the BIROW Web site (www.birow.org).

BIROW II again used the format established in the first BIROW, which included plenary sessions related to the four topics followed by two sessions for break-out groups on the topics. In each of the initial topical plenary sessions, three invited leaders in the field summarized the state of the art and provided their thoughts on outstanding research opportunities. See the Appendix for a list of group leaders and participants. Also, a challenging summary of opportunities in biomedical imaging research was presented by the keynote speaker, James H. Thrall, MD, Professor and Chairman of the Department of Radiology at Massachusetts General Hospital, Harvard Medical School (Boston).

During and after the meeting, topical session chairs and break-out group leaders drafted white papers to summarize the state of the art and the research opportunities in their topics. It was planned that development, evaluation, and wide dissemination of the white papers for each topic in the archival literature and on the Internet would provide an unusual opportunity to stimulate thought and activity in a wide segment of medical imaging and related communities. A summary report of these four white papers follows this introduction.

The four BIROW II topics were chosen to bring together researchers in medical imaging, including basic scientists, engineers, and physicians. It is anticipated that the BIROW series will continue as an annual workshop; the topics in each workshop may be narrowed and perhaps chosen to be more closely related to allow for further scientific depth, as well as for input from the outside medical imaging community.

The organization of BIROW by a wide consortium of medical, scientific, and engineering societies strongly involved in medical imaging should help ensure continuation as a dynamic undertaking. The workshop offers insights for a wide range of recognized leaders, including, but not limited to, the most recognized National Institutes of Health (NIH) advisors. The organization consists of representatives from each group of societies, who direct the workshop planning and meeting arrangements. A larger group of societies provided members to the Program Committee, as well as key workshop participants, and released announcements of the meeting results. Strong input support was provided by representatives from NIH and other government agencies with particular contributions to the support of medical imaging research.

The workshop was financially supported in part by grants from the National Institute of Biomedical Imaging and Bioengineering (NIBIB) and from the Whitaker Foundation. C. Leon Partain, MD, PhD, served as principal investigator for each of these grants, which were submitted from and managed by Vanderbilt University Medical Center (Nashville, Tenn). The RSNA in cooperation with the American Association of Physicists in Medicine (AAPM) assumed the major financial support and responsibility, and participating societies committed financial support for their representatives' travel.

The strong management of BIROW II by RSNA staff was critical to the success of BIROW II. Contributions from AAPM were also important for success. BIROW III and subsequent workshops will be managed by RSNA with support from AAPM and other sponsoring societies. BIROW III will be organized by the co-chairs of the executive committee: William H. Hendee, PhD, and G. Scott Gazelle, MD, PhD, and by the co-chairs of the program committee, Kris Ropella, PhD, and William F. Walker, PhD.

BIOMEDICAL OPTICAL IMAGING: JOSEPH A. IZATT

The optical imaging session reported on recent advances in structural, functional, and multimodality optical imaging in the effort to identify emerging opportunities for basic research and clinical applications in optical imaging and microscopy and to identify methods to facilitate coordinated optical imaging research among medical and scientific disciplines. Formal invited presentations included reports on functional diffuse optical imaging, optical coherence tomography, and high-resolution optical microscopy. An optical imaging break-out session was charged with identifying important issues, challenges, and opportunities facing the growth of this field, including consideration of recommendations for future program initiatives. What follows is a summary of the findings and recommendations.

State of the Art

The rapidly developing field of biomedical optical imaging draws from the techniques and methods of the life sciences and of photonics to record unprecedented achievements in the detection, imaging, identification, kinetics, and manipulation of biologic structures and pro-

cesses. Optical imaging is used in biology to probe for mechanisms, function, and morphology across a range of scales from the subnanometer level to the organism level. In medicine, optical imaging is used to study tissue from the organelle level to the organ level to help detect, diagnose, and treat pathologic processes in ways that are noninvasive or minimally invasive to the body.

Widespread current applications of biomedical optical imaging range from the use of fluorescence techniques to help identify biomolecular distributions within cells, to micrometer-scale cross-sectional imaging of the retina, to imaging and selective treatment of tumors. Current research into next-generation biomedical optical imaging techniques is being conducted in a wide variety of areas and encompasses an equally wide variety of methods.

Nonlinear microscopy uses nonlinear optical techniques such as multiphoton molecular excitation, optical harmonic generation, and depletion of stimulated emission to image subcellular morphology and trace molecular dynamics down to subnanometer resolution and up to hundreds of micrometers deep into living tissues. Optical coherence imaging techniques such as optical coherence tomography and phase-resolved microscopy allow real-time, micrometer-scale, cross-sectional imaging and ultrasensitive detection of cellular dynamics down to millimeter-scale depths in living human patients. Diffuse optical tomography allows completely noninvasive measurements of hemodynamics and neural activation many centimeters deep into bulk tissues such as the brain, particularly when used in combination with conventional deep-penetration imaging techniques as part of a multimodality approach. Research efforts continue on the validation of fluorescent and Raman techniques in the spectroscopic diagnosis of disease, including the accumulation of clinical data demonstrating efficacy in specific applications such as detection of cervical dysplasia. Many of the recent advances in molecular imaging employ luminescent or fluorescent genetically expressible markers in combination with advanced photonic sensor systems.

These and other recent research advances demonstrate the continuing potency of photonics as a venue for new biomedical imaging technology development. As optical imaging continues to mature, it will become necessary to identify larger issues and challenges in this

field that can be used for the development of future strategic initiatives.

Issues and Challenges

Some issues and challenges facing optical imaging research are particular to optical imaging, while others are shared by all biomedical technology development activities.

Appropriate validation methods for optical imaging need to be developed, including surrogate markers and appropriate benchmarks. Most optical techniques have had limited clinical exposure. Since many optical imaging techniques surpass the limits of resolution or sensitivity available to established imaging techniques *in vivo*, the development of validation methods is especially challenging and important.

Owing to the highly scattering nature of tissues at optical wavelengths, the development and interpretation of optical images requires complex mathematic models for image reconstruction. Instrumentation-based approaches for imaging in the presence of dominant scattering have been successful near tissue surfaces; however, model-based approaches for deep tissue imaging in the absence of structural information from complementary imaging modalities remains problematic.

As in many imaging modalities, optical imaging in tissues involves a trade-off between image resolution and maximum imaging depth. High-resolution techniques capable of micrometer-scale imaging are generally limited to image depths on the order of millimeters or less. The technical challenges of high-resolution imaging well below the surface of soft tissues (eg, in the brain or inside tumors) must be overcome to advance the use of optical imaging for diagnostic applications and measurement of treatment response. While optical imaging techniques are naturally amenable to subsurface delivery by means of optical fiber probes, probe-guided optical imaging instruments increase invasiveness and face increased regulatory challenges.

Optical imaging may have its greatest clinical promise when it is combined with other imaging modalities. However, this research requires interdisciplinary cooperation that is difficult to foster and support.

Strategic Objectives

The following are the major strategic objectives for the near-term future of biomedical optical imaging research:

Translational research.—Translational research is defined as the development of new technologies with near-term potential for biomedical or clinical applications, where demonstration of the application is included in the definition of the research project. Translational research requires funding mechanisms for and the participation of multidisciplinary teams of basic scientists, engineers, and physicians in all aspects of the research project, including conception of the instrument, prototype development, biomedical and clinical deployment, and closure of the feedback loop for next-generation prototype improvement. A critical element of translational research involves validation of clinical applications of new optical imaging technologies.

An additional problem facing translational research is the gap in many new technologies between successful demonstration in a single application or center and widespread dissemination to the clinical community. The creation of new funding mechanisms to enable dissemination of promising optical imaging instruments and technologies to the clinical community prior to commercialization should also be encouraged.

Multimodality imaging.—Multimodality imaging consists of combinations of optical imaging methods with other imaging modalities to perform combined structural and/or functional imaging or, alternatively, to use complementary and synergistic optical imaging methods to achieve a clinical goal. The use of structural information from well-developed imaging modalities such as magnetic resonance (MR) imaging and computed tomography (CT) in deep-tissue optical image reconstruction enables increased-resolution extraction of spectroscopy-based functional information such as oxygenation status. Alternatively, to approach problems such as early cancer detection in large organs, a composite approach that combines a low-resolution, wide-field-of-view modality such as spectroscopic diagnosis with a high-resolution, small-field-of-view modality such as optical coherence tomography may be promising.

The distinctive problems posed by multimodality imaging include the development of specialized instrumentation compatible with multiple modalities, as well as the development of platforms and algorithms for data correlation, registration, and management to enable simultaneous visualization of correlated data. Even in the absence of multiple modalities, many cur-

rent high-resolution optical imaging approaches generate large and unusually shaped data sets (eg, micrometer-scale resolution images with millimeter-scale imaging depths but centimeter-scale or larger image widths). The development of advanced algorithms and techniques for display of such data sets or, alternatively, for automated mining of such data sets for abnormalities is also an important issue that would appropriately be addressed in new initiatives.

Research Priorities

The following represent particularly germane problems at the current time: (a) *in vivo* imaging at the cellular level; (b) optical imaging methods to assess early neoplastic changes; (c) optical imaging techniques to enhance molecular imaging performance; (d) improved resolution of *in vivo* molecular imaging; (e) development and application of novel imaging devices, such as guided biopsy probes, “smart” interventional devices, and devices for imaging inside the body; (f) optical imaging methods for cognition and brain functions; and (g) portable low-cost optical imaging methods for brain function.

Training and Education

Pursuit of the recommended strategic objectives and research priorities will require increased interdisciplinary cooperation, collaboration, and communication. To prepare researchers who are capable of and receptive to these collaborations, the panel recommends the design and funding of training programs that expose engineers to clinical and basic science and expose medical students to basic science and engineering research and allow them to engage in research during their medical school training.

COMPUTERIZED ANALYSIS OF MEDICAL IMAGES: IMPORTANT ISSUES AND CHALLENGES FOR COMPUTER-AIDED DETECTION AND DIAGNOSIS—SANDY NAPEL, HEANG-PING CHAN, MARYELLEN L. GIGER, MICHAEL MCNITT-GRAY, AND RONALD M. SUMMERS

The past decade and a half has seen tremendous advancement in the fidelity and resolution of medical images. Whereas in 1990 a typical CT examination consisted of 50 images, today it is not uncommon for a study to result in

1500 or more 1-mm-thick cross sections. Similar trends are evident in MR imaging, ultrasonography (US), and other modalities. Unfortunately, contributions to the data logjam include a shortage of radiologists and a trend toward an increased number of examinations performed, the latter resulting from new treatment opportunities (eg, stent-grafts for aneurysms), the required preintervention images, and possibilities for new screening examinations (eg, for colon and lung cancer).

Advances in digital computing during this same time frame have created opportunities for solutions to this “data explosion.” First, medical imaging is rapidly becoming an all-digital proposition, with many hospitals and clinics fully converted and many others in various stages of transition. High-bandwidth networks are used to move images rapidly from acquisition to interpretation stations and long-term storage. Second, the cost per computation cycle has decreased substantially, and algorithms for computer recognition of features in images are being developed for many applications. Several medical disciplines already use computers in diagnostic applications (eg, electrocardiograph and Papanicolaou smear analysis), and clinical radiology has recently embraced computer-aided detection (CAD) and computer-aided diagnosis (CADx) devices in mammography, with several other applications (eg, for lung and colon cancer) on the horizon. More general uses for CAD, such as to assist in the discovery of findings incidental to the indications for imaging, have also been envisioned (2). In our break-out session, we elected to focus on the opportunities and challenges regarding CAD and CADx with regard to medical images.

Background: CAD of Breast Cancer with Mammography

Breast cancer is the second most common fatal cancer in women (3). Yearly mammograms are recommended starting at the age of 40 years and continuing for as long as a woman is in good health. Computerized image analysis may be useful in helping radiologists in detection and diagnosis and may improve the overall interpretation of breast images and subsequent patient care. Screening mammography was the first radiologic examination to benefit from CAD, when the Food and Drug Administration (FDA) approved the first clinical device in 1998. Since then, moderate-scale prospective

clinical studies of CAD systems have also been conducted (4–6).

The currently accepted paradigm for CAD in mammography is to use it as a “second reader”—that is, the radiologist first searches the images for masses and microcalcifications, and the then computer points him or her to additional suspicious regions that may be cancerous, with the final diagnosis and decisions concerning patient care being made by the radiologist. In this role, the computer must yield output at a sufficient level of accuracy; in addition, the output must be displayed in a user-friendly format for effective and efficient use by the radiologist (7–10). The ultimate test of a CAD system is of its additive value—namely, whether the performance of the radiologist is improved when the system is used in the clinical interpretation process. Thus, new computerized image analysis methods are being developed to aid in distinguishing between malignant and benign lesions to improve both the sensitivity and the specificity of breast imaging, as well as to reduce the variability in interpretation between readers (11,12). The goal of such methods is to use computer output to help characterize and potentially indicate a computer-determined probability of malignancy of a found lesion.

Use of such a CADx system in the diagnostic work-up may prevent a malignant lesion from being misclassified as benign by the radiologist. Owing to currently low positive predictive values for biopsy in many practices, CADx systems also may help reduce the number of biopsy recommendations for benign lesions. These computerized image analysis systems also are being developed for multiple diagnostic breast imaging modalities, including special-view diagnostic mammography, US, and MR imaging.

Background: CAD of Colon Cancer with CT

Colon cancer is the second leading cause of cancer-related death in the United States. Early detection and removal of colonic polyps can substantially reduce the risk of contracting colon cancer. CT colonography, or virtual colonoscopy, has shown promise as a minimally invasive technique to help detect polyps (13–16).

CT colonographic examinations can consist of over 1000 images and can be time consuming to interpret. In addition, evidence suggests that perceptual error may be a common cause of reduced sen-

sitivity at CT colonography (15,17). To address these issues, a number of investigators have developed versions of CAD methods specifically for CT colonography (18).

As for other types of CAD software, CT colonography CAD consists of segmentation, feature extraction, and classification. Segmentation locates the colonic wall and excludes other air-filled abdominal structures that are not of interest. Feature extraction quantifies characteristics of the colonic wall, with the purpose of identifying features characteristic of polyps. Successful features developed to date include surface shape, CT attenuation, and wall thickness (18). Surface shape is an intuitive feature used to identify polyps because, by definition, a polyp is a surface distortion (19–21). CT attenuation can be useful to help distinguish polyps from false-positive findings such as residual fecal matter or barium. Colonic wall thickening may also indicate potential polyp sites. Finally, classification uses the extracted features to assign each candidate feature as true-positive or true-negative.

A number of early clinical trials of CAD for the colon have been published. Sensitivities have ranged from 70% to 100%, and false-positive findings have ranged from two to eight per patient. These numbers are dependent on polyp size and patient selection criteria (22–25). In addition, CAD has been shown to be capable of detecting polyps missed by trained radiologists (26). Sizes of data sets used in these trials have been relatively small to date, which limits the ability to generalize the results.

Future research is likely to focus on development of large well-annotated image databases, reduction in false-positive rates, and the use of CAD in the setting of electronic bowel cleansing (stool subtraction) (27). Improvements in sensitivity for polyps in the 6–9-mm size range will also be an area of active research. Ultimately, these CAD systems will need to be validated in a clinical setting according to their intended use to determine whether they actually improve radiologists' performance.

Background: CAD of Lung Cancer with CT

Lung cancer is the most common fatal malignancy in both men and women, accounting for 32% of cancer deaths among men and 25% of cancer deaths among women in the United States (28). Early detection of lung cancer may have

important implications for improved prognosis in patients with this disease.

Recently, low-dose CT has been investigated for lung cancer screening (29–32). Results from these studies indicate that CT screening may enable early detection of lung cancers that are of a smaller size and at an earlier stage than those detected by using chest radiography and current clinical practice. It is this potential for improved survival due to early detection of non-small cell lung cancer that provides the rationale for CT screening for lung cancer.

Modern multi-detector row CT scanners allow the rapid acquisition of thin sections through the entire thorax, which result in nearly isotropic high-resolution data sets and enable the detection of smaller lung nodules. This, however, occurs at the cost of a substantial increase in the number of images for radiologists to interpret (33,34), which can become a time-consuming task. Thus, increased interest in CAD methods for lung nodules imaged with CT has resulted (35–40).

While screening and related studies have shown that CT is very sensitive for the detection of lung nodules, it is not very specific for the detection of lung cancers. In two major studies (30,31) with at least 1000 high-risk participants each, nodules were detected in 23%–65% of participants, but only 1.6%–2.7% of participants turned out to have a primary lung cancer at the initial screening examination. Hence, there is also substantial interest in the development of CADx schemes to assist with the characterization of detected nodules as cancerous or noncancerous. Two major approaches have been investigated: measurement of the change over time (41) or evaluation of the features of the image from a single examination (42–46).

Hindering the development of CAD and CADx systems for lung CT is a shortage of both image data and documented cases of cancer. There has also been a lack of standardization regarding imaging protocols, detection truth (ie, what is and is not a nodule and/or cancer), and evaluation metrics. Some of these issues are being addressed by the development activities of the Lung Image Database Consortium (described in detail elsewhere [47]), that seek to develop a publicly available database of CT images with known truth, as well as to provide guidance for method evaluation.

Break-out Session Recommendations

In our break-out session, we identified five major areas and developed specific recommendations for each that would facilitate major advances in CAD and CADx. These areas are common to both CAD and CADx. For simplicity, CAD and CADx are collectively referred to as CAD in the following discussions.

Databases

The development and validation of all CAD approaches and algorithms requires access to imaging data, both for healthy patients or tissues and for patients or tissues that have or express the objective disease or lesion. All preliminary CAD efforts have involved collection of these data and the establishment of the reference standard (ie, which patients and diseases are true-positive for the disease or lesion) for the study. The achievement of statistically significant results requires large numbers of cases, particularly when the prevalence of the disease or lesion is low. Because these collection and curatorial activities are expensive, it would be desirable to collect and maintain these data in a form suitable for sharing (ie, for use by others in the same field).

Establishment of such a database would greatly enhance the effort needed to acquire these data in several ways. First, the data could be used by all researchers in the field for algorithm training and preliminary testing. Second, the data would facilitate the participation in CAD development by experts in computer vision and other fields who may not otherwise have access to medical images. Third, the data would allow first-order comparison of algorithms and demonstration of improvements. (We note that these public databases would not be useful for true evaluations or comparisons of algorithms, which require a previously unseen database with its reference standard securely and privately maintained prior to testing.)

While there are several efforts underway (eg, National Lung Screening Trial, Digital Mammography Imaging Screening Trial), the availability of databases containing images, truth, and other relevant clinical data will allow better development, optimization, and preliminary comparison both of CAD algorithms and of other image-processing software. To facilitate continued development of databases and database tools for CAD, the group recommended the following:

1. An infrastructure for user-friendly storage and sharing of data should be nationally funded.

2. The culture should be encouraged to share data by taking the following specific actions:
 - (a) Prospectively, the NIH and other funding agencies must allow budgeting for the cost of collecting, curating, and preparing data according to standard templates for inclusion in shared databases.
 - (b) Retrospectively, because many potentially useful databases already exist in the hands of previously funded investigators, the NIH and other funding agencies should develop a contract or other mechanism to fund the effort needed to standardize and share these databases.
 - (c) Journal editors should encourage and later require (after the community begins to take part) data and software sharing through explicit policies in their instructions to authors.
 - (d) Standard templates should be developed and made available to facilitate data sharing while maintaining compliance with local institutional review boards and Health Insurance Portability and Accountability Act guidelines.

Toward Standardized Reporting

As more studies appear in the literature, it would be desirable to facilitate their comparison. This often is not a trivial matter because each investigator not only writes in his or her own style but may leave out methodological details and/or results that are overlooked during peer review, which thereby weakens not only the manuscript itself but the advancement of the field. The group recommended that a national-level committee (eg, from NIH or the American College of Radiology Imaging Network) should work with journal editors and reviewers to require that a standard format for publications of CAD research be developed that would facilitate peer review of manuscripts and grant proposals, permit comparison of methods and results, and yield better studies overall.

The checklist should require the inclusion of descriptions of

- (a) the database in terms of disease type, lesion size, et cetera;
- (b) the appropriateness of the database relative to the general population;
- (c) the method used for the classifier feature selection;
- (d) the method of CAD training (eg, types of classifier, number of cases, training data, cross validation);
- (e) the methods used for truth determination;
- (f) the method for scoring (ie, determination of true- and false-positives and true- and false-negatives);
- (g) the method

for assessing performance (eg, receiver operating characteristic [ROC] analysis) and the associated statistical analyses; and

- (h) the results in terms not only of sensitivity but of specificity or false-positive rate; ideally, ROC or free-response ROC, where appropriate, should be used to characterize performance at a range of operating points. Furthermore,
- (i) results should also be related to the characteristics of the database (eg, stratified appropriately by size or some other features) into agreed on ranges (varies by CAD application).
- (j) For observer performance studies with CAD, detailed descriptions of the study design, how CAD results were presented to observers, and what observers were told about CAD performance are needed.
- (k) Discussion should relate results to clinical relevance where possible; for example, what would be the increase in the number of how many increased actionable lesions?

Use of public databases should be acknowledged. Authors would, of course, have the option to discuss why, in some cases, one or more of the required items are not included, but the existence of the checklist and its availability to authors and reviewers will go a long way toward improving the understandability and comparison of the reported studies. Ultimately, it may one day be useful to provide links so a reader can download images and code for further evaluations and comparisons, as well as for extending the algorithms to other domains.

Foster Interdisciplinary Collaborations

Breakthroughs in many areas of medicine are being made as a result of interdisciplinary collaborations. CAD is an example of this. To facilitate the establishment of these types of collaborations, societies should

- (a) support a "bulletin board" of who is doing what, conferences, opportunities, et cetera in computerized medical image analysis and
- (b) encourage continued and increased attendance at BIROW and Bioengineering Consortium meetings.

Recognize Innovative Trends in CAD

Many important contributions to CAD come from novel modifications to and combinations of existing tools and techniques. As the CAD community matures, we must recognize that such synergies are innovative in themselves; in other words, perhaps no new fundamental

knowledge is developed, but the combination of data, tools, and techniques from new sources is fundamentally innovative if it advances the field.

Some ideas of innovative trends in CAD that should be encouraged are (a) patient-based CAD, or approaches that incorporate other (eg, multimodality imaging and nonimaging) clinical data into detection and classification schemes; (b) research on the relationship between image acquisition methods and CAD algorithms that promote a move toward platform-independent CAD; (c) evaluation of systems in clinical practice (eg, answering questions on the ultimate effect of a given approach on patient care); (d) evaluation of systems after upgrades (ie, comparing results of prior and recently improved algorithms in the field with real patients); (e) evaluation of existing CAD algorithms in untested paradigms (eg, CAD is currently used as a second opinion for microcalcifications in mammograms; how would it perform as primary reader?); (f) understanding the performance of human plus CAD as a function of paradigm (eg, second vs first reader), human's assumptions (eg, how the algorithm works, data, assumed prevalence), training, familiarity, et cetera; and (g) expansion of fields and techniques for CAD: (i) detection of lesions in other organs (eg, vascular, skeletal), (ii) lesion response to therapy, and (iii) prescreening for healthy individuals, risk assessment.

Evaluation Methods

The ultimate results of the study of a CAD algorithm rest on a well-founded and easily understood statistical evaluation. Although ROC (48,49) studies are well understood in certain contexts (eg, detection of healthy vs sick patients, responders vs nonresponders to therapy), ROC analysis is not immediately applicable to all CAD research (eg, detection of one or more lesions in a given patient, algorithms that improve performance in certain important operating ranges [eg, sensitivity above 95% as opposed to over the entire ROC curve]). Several other methods have become available or are under development (eg, free-response ROC [50,51], alternative free-response ROC [51,52], extended free-response ROC [53]), but the best choice is not always obvious, and many researchers choose different approaches in the same circumstances. Encouraging research in the area of evaluation methods and when

and how to use them will result in better, more efficiently performed, and more easily comparable CAD studies. Examples of these are (a) evaluations of how to best perform observer studies, (b) investigations that relate ROC measures to clinical relevance, and (c) extension of existing methods (eg, partial-area ROC, partial-area free-response ROC, partial-area alternative free-response ROC, modifications that normalize for case enrichment [prevalence issue] in databases).

IMAGING GENE EXPRESSION: JURI G. GELOVANI AND KING C. P. LI

Preclinical Gene Expression Imaging

Fund intrainstitutional groups and networks for imaging gene expression.—The field of molecular imaging has made substantial advances in recent years. The formation of multidisciplinary research teams has stimulated and streamlined cancer imaging research from inception to use in patient care. The success of National Cancer Institute–initiated funding of In Vivo Cellular and Molecular Imaging Centers (ICMICs) allowed multidisciplinary groups of researchers and clinicians at several institutions in the United States to capitalize on their particular scientific strengths and clinical expertise and to define the structure and research objectives that create the most synergistic and productive scientific interactions. This initiative was designed to capitalize on the extraordinary opportunity for molecular imaging to have an impact on diagnosis and the treatment of cancer patients noninvasively and quantitatively. Molecular imaging technologies, developed as the result of the ICMIC initiative, provide valuable laboratory tools for the interrogation of biologic pathways relevant to cancer. Some of the newly developed imaging agents and technologies are ready for translation to the clinic.

Therefore, it is very important not only to continue but to further increase the funding of the ICMIC program and establish molecular imaging centers (MICs) with a focus on various diseases, as well as on cancer. Additional funds are required to support the development of new MICs, interinstitutional networks, and interdisciplinary scientific teams that can lead the nation in cutting-edge molecular imaging cancer research. Such centers and interinstitutional networks should have clinical relevance, provide core facilities to support preclinical imag-

ing research, provide flexibility to respond to exciting pilot research opportunities, and provide interdisciplinary career development opportunities for investigators new to the field of molecular imaging. This funding mechanism should promote coordination, interrelationships, and scientific synergy among the research components and resources, leading to a highly integrated imaging center or an interinstitutional network.

MICs should provide researchers and clinicians with several critical resources: an organizational structure specifically designed to facilitate multidisciplinary interactions, develop and translate molecular imaging technologies that will have an eventual effect in the clinic, provide access to a concentrated pool of expertise in a wide range of disciplines, and foster a highly collaborative atmosphere and consistent access to expertise with minimal wasted time and effort. The establishment of specialized resources dedicated to MIC-related research will widen access. The specialized resources will be determined by the requirements of the institution, the defined scientific goals of the research components of the MIC, and budgetary limits. Prioritization of the research projects supported through MIC specialized resources will be an essential function of the MIC leadership, and the mechanism to be employed for prioritization must be delineated by the applicants.

In addition, NIH and NIBIB should provide funding opportunities to support new collaborative basic research with molecular and genetic imaging components and provide supplemental funding to introduce molecular-genetic and cellular imaging technologies into ongoing basic research projects and programs. Also, NIH and NIBIB should provide supplemental funding for joint molecular imaging and transgenic murine models programs aimed to develop "imageable" transgenic murine models of disease that make use of more refined and complex reporter gene systems.

Fund education in molecular imaging.—Current graduate programs tend to be focused on single disciplines and may be inadequate for training of the needed cadre of interdisciplinary imaging scientists. Education Centers in Molecular Imaging and Education Networks in Molecular Imaging should provide both support for a number of pre- and postdoctoral trainees and career development opportunities for new and established investigators. Although T32 and other educational grant mechanisms exist at NIH, these are not focused on molecular

imaging and are insufficient to support the multidisciplinary nature of education and training in molecular imaging.

Infrastructure and educational facilities should be established for junior, mid-career, and senior investigator fellowships in molecular imaging. Funding support for seminar series, training courses, and hands-on workshops should be provided. In addition, stipends for undergraduates, graduate students, and clinical research fellows in molecular imaging should also be funded. Such educational programs, in collaboration with radiology residency training programs, will breed a new generation of molecular imaging practitioners and physician-scientists.

Therefore, it is important to develop funding opportunities for Education Centers in Molecular Imaging and Education Networks in Molecular Imaging. These centers or networks should develop a multidisciplinary curriculum for studies in molecular imaging and provide the infrastructure and facilities for graduate programs in molecular imaging as part of a local university or medical school.

Fund small-animal multimodality imaging facilities.—The need to support the discovery and development of biomedical imaging methods and molecular imaging agents requires small-animal (eg, rodents, rabbits) models of human disease, in particular mouse models. Small-animal imaging provides the means for noninvasive monitoring of biologic processes, disease progression, and response to therapy, with the potential to provide a natural bridge to the clinical environment and contribute substantially to the development of human medicine. The existing devices and methods of small-animal imaging require further improvement and novel approaches to imaging that enhance spatial or temporal resolution, measurement sensitivity and specificity, and throughput for the more accurate detection, diagnosis, or measurement of treatment efficacy for different disease processes.

Therefore, it is important not only to support but to further increase funding opportunities aimed at the integration of different molecular imaging modalities and methods with anatomic or functional imaging methods, such as optical imaging, US, and/or spectroscopy to provide more effective tools for biomedical research. These advanced multimodality systems for small-animal imaging should provide the flexibility to accommodate a variety of protocols for investigations of

different diseases and the development of platform-independent imaging methods for multicenter research.

Examples of such integrated multimodality systems include (a) CT/optical imaging (near-infrared frequency- and time-domain or diffuse optical tomography), (b) MR/optical imaging (near-infrared frequency- and time-domain or diffuse optical tomography), (c) positron emission tomography (PET)/MR imaging (new avalanche detector-based PET within an MR system), and (d) software-based fusion imaging platforms and analysis tools.

Furthermore, because the cost of in vivo bioluminescence imaging equipment is still prohibitively high for many institutions, the need for supplemental funds to procure high-throughput optical imaging equipment such as bioluminescence imaging systems has been recognized by the molecular imaging community for quite some time. Owing to the potential for wide applicability in pre-clinical research and the ease of operation and image analysis, bioluminescence imaging systems should become “the next PCR [polymerase chain reaction] machine on every bench top” in every vivarium. Also, NIH and NIBIB should develop modular grant mechanisms or supplemental funds for multimodality upgrades (eg, from bioluminescence imaging to PET) to existing small-animal imaging grants and programs.

Fund large-animal multimodality imaging facilities.—The optimization and pre-clinical validation of biomedical imaging methods and molecular imaging agents often requires large-animal models of human disease, in particular dogs, pigs, sheep, and, ultimately, nonhuman primates. Imaging in large animals provides a natural bridge to the clinical environment and contributes substantially to the development of novel complex therapeutic approaches that cannot be scaled from mice directly to humans because of safety reasons. Studies in even a limited number of large animals, especially in monkeys, should provide highly relevant pre-investigational new drug information about the safety and efficacy of the investigational imaging approaches.

Therefore, it is important not only to support but to further increase funding opportunities aimed at establishing large-animal imaging programs that would include different molecular imaging modalities and methods with anatomic or functional imaging methods such as optical, US, and/or spectroscopy to provide more effective tools for large-animal im-

aging research. In principle, commercially available clinical imaging equipment (new or used or decommissioned models) could be dedicated for large-animal imaging, which will also facilitate the translation of imaging protocols and image analysis techniques into clinical practice.

Fund integration of gene expression imaging with genomic and proteomic databases for comprehensive analysis.—Tissue and imaging biomarkers should enable the characterization of specific molecular pathologic processes, improve our understanding of various diseases and patient populations, and assess the extent to which new target-specific drugs reach intended targets, alter proposed pathophysiologic mechanisms, and achieve clinical outcomes. In genomics and proteomics, the tissue biomarker challenge is to identify unique molecular signatures in complex biologic mixtures that can be unambiguously correlated to biologic events in order to validate novel drug targets and predict drug response. In imaging, the challenge is to develop molecular imaging probes (agents) that allow noninvasive whole-body imaging of particular tissue-biomarkers levels in tissues. Both tissue biomarkers and imaging can allow stratification of patient populations or quantification of drug benefit in primary prevention or disease-modification studies in areas where they are sorely needed, such as neurodegeneration and cancer. Clinically useful biomarkers are needed to inform regulatory and therapeutic decision making regarding candidate drugs and their indications, to help bring new medicines to the right patients faster than occurs today.

Therefore, it is important to provide funding opportunities for the integration of gene expression imaging and molecular imaging (in general) with genomic and proteomic, morphologic (tissue banks), and functional databases for comprehensive analysis.

Fund development of clinically applicable and translatable multimodality imaging approaches and probes for monitoring gene and cellular therapies.—Long-term repetitive monitoring of many genetic and cellular-based therapeutic approaches cannot be conducted by using invasive methods (eg, multiple biopsies). Noninvasive whole-body imaging will substantially aid in the development and clinical implementation of various gene therapies, immune therapies, and stem cell therapies by allowing noninvasive monitoring of the location, magnitude, and durability of gene expression in target tissues or

of the fate of the injected progenitor cells over a long period of observation. Non-invasive imaging could help answer several questions related to the biology of immunocompetent and progenitor cells in terms of their migration and homing, their long-term viability, and the organ-specific checkpoints, activity status, or lineage of their differentiation. The ability to image the spatial and temporal dynamics of progenitor cell physiology in patients will aid the development of new therapeutic strategies to control and direct gene expression, immune responses, or stem cell differentiation toward the desired tissue phenotype and function.

The majority of imaging approaches developed to date allow monitoring of the distribution and tissue targeting by various gene-delivery vectors and therapeutic cells. For example, there have been several reports on the use of various superparamagnetic iron oxide (SPIO) nanoparticles to label mammalian cells for monitoring the cells' temporal and spatial migration in vivo with MR imaging.

Although these methods are efficient for in vitro cell separations, cell-surface labeling is generally not suitable for in vivo use because of the rapid recognition and clearance of such labeled cells by the reticuloendothelial system. Alternatively, lymphocytes and other cells have been labeled with small monocrySTALLINE nanoparticles (size range, 10–40 nm) by using fluid-phase or receptor-mediated endocytosis. The efficiency and toxicity of cell labeling with two commercially available, FDA-approved agents has been reported recently (54): ferumoxides, a suspension of dextran-coated SPIOs used as an MR contrast agent, and protamine sulfate, conventionally used to reverse heparin anticoagulation but also used ex vivo as a cationic transfection agent. Labeling of human mesenchymal stem cells, hematopoietic (CD34⁺) stem cells, and other mammalian cells with ferumoxides–protamine sulfate complexes demonstrated no short- or long-term toxic effects, changes in differentiation capacity of the stem cells, or changes in phenotype when compared with unlabeled cells. SPIO labeling of cells does not provide information about the lineage of cell differentiation in vivo or of cell viability, because SPIO particles released from the dead cells are cleared by reticuloendothelial cells (eg, activated microglia in the brain) in a manner similar to clearance of hemoglobin-derived iron in case of a hemorrhage. Moreover, recent studies by the group led by Dr J. Frank at NIH have found that the SPIO-labeled progenitor cells lose

the SPIO label after only five divisions, which markedly limits the applicability of this technology to the long-term monitoring of progeny tissue development, differentiation, viability, and function.

Similar limitations exist for scintigraphic methods of imaging (gamma camera, single photon emission computed tomography [SPECT], PET). For example, ex vivo labeling of lymphocytes or other adoptively transferred cells is limited by a relatively low attainable level of radioactivity per cell when labeling cells with passively equilibrating radiotracers such as the indium 111 (¹¹¹In) oxime and copper 64 (⁶⁴Cu) pyruvaldehyde bis[N4-methylthiosemicarbazone] (PTSM). Substantially higher levels of radioactivity per cell could be obtained with tracers such as fluorine 18 (¹⁸F) fluorodeoxyglucose (FDG) that use facilitated transport and enzyme-amplified accumulation. However, both ⁶⁴Cu PTSM and FDG, have been shown to gradually efflux out of the labeled cells. Progressive loss of radiolabel also occurs during cell division in vivo. Another shortcoming of ex vivo radiolabeling approach is the limited monitoring period, which is due to radiolabel decay and/or biologic clearance. The exposure of cells to higher doses of radioactivity during labeling is limited by toxic radiation effects.

Bioluminescence imaging of cells that express luciferase allows assessment of the cells' distribution throughout the organism in small-animal (eg, mice) experiments. This method is semiquantitative and spatially inaccurate because the intensity of emitted bioluminescent light largely depends on the thickness and variable optical characteristics of tissues. Furthermore, bioluminescence-based approaches currently lack detailed tomographic information and are limited to use in relatively small animals, although it may become feasible in larger animals with use of fluorescence-based diffuse optical tomography. The possibility of administering D-luciferin to humans and its toxicity have not been studied yet. Because of these limitations, bioluminescence imaging of luciferase gene expression is currently not clinically applicable. Furthermore, clinical bioluminescence imaging of reporter-gene transduced cells for long-term monitoring of stem cell therapies dictates the need for nonimmunogenic bioluminescence reporter enzymes and nontoxic substrates suitable for intravenous administration.

Stable genetic labeling of adoptively transferred cells (eg, lymphocytes) with various PET reporter genes has been used

to circumvent the temporal limitations of in vitro radiolabeling or magnetic labeling of cells. Different combinations PET reporter genes and PET reporter probes have been developed (eg, HSV1-TK, ¹⁸F-FHGB, and iodine 124 [¹²⁴I] FIAU; human thymidine kinase type 2 and ¹⁸F FEAU; human SSTR2 and ¹¹¹In octreotide; human D2R and ¹⁸F FESP; human NIS for imaging with different radioactive isotopes of iodine), as well as MR imaging of engineered transferrin receptor gene by using monocrySTALLINE iron oxide nanoparticles. These PET and MR imaging reporter genes allow monitoring of the temporal dynamics of the spatial distribution of therapeutic cells by means of repetitive systemic administration of reporter probes. However, this technology does not currently allow for simultaneous monitoring of the lineage of cellular differentiation and/or function.

Therefore, it is important to provide funding opportunities for a select number of proposals to develop molecular-genetic imaging approaches for monitoring genetic and cellular therapies, which also allow simultaneous visualization and quantification of tissue-specific cellular differentiation and/or function in vivo and noninvasively (whole-body imaging). Such projects could be aimed at preclinical validation of such technologies, with the aim of future implementation in clinical studies. A combination of various imaging modalities, including MR, PET/CT, and SPECT, is thought to provide anatomic, physiologic, and molecular-genetic imaging of cell trafficking, organ and tissue targeting, differentiation, and function.

Clinical Gene Expression Imaging

Fund translational studies to validate imaging of genetic and cellular PET, SPECT, and MR tracers and optical reporter-gene imaging tracers.—A number of promising diagnostic imaging approaches and probes have been developed over the past decade, since the inception of molecular-genetic imaging as a field of biomedical imaging. However, these approaches are not available for use in clinical trials yet. Many of the molecular imaging probes could enhance clinical medicine either by providing a measure of therapeutic gene delivery and expression or of the response to chemotherapeutic interventions or radiation therapy by serving as valuable end points to measures or therapeutic efficacy. Multiple barriers inhibit successful development, but three of the most important are (a) the complex mul-

ticomponent nature of molecular-genetic imaging, (b) the uncertain economic potential that prohibits access to necessary resources, and (c) the lack of coherence between clinical and regulatory requirements.

These barriers have become more obvious as interdisciplinary boundaries have expanded to include molecular and cell biologists, virologists, immunologists, chemists, radiochemists, radiologists, and clinicians in various fields of medicine. Although researchers in an academic medical environment may have access to the necessary resources for product development, there are no effective mechanisms for financial support of costly clinical translational studies on molecular imaging in various genetic and cellular therapies.

A regulatory conundrum that exists because of the complex multicomponent nature of molecular-genetic imaging substantially impedes the translation of molecular-genetic imaging to the clinic. For example, molecular imaging for monitoring tissue-specific targeted gene therapy (eg, the *VEGF* gene into myocardium of patients with chronic cardiovascular insufficiency or the wild-type *p53* gene for treatment of tumors) requires coexpression of a therapeutic and a reporter gene (ie, genetic tracer) such as the *HSV1-tk* gene, which can be imaged with PET or SPECT by using a number of radiolabeled probes (^{18}F -FEAU, ^{18}F -FHBG, ^{124}I -FIAU, ^{123}I -FIAU). These molecular imaging probes can be tested in patients by means of a well-established regulatory mechanism for clinical evaluation of new radiolabeled imaging agents involving an Institutional Radioactive Drug Research Committee, or RDRC. This mechanism allows administration of single or multiple doses of radiolabeled agents in up to 30 patients, provided that these doses will not cause toxic radiation effects in patients. On the one hand, testing of the biodistribution in patients who are not undergoing gene therapy is useless and unethical because there is no potential benefit to individual patients. On the other hand, investigational new drug protocols of clinical gene therapy studies usually do not include imaging for monitoring of gene delivery and expression, because gene-delivery vectors are not designed to coexpress a therapeutic and a PET reporter gene, and the introduction of a new gene-delivery vector that provides coexpression of PET and therapeutic genes requires approval by the Recombinant DNA Committee and a new investigational new drug protocol. Even in gene- and adoptive cell-therapy proto-

cols that are based on the *HSV1-tk* therapeutic-reporter gene, the addition of a previously approved investigational new drug protocol with an RDRC protocol for *HSV1-tk* imaging with a PET reporter probe is not possible, and a completely new protocol has to be approved by the FDA.

Financially, such clinical translational gene expression imaging studies are becoming very expensive due to the addition of the chemistry-radiochemistry and diagnostic PET imaging components to clinical trials. However, without a rapid clinical implementation of already established, preclinically validated gene expression imaging technologies, the whole field of molecular-genetic imaging is likely to collapse.

Therefore, it is important to provide funding opportunities for a select number of proposals that focus on clinical translation and validation of molecular-genetic imaging approaches for monitoring of genetic and cellular therapies. Such projects should be aimed at immediate clinical validation of already established technologies and molecular imaging probes for monitoring gene delivery and expression by using genetic tracers or for monitoring cellular tracers that are genetically enhanced to express PET, SPECT, or MR imaging reporter genes. It should be emphasized that funds will not be supporting preclinical studies aimed at the development of gene expression imaging technologies.

Because of the complexity and expense associated with such clinical trials, it is important to encourage and provide funding supplements to joint academic-industrial research projects and programs. Such academic-industrial collaboration should facilitate the development, optimization, clinical validation, and accelerated approval of novel tracers for imaging of gene expression and activity.

Because FDA requirements dictate that biologic agents and chemicals used in molecular-genetic and cellular therapeutic trials in humans should be of FDA current good manufacturing practice (CGMP) grade, the development of genetic and cellular tracers should also conform to these requirements. Therefore, it is important to fund the development of specialized CGMP facilities to produce precursors for labeling established tracers for molecular-genetic imaging, production of genetic tracers (diagnostic reporter-gene-delivery vectors) for gene expression imaging, and production of cellular tracers (reporter-gene-bearing T cells, NK

cells, stem cells) for monitoring various cellular therapies.

Funding opportunities should also be provided in the form of supplemental funds to support the introduction of molecular imaging of gene expression and cellular trafficking into existing therapeutic clinical trials.

Lobbying and patient advocacy groups should promote molecular imaging of gene expression in clinical studies for individualization and monitoring of therapy (eg, new target-specific tracers to extend beyond FDG).

Fund development and implementation of image-based navigation devices for image-guided biopsy for in situ molecular-biologic validation of noninvasive imaging for target expression and activity.—Because various diseases and pathophysiologic, pathomorphologic, and underlying molecular-pathologic processes are heterogeneous, it is important to account for such heterogeneities when validating newly developed molecular imaging agents. To validate novel target- or process-specific molecular imaging agents, the signal intensity on the images obtained noninvasively (in vivo) should be compared with in situ molecular-biologic measures of target expression and activity, as well as with other target-associated processes.

This paradigm of validation of novel imaging agents should become the main route of approval of the agents by the FDA (although not necessarily of demonstrating diagnostic efficacy for a particular disease or as a statistical predictor of the efficacy of a particular drug or combination therapy).

Recent technologic innovations have almost eliminated the need for real-time imaging during interventional (eg, biopsy) or therapeutic (eg, radiation therapy) procedures or for intraoperative navigation. Such technologies do not require the acquisition of images during interventional procedures and are currently widely used in stereotactic neurosurgery, for intraoperative navigation during open skull interventions and head and neck surgery, for intensity-modulated radiation therapy, and in gamma knife neurosurgery. The contrary of this technology is near-real-time imaging during interventional procedures (eg, angiography-, CT-, or US-assisted tissue biopsy or radiofrequency ablation). From the clinical point of view, the most advantageous approach would be to combine real-time anatomic imaging (eg, CT, MR, or US assisted) with previously acquired and molecular-genetic images to enable precise localization and projec-

tion of an interventional probe (eg, biopsy needle) within the same three-dimensional space.

Therefore, it is important to provide funding opportunities for preclinical and clinical proposals that are focused on integrating the existing or developing novel devices that facilitate image-based navigation for biopsy and surgical resection of tissues and that allow precise registration of the location and orientation of sampled tissue in three-dimensional space on anatomic (CT, MR, angiography, US) and molecular images (PET, SPECT, MR) acquired before the invasive or surgical interventions. Specific emphasis should be made on the development of image-based navigation devices that could be used in preclinical research in small and large animals. Also, specific emphasis should be made on the development of image-based navigation devices that could be used in clinical research in patients, especially for body regions other than the head and neck.

This image-based intraoperative navigation technology will also facilitate the development of image-tagged (spatial heterogeneity-resolved) tissue banks and databases for comprehensive analysis of the established molecular imaging agents and technologies and for the development of new diagnostic and therapeutic tissue and imaging biomarkers.

Fund integration of gene expression and molecular imaging with genomic and proteomic, morphologic, and functional databases.—Tissue and imaging biomarkers enable the characterization of patient populations and the quantification of the extent to which new target-specific drugs reach intended targets, alter proposed pathophysiologic mechanisms, and achieve clinical outcomes. In genomics and proteomics, the tissue biomarker challenge is to identify unique molecular signatures in complex biologic mixtures that can be unambiguously correlated to biologic events to validate novel drug targets and predict drug response. In imaging, the challenge is to develop molecular imaging probes (agents) that allow noninvasive whole-body imaging of particular tissue biomarker levels in tissues. Both tissue biomarkers and imaging can help stratify patient populations or quantify drug benefit in primary prevention or disease-modification studies in areas where they are sorely needed, such as neurodegeneration and cancer. Clinically useful biomarkers are required to inform regulatory and therapeutic decision making regarding candidate drugs and their indications, to help

bring new medicines to the right patients faster than happens today.

Therefore, it is important to provide funding opportunities for the integration of gene expression imaging and molecular imaging, in general, with genomic and proteomic, morphologic (eg, tissue banks), and functional databases for comprehensive analysis.

IMAGE-GUIDED VASCULAR INTERVENTIONS: KRISHNA KANDARPA AND FERENC A. JOLESZ

To address the issues and challenges facing practitioners of endovascular interventions, it was decided in our break-out session to present a vision of the future and the required road map to achieve it, rather than the current state of the art. Endovascular transcatheter interventions primarily consist of recanalization of vascular obstructions or occlusion of blood flow to tumors, vascular malformations, and hemorrhagic lesions (or lesions so prone, such as aneurysms). Today, imaging with x-rays is frequently the only means of assessing on-table treatment end points. Translesion pressure gradient reduction is occasionally employed after treatment of certain stenoses, but this evaluation often ends with a purely anatomic or a delayed clinical assessment. Devices, as well, are designed to (guide or) help perform therapy (eg, angioplasty balloons, stents, bland embolic materials) on the basis of anatomic rather than physiologic end points. Therapeutic agents that are infused locally through catheters (eg, chemotherapeutics, thrombolytics) are often nonspecific in their action and can produce unintended remote systemic side effects that lead to complications.

Vision for the Future

Inasmuch as the current clinical “drivers”—cardiovascular disease (primarily atherosclerosis), cancer, and neurologic disease—are expected to remain so in the intermediate term, there is general support for the idea that related vascular interventions should be guided in the near future by functional imaging and assessment (eg, physiology and motion) rather than merely by anatomy alone.

There is a clear realization that there will be an increasing push to move away from ionizing radiation (ie, x-rays) as the primary means of generating images that guide catheter-based vascular interventions. Thus, US and MR imaging should

be further developed to play a more central role in providing such image guidance. Improvements in imaging motion in real-time with these modalities, which are better able to provide tissue contrast and characterization, will lead to new, less invasive, localized treatments in the heart, abdominal organs, and musculoskeletal structures.

Cross-sectional imaging modalities should be developed to provide robust, multiplanar, real-time imaging information and guidance. Fused or cross-registered multimodality images will provide both anatomic and functional information about the target lesion. Rapidly acquired and displayed information will enable local treatment with rapid assessment of therapeutic end points (eg, tumor viability, perfusion and metabolism, pre- and posttherapy). In addition, better detection of vulnerable atherosclerotic plaques and their tailored treatment could become a reality with further development of optical imaging methods.

In parallel with the above refinements in therapy, there is an urgent need for ergonomic redesign of the procedure suites to incorporate “smart” interactive picture archiving and display systems. Such systems could, for example, respond to the voice commands or eye movements of an operator whose hands would otherwise be occupied.

Therapeutic devices will become more customized and disease specific. The design of these devices will accommodate not only anatomy but also pertinent local biochemical and biophysical (eg, tissue mechanical and thermal properties) responses. “Smart devices” will have sensors that monitor the local biomechanical environment and respond as needed by either adapting their own behavior, emitting the information to external detectors, or triggering local therapeutic cascades (eg, timed drug release).

The activity of therapeutic agents should become more biologically specific to enable a rapid local response without related systemic toxic effects or undesired remote side effects and complications. There will also be new techniques that potentiate therapy within specific sites or organs (eg, enabling selective transgression of the blood-brain barrier), augmenting the therapeutic effect of locally delivered drugs or agents that use energies delivered from external sources (eg, combined ablative therapy with radiofrequency energy plus local intraarterial chemotherapy, local potentiation of carbon dioxide bubbles such as US contrast agents that are presently being ex-

plored to destroy tumors by causing the bubbles to implode by means of cavitation through the application of appropriate external US energy). Finally, on the more distant horizon, there will be as yet unforeseen and unexplored opportunities that will arise from advances in stem cell research.

Challenges and Opportunities for Image-guided Vascular Interventions

The challenges and opportunities facing investigators and funding agencies were categorized in terms of the developments that would be required for each stage in an image-guided vascular intervention: vascular access and device introduction, device visualization and navigation, target visualization, delivery of therapy, and monitoring of the therapeutic response.

Vascular access, device introduction, device visualization, and navigation.—There has to be more research and related funding to help image guidance, in general, to advance from ionizing radiation-based methods (eg, x-ray) to safer methods such as US, MR imaging, and, where appropriate, optical imaging.

Since US and MR imaging presently provide much poorer visibility of current devices than does imaging with x-rays, it is absolutely imperative to encourage a three-way accelerated collaboration between investigators (through funded research), therapeutic device manufacturers (through their programs in advanced materials sciences and miniaturization), and imaging equipment manufacturers (through their programs in image acquisition and display devices) to improve the visualization of devices and delivery systems. Since the need for real-time guidance will demand faster imaging to enable visualization of devices in motion, it is important to fund investigations that will produce the necessary and clever innovative imaging, reconstruction, and display algorithms to accommodate known barriers to accurate visualization (eg, trade-off between spatial and temporal resolution with MR).

Further development of virtual and real-time guidance algorithms that will enable navigation through three-dimensional data sets will also be necessary. By extension, this work should lead to improvements in computer-aided navigation and robot-assisted procedures.

Procedure performance and safety can also be improved by means of further miniaturization of delivery systems and

therapeutic devices. These developments can be accelerated through the incorporation of advances in applied materials sciences.

Target visualization.—Imaging with x-rays, with all its inadequacies, has historically served well in the creation of regional maps of the vascular system. Recently, CT angiography has proved its superiority to conventional angiography in certain applications; however, MR angiography is better able to map the entire vascular tree and is rapidly replacing conventional angiography. The latter is now often used only in a tailored fashion during a planned interventional procedure. The traditionally poor assessment of lesion characteristics (ie, characterization of wall and plaque contents or assessment of flow abnormalities) with conventional (x-ray) fluoroscopy is overcome by modalities such as US and MR imaging, with their superior ability to characterize and differentiate the various components of lesions. CT is able to characterize tissues well but is limited because it requires high doses of ionizing radiation to create the images. Nonetheless, CT remains the most commonly used diagnostic imaging modality and provides the highest resolution three-dimensional clinical data sets that can be adapted for use in image-guidance systems. With further development, optical imaging methods can potentially provide a powerful means to characterize vulnerable plaques in a routine clinical setting.

Improvements are needed in the delineation and definition of target vascular lesions to enable us to provide treatments that are not only more anatomically accurate but that are also biologically tailored. This applies to arterial plaques but will be equally, if not more, useful for endovascular treatment of tumors. Specificity in tumor targeting is expected to improve with the increased use of functional imaging modalities such as PET and SPECT. New developments in functional and molecular imaging will enable us to better assess therapeutic targets and end points.

Advances in multimodality fusion imaging will also vastly improve our ability to treat lesions with better anatomic accuracy and biologic specificity. Also, as optical coherence tomography is further developed, novel endovascular applications may evolve.

Therapy.—Advances in imaging and device design are needed to improve the effectiveness and safety of endovascular therapies. Eventually, whether these ad-

vances do or do not, in fact, result in improved clinical outcomes should be tested through appropriately designed clinical trials. Nevertheless, advances in applied materials science should allow new devices that are compatible with and better depicted with MR and US. The combination of expertise in materials science and our knowledge of normal and diseased tissue biomechanics should allow the design of safer delivery systems and more effective devices. This would include patient-customized and the smart devices mentioned previously.

Computational (ie, mathematic) modeling of therapeutic device performance in relation to the tissue (eg, tissue constitutive and thermal properties) being treated and its local environment (eg, pressure, blood flow patterns, perfusion, diffusion, temperature) will enable a new generation of delivery platforms and devices that are optimized for their physical and biologic action. For example, drug-eluting stents can be developed by means of computer-aided design to provide buttressing optimized to the in situ mechanical properties of the arterial wall, along with a drug-release profile that is tailored to the predetermined local transport phenomena. Resorbable devices could be designed so that the breakdown products are biologically inert and harmless or are rapidly excreted. New non-stent-delivery platforms, such as locally injected drug-carrying microbeads or liquids (eg, ones that change properties near the target, resulting in local stasis with or without release of drugs), should be explored to improve local tumor therapy. Some of these devices may be externally triggered to release agents locally within the target lesion in desired sequences or at times for optimal or maximal biologic effect.

Advances in the design of pharmaceuticals should be aimed to produce agents that are highly specific and whose actions are localized, thereby avoiding undesired systemic effects. In the longer term, specific genes, stem cells, and cell constituents (eg, mitochondria, liposomes) and combinations thereof will certainly provide fertile ground for investigations leading to improved locally targeted transcatheter therapy.

Monitoring.—The newer imaging modalities, especially functional methods such as molecular imaging, combined with real-time multimodality fusion imaging will lead to improvements in therapy planning, procedural guidance, and monitoring.

Challenges to Be Addressed in the Next 5 Years

The most important challenge to be addressed in the near future (ie, 5 years) is to encourage and facilitate interdisciplinary collaboration (eg, among clinical scientists, physicists, chemists, biologists and physiologists, engineering scientists, materials scientists) to improve "cross-fertilization" between these specialists, with the goal of decreasing the "bench-to-bedside" period from development to clinical utilization.

The tasks for this collaboration have been stated previously. There is an urgent need to (a) improve the accuracy of therapy by enabling better target definition and therapeutic end points, (b) characterize the mechanical and physiologic properties of normal and diseased tissues (information that is essential for the design of biologically compatible therapeutic devices), (c) improve the specificity of therapeutic agents across the board; and (d) focus attention on the ergonomic redesign of the imaging suite (eg, "smart" picture archiving and communication systems).

There is a need for change in the culture within departments of medical imaging and, specifically, interventional radiology. These departments need to improve their research profile and the size of the pool of investigators. There is an important need to improve training in research methods, as well as a need for more mentors with research experience. More use of alternative pathways that include research time during the residency years is deemed worthy. With the current shortage of radiologists, it was thought that there was an urgent need to adopt methods and means for retaining graduates and faculty in academic departments. In this regard, it was thought that a call for action should be addressed to funding agencies to help academic departments pay for research programs (eg, time and facilities) at a time when clinical revenues are declining and the disparity between compensation for clinical work versus that for academic work is providing the wrong incentives to potential academicians.

Opportunities to Be Developed in the Next 10 Years

On the 10-year horizon, progress in stem cell research can provide unforeseen opportunities for advancing the treatment of vascular diseases. Better understanding of the role of stem cells and

cellular products can potentially contribute to the armamentarium of the vascular interventionalist in the longer term.

Opportunities are also expected from advances in tissue engineering technology that will allow the development of more biologically compatible devices. Improved understanding of the molecular pathophysiology of disease will also substantially impact the efficacy and safety of catheter-based vascular therapies.

Next Advancements Needed in This Field

In our break-out session, we identified five areas for advancement in endovascular therapy: (a) enhancement of imaging modalities that do not use ionizing radiation to the level needed to guide endovascular interventions and the development of multimodality imaging (and rapid display) in the interventional suite, (b) development of smarter delivery and therapeutic devices, (c) development of biologically specific therapeutic agents, (d) combination of pharmaceuticals and locally destructive technologies, and (e) more fully developed databases on imaging and physiology to allow better simulators and/or robotic interventions.

Current efforts to develop MR-guided vascular interventions need to be accelerated. Although there have been strides made in developing MR imaging for neurosurgical planning and monitoring of treatment delivered by external energy sources (eg, high-intensity focused ultrasound, radiofrequency ablation), little has been accomplished in the area of transcatheter vascular interventions guided by using MR imaging. To date, vascular access almost always is aided by using conventional fluoroscopy or US. Poor device visualization and MR compatibility relegate guidance and navigation to a combination of modalities (eg, MR plus fluoroscopy, US, or visual) rather than to MR imaging alone. MR imaging needs to become an all-encompassing modality for interventions that is used for access, guidance and navigation, and monitoring. This will not be possible unless investigators strongly push both equipment and device manufacturers to see that, in order to realize this vision, their destinies are tied.

Regardless of the modality, there is a clear need for further development and wider deployment of real-time, three-dimensional, multimodality image-registration and display (ie, to account for tissue motion and deformability) software that can be used for guiding com-

plexed interventional procedures either by humans alone or by dedicated robots. The role of optical coherence tomography in diagnosis and treatment of vascular lesions also needs to be better defined and refined.

Device companies should collaborate with imaging equipment manufacturers to improve the depiction of delivery devices as they are navigated in real time. Also, more focused attention needs to be brought to developing the smart devices described earlier.

Pharmaceutical companies have to develop agents that are more biologically specific for the treatment of lesions. The use of destructive energies, such as radiofrequency, high-intensity focused ultrasound, and cryotherapy, needs to be further developed and the specific uses better defined. The combined use of external destructive energies and locally delivered pharmaceuticals or other agents (eg, carbon dioxide bubbles) needs further investigation.

Shared databases (anatomic and physiologic) and, perhaps, simulators need to be developed in order to help engineers and scientists advance both the basic understanding of the mechanisms of disease and the development of novel devices and therapies for vascular disease.

What Will Expedite These Next Advancements?

The development of MR-guided interventions will be expedited by advancements in MR-compatible materials (eg, devices), novel pulse sequences, and postprocessing software. The acceptance of MR imaging as a viable modality for vascular interventions may be enabled by intermediate transitional technologies that combine the use of x-ray and MR imaging. Furthermore, imaging technologies (eg, endoluminal coils that provide better signal-to-noise ratio) that are better at demonstrating and helping define lesions will also accelerate the acceptance of MR imaging for transvascular interventions. Such lesion definition will also improve as real-time, multimodality, three-dimensional image-registration software is improved. Target definition and treatment accuracy will benefit as our understanding of tissue properties (eg, mechanical, thermal) advances. The accuracy of the computational methods used in these developments must be validated with *in vitro* or *in vivo* experiments to verify that the advances do indeed improve target definition and guidance of navigational devices.

The accuracy of locally delivered ther-

apy is important. Targeted delivery of biologically specific pharmaceuticals, biologically active embolic agents, stem cells, cell products, and destructive energies need to be further developed along with noninvasive assessment of cell viability and function, perhaps through the application of newer molecular imaging methods. Such strategies can potentially lead to a quicker assessment of therapeutic end points and readjustment of treatment strategies. Interdisciplinary collaboration will be absolutely necessary to bring about these developments in a timely manner.

Optical imaging methods have not been fully explored for endoluminal applications. Transcatheter techniques should be leveraged because they enable relatively easy access and safer navigation to sites of interest through body conduits for a "local look." These applications can range from enhancing tissue characterization, to guiding tissue biopsy, to completely circumventing tissue biopsy, to delivering local therapy by using photograph-activation techniques.

Robotic methods need accelerated development along with MR-compatible devices. Development of real-time three-dimensional data sets to help navigation also needs more attention from investigators. Sophisticated "augmented-reality" and "pseudoholography" methods also will enable better planning and execution of therapy.

Most important, clinicians should actively identify and communicate their needs to scientists and engineers. Medical schools should encourage and facilitate greater collaboration between their basic science and clinical departments. Databases of anatomic measurements and physiologic information are needed by engineers and scientists to further their design and development work. Finally, clinical trial networks and registries should be established to coordinate research through centralized facilities and databases.

Limitations and Obstacles to Next Advancement?

Clinical workforce shortages in medical imaging departments and ongoing "turf losses" can negatively affect the type, quantity, and quality of future research from these departments. Furthermore, increasing clinical workloads and misaligned financial incentives for academic medical imaging professionals are driving many to seek jobs in private practice, thereby depriving academic depart-

ments of teaching and research faculty. This can result in a shortage of trained investigators and understaffed research training programs. Finally, poor intrainstitutional collaboration and communication (especially between clinical and basic science) can also hinder timely bench-to-bedside research.

What Funding Mechanisms Could Expedite Progress?

New training grants that encourage interdisciplinary collaborations will be important to expedite the research outlined in this document. Funding agencies should consider and provide mechanisms that will enable departments to recruit and retain academically active faculty who can be paid competitively without being drowned in clinical responsibilities or lured away by more financially lucrative options.

To help develop the advancements highlighted by the panel, funding agencies should consider priority areas in image-guided research to focus on integration of imaging data into the interventional suite and programs that encourage development of targeted therapeutic agents (ie, agents that treat the physiologic defect that causes the disease). In addition, the introduction of specific requests for applications, or RFAs, for R01 grant applications that address topics of major anticipated advancements described here would be helpful.

What Educational Mechanisms and Initiatives Could Expedite Progress?

Specialty societies and clinical departments must encourage and facilitate collaboration between biomedical engineering students and their own members. Funding should also be made available for the development of clinical scientists during their clinical training years. This will be one means by which to recruit and retain bright, academically oriented faculty. These faculty members should be nurtured by removing obstacles such as excessive clinical obligations and providing institutional support where necessary. Small-animal imaging facilities ("core laboratories") or human imaging research laboratories should be established within imaging departments. These facilities must be thought of as important resources for the entire institution and should be used to provide training and intrainstitutional interdisciplinary collaboration.

Conclusion

Endovascular therapy will play an important role in the management of cardiovascular, neurologic, and oncologic diseases for the foreseeable future. Since present-day vascular interventions require the use of ionizing radiation, there is a need to develop imaging modalities such as MR and US along with new devices that are compatible with these modalities. In addition, there is a need for display of images in a manner that will facilitate the navigation of therapeutic devices by humans and/or robots. Application of advances in the materials and pharmaceutical sciences will lead to novel vascular devices and therapies that make interventions safer and more effective. Imaging techniques that help rapidly assess treatment and allow for immediate readjustment of the treatment to achieve the desired end points are needed. Interdisciplinary collaboration, especially between the basic and applied sciences, will be key to such progress. Collaboration between academic investigators and device and imaging equipment manufacturers will be important. Funding agencies should encourage such collaboration to accelerate bench-to-bedside projects. As these treatments reach maturity, definitive large trials must be conducted to establish their clinical usefulness.

APPENDIX

The BIROW II Executive Committee acknowledges with appreciation the important contributions of each person listed below in helping enable this successful workshop.

Faculty

Optical imaging: Joseph A. Izatt, PhD, Duke University (moderator); Maria Angela Franceschini, PhD, Massachusetts General Hospital; James G. Fujimoto, PhD, Massachusetts Institute of Technology; Karel Svoboda, PhD, Howard Hughes Medical Institute

Computerized image analysis: Heang-Ping Chan, PhD, University of Michigan (moderator); Sandy Napel, PhD, Stanford University School of Medicine (break-out session leader); Maryellen L. Giger, PhD, University of Chicago; Michael McNitt-Gray, PhD, David Geffen School of Medicine, UCLA; Ronald M. Summers, MD, PhD, NIH.

Imaging of gene expression: Juri G. Gelovani, MD, University of Texas (moderator); King C. P. Li, MD, MBA, NIH (break-

out session leader); Michael Bachman, MD, DSc, Stanford University; David R. Piwnica-Worms, MD, PhD, Mallinckrodt Institute of Radiology, Washington University.

Image-guided vascular interventions: Ferenc A. Jolesz, MD, Brigham and Women's Hospital (moderator); Krishna Kandarpa, MD, PhD, University of Massachusetts Medical School (break-out session leader); Michael Dake, MD, Stanford University; Lindsey S. Machan, MD, Vancouver Hospital and Health Science Centre; Michael C. Soulen, MD, Hospital of the University of Pennsylvania.

Government response on topics, funding opportunities, thoughts on future topics: David W. Feigal, Jr, MD, PhD, FDA; John Haller, PhD, NIBIB; Carol Lucas, PhD, National Science Foundation; Daniel C. Sullivan, MD, National Cancer Institute.

Keynote address: The Imaging Mandate, James H. Thrall, MD, Massachusetts General Hospital.

Executive Committee and Sponsoring Organization Speakers

Ronald Arenson, MD, Academy of Radiology Research; Gary J. Becker, MD, RSNA; Arthur J. Coury, PhD, American Institute for Medical and Biological Engineering; Katherine Ferrara, PhD, Biomedical Engineering Society; C. Donald Frey, PhD, American Association of Physicists in Medicine; G. Scott Gazelle, MD, MPH, PhD, RSNA; C. Leon Partain, MD, PhD, RSNA.

Executive and Program Committees

C. Leon Partain, MD, PhD, RSNA (Executive Committee chair); G. Scott Gazelle, MD, MPH, PhD, RSNA (Program Committee chair); William R. Hendee, PhD, American Institute for Medical and Biological Engineering/Biomedical Engineering Society (Program Committee co-chair); Kristina M. Ropella, PhD, Biomedical Engineering Society (Program Committee co-chair); Katherine P. Andriole, PhD, Society for Computer Applications in Radiology; Gary J. Becker, MD, RSNA; J. Daniel Bourland, PhD, American Association of Physicists in Medicine/American Society for Therapeutic Radiology and Oncology; Paul L. Carson, PhD, American Association of Physicists in Medicine; Laurence Clarke, PhD, NCI; N. Reed Dunnick, MD, Academy of Radiology Research; Robert Edelman, MD, International Society for Magnetic Resonance in Medicine; Katherine W. Ferrara, PhD, Biomedical Engineering Society; Isaac R. Francis, MD, American Roentgen Ray Society; Maryellen L. Giger, PhD, American Association of Physicists in Medicine; Joseph Helpert, PhD; Philip F. Judy, PhD, Medical Image Perception Society; Krishna Kandarpa, MD, PhD; Anna Maria Mason, Society for Com-

puter Applications in Radiology; Edward C. Nagy, Academy of Radiology Research; Theron W. Oviatt, MD, Society of Chairmen of Academic Radiology Departments; Etta Pisano, MD, Association of University Radiologists; Steven Seltzer, MD, Academy of Radiology Research; Richard Swaja, PhD, NIBIB; Michael Vannier, MD, Institute of Electrical and Electronic Engineers; William F. Walker, PhD, BMES; Michael J. Welch, PhD, Society of Nuclear Medicine.

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