From June 28 to July 1, 2008, a group of invited leaders in nuclear cardiology and related disciplines met in Annapolis, Maryland, to examine the current state of nuclear cardiology and to determine where our field needs to go to achieve its full potential of using the tracer principle to detect, assess, and manage cardiac disease. More importantly, the main goal of the meeting was to develop recommendations that would provide a roadmap to focus the efforts of professional societies, clinicians, scientists, government agencies, and industry to clinically manage patients with cardiac disease. A longstanding feature of this conference has been the invitation of experts outside of the field to broaden our perspective. This year, R. Wayne Alexander, MD, PhD, Chairman of Medicine at Emory University, and Michael Lauer, MD, Director of the Division of Prevention and Population Sciences at the National Heart, Lung, and Blood Institute, provided keynote lectures to stimulate all attendees. The conference was funded, coordinated, and superbly staffed by the Nuclear Cardiology Foundation.

Five areas were identified for panels for the conference: imaging of the vascular wall, perfusion imaging using new technologic advances, integrating multimodality imaging with nuclear cardiology, nonperfusion cardiac imaging, and coordinating society efforts to advance cardiovascular molecular imaging. The nonperfusion panel was further subdivided into metabolic, neuronal, dyssynchrony, and remodeling cardiac imaging. Invited members from the American Society of Nuclear Cardiology (ASNC), Society of Nuclear Medicine (SNM), Radiological Society of North America (RSNA), and Academy of Molecular Imaging (AMI) participated in the molecular imaging panel. Members from all 5 panels did an exhaustive amount of work before the meeting and during their sessions. Each panel provided an overview of their consensus to answer the following 4 questions:

- Where is our field today?
- What has our field accomplished since the last invitational conference 2 years ago?
- Where does our field need to go?
- How do we get there?

After each panel’s presentation, there was ample time for discussion of the topic at hand. Breakout sessions with topical experts, nuclear cardiology physicians and scientists, and members of industry allowed the original material to be further modified and organized for final presentation and group discussion to reach consensus on all recommendations.

The tone of the discussions was clearly indicative of a high enthusiasm for the technologic rebirth that the nuclear cardiology field is experiencing. This document summarizes technologic and clinical breakthroughs in emission, transmission, and hybrid imaging devices; investigational radiopharmaceuticals undergoing clinical trials for advanced perfusion, metabolic, and neuronal imaging; new, clinically available pharmacologic stressors with fewer side effects; and new software for improved reconstruction, processing, quantification, and display of cardiac imagery. Moreover, it provides recommendations for potential synergistic efforts with other stakeholder societies to accelerate the development and translation to the clinic of cardiovascular molecular imaging techniques. Taken in sum, these technologic advancements promise to usher in a new era where nuclear cardiology procedures will achieve the simultaneous goals of identifying cardiac disease earlier and more comprehensively while further improving the patient experience during imaging and with a radiation exposure that is lower than has already been reasonably achievable.

We thank the Nuclear Cardiology Foundation and all who participated in this event and hope that the recommendations in this document will spur all stakeholders to work together at this opportune time to make our full potential a reality. We also gratefully acknowledge the support of this conference and this document, which were made possible in part by grants from Astellas Pharma US, Inc; Bracco Diagnostics Inc; Capintec, Inc; Covidien; Digirad; GE Healthcare; INVIA Medical Imaging Solutions; King Pharmaceuticals; Lantheus Medical Imaging; MDS Nordion; Molecular Insight Pharmaceuticals; and Philips Medical Systems.
Imaging of the Vascular Wall

Co-Chairs: Paolo Raggi, MD, and H. William Strauss, MD
Speakers: William C. Eckelman, PhD, Christopher M. Kramer, MD, H. William Strauss, MD, and Benjamin M.W. Tsui, PhD

Panelists not listed above: S. James Cullom, PhD, Andrew J. Einstein, MD, PhD, Edmund M. Herrold, MD, PhD, Lynne L. Johnson, MD, Eileen M. Rattigan, MD, Simon Robinson, PhD, and L. Samuel Wann, MD

Panel 1 addressed the potential role of nuclear imaging of the vascular wall in the management of patients with atherosclerosis. One important area of discussion included the challenges of vascular imaging such as the requirement for imaging systems with very high spatial resolution and the need for imaging biomarkers that target processes that are specific to the dynamic state of atherosclerosis and that are in high enough abundance to be visualized. Another area of discussion was the relative advantages and disadvantages of the various imaging technologies to perform this task such as nuclear imaging, cardiovascular computed tomography (CT), magnetic resonance imaging (MRI), echocardiography, and hybrid systems. The potential clinical role of vascular imaging was discussed, focusing on potential applications such as enhanced risk stratification in selected patient subgroups or in the monitoring of novel therapeutics. In the following text is a more complete discussion of these areas and the panel’s recommendations for how to best move imaging of the vascular wall to the clinical fore.

Importance of Imaging the Vascular Wall

Atherosclerosis is a dynamic immune inflammatory process characterized by cycles of intense activity and progression followed by intervals of stabilization. In the coronary arteries, luminal stenoses that compromise myocardial blood flow (MBF) and induce ischemia during stress are frequently the end product of these events. However, the most devastating event is acute plaque rupture with thrombosis leading to vessel occlusion, myocardial infarction, and frequently, sudden cardiac death. Moreover, for many patients with coronary atherosclerosis, acute plaque rupture is the initial clinical event. Despite the plethora of currently available imaging tools to detect and characterize the extent and severity of coronary atherosclerosis, none of them identify patients with active disease and who are at risk of plaque rupture. Consequently, approaches to image the vascular wall are desperately needed to improve understanding of the pathobiology of atherosclerosis, to better stratify patients and thereby affect management, and to provide surrogate endpoints that are valuable for the evaluation of new interventions directed at the management of vascular disease.

Targeting the Biology of Atherosclerosis—Challenges

Advances in imaging probe design. To characterize an atherosclerotic plaque with noninvasive techniques, the ideal imaging probe must localize in the lesion where it will concentrate with the desired specificity to a biologic process of interest and be retained long enough to permit imaging while it clears from the blood and normal tissues. Potential imaging targets include lipids (low-density lipoprotein or oxidized lipoprotein), inflammatory cell attractants (integrins and chemoattractant factors), metabolic pathways in the inflammatory cells (macrophage glucose metabolism), proliferating vasa vasorum, and in severely inflamed lesions, lymphocytes and granulocytes. In addition to their metabolic activity, foam cells undergo apoptosis, which also can be imaged. Currently, fluorine 18 fluorodeoxyglucose (FDG) is being evaluated for the detection of “biologically active” atherosclerosis based on the premise that the tracer accumulates in activated macrophages, which are a key component of atherosclerotic plaque. Initial results are promising, but many questions remain such as the site of localization of radiotracer (eg, plaque or smooth muscle), the suitability of the method for evaluating the coronary arteries, and whether the information provides more refined risk stratification compared with other more widely applicable methods or whether it alters therapy. Similarly, radiolabeled annexin V has shown the capability to image apoptosis in atherosclerotic plaque in animals, although the suitability of this approach in humans for this purpose is unknown. It should be noted that both of these imaging targets represent late-stage biologic events. Consequently, new molecular imaging approaches are being implemented in an attempt to develop imaging probes that permit the noninvasive detection of earlier stages of atherosclerosis. Examples include post-genomic techniques to identify potential targets and enhance specificity, novel schemes for signal amplification, and new radiochemistry methodologies to enhance specific activity. Robust development and integration of these various areas will be critical to the successful development of clinically useful imaging probes of atherosclerosis.
**Advances in instrumentation.** In the past few years major advances have occurred in the design of all types of imaging systems. Two of the most notable accomplishments have been in the development of hybrid systems (eg, positron emission tomography [PET]/CT and single photon emission computed tomography [SPECT]/CT), which incorporate high sensitivity with high-resolution detection schemes, and the miniaturization of these imaging systems, which permit in vivo visualization of the vascular wall in rodent models of atherosclerosis, facilitating the research cross-talk between mouse and human. However, further improvements, particularly with respect to spatial resolution, are needed. For example, for SPECT and PET, 1.0- to 1.5-mm resolution should be the goal, whereas for MRI and CT, resolution of less than 1 mm and less than 0.5 mm, respectively, needs to be achieved. It is likely that imaging of atherosclerotic plaque biology will require hybrid systems. In addition to optimizing image resolution and sensitivity, these systems will need to minimize radiation exposure. In this regard, the development of PET/MRI systems may hold particular promise.

**Imaging technologies.** In addition to nuclear imaging, several noninvasive imaging technologies can be used at present to image the vessel wall, such as MRI, CT, and ultrasound by use of carotid intimal-medial thickness (CIMT). MRI can image the vessel wall in the aorta, carotid, and peripheral vessels, as well as the wall thickness of coronary arteries. In vitro and in vivo studies have validated the ability of multispectral MRI to differentiate the major components of atherosclerotic plaque including fibrous cap, lipid core, calcium, and hemorrhage. A thin fibrous cap, extensive lipid-rich necrotic core, and hemorrhage into plaque have been identified as high-risk features associated with adverse outcomes in retrospective and prospective studies. Given the reproducibility of measurement of plaque volume by MRI, it has been used in studies with relatively small sample sizes to demonstrate carotid and aortic plaque regression with lipid-lowering therapy. Disadvantages include equipment expense and the inability to image patients with pacemakers and defibrillators. Multiple studies over the last 2 decades have confirmed the prognostic utility of coronary calcium scoring (CCS) by CT. Recent studies suggest that the utility of CCS may be highest in asymptomatic patients aged 45-55 years with intermediate Framingham risk. CIMT has yet to be integrated into routine clinical practice because of the lack of a randomized controlled trial of its use to improve preventive therapies and outcomes.

**Recommendations**

What follows are the top priorities where significant progress is needed in the next 2 years:

1. There should be a primary focus on vascular imaging with PET-CT and FDG with specific research areas including the following:
   - Technical advances
     - Perform studies to better localize the source of increased tracer uptake (eg, activated macrophages and smooth muscle cells).
     - Optimize the imaging protocol to maximize signal intensity while at the same time minimizing radiation exposure. This will require further advances in both PET and CT design to enhance signal sensitivity and localization as well as devising protocols that minimize background activity while maintaining signal strength.
     - Standardize image analysis with respect to extent and severity of disease and reproducibility using qualitative, semiquantitative, or quantitative techniques.
   - Identifying clinical applications and proving clinical utility
     - Identify appropriate patient populations (eg, asymptomatic patients aged 45-55 years with intermediate Framingham risk) where current prognostic paradigms are adequate for assigning risk.
     - Identify endpoints that will be measured and demonstrate that FDG uptake as an imaging biomarker is superior to other benchmarks (eg, other clinical or blood biomarkers). The relative prognostic value of carotid artery as opposed to coronary artery FDG uptake should be assessed.
     - Consider a variety of funding options including multivendor support with and without National
Institutes of Health (NIH) partnership. The panel recommends discussing potential funding strategies (eg, registry trials) with imaging societies that were instrumental in the performance of clinical PET-FDG trials for oncologic applications (eg, Academy of Molecular Imaging and Society of Nuclear Medicine).

2. Efforts should still continue to determine the utility of non-nuclear approaches for assessing atherosclerotic plaque. Cardiac CT can potentially identify soft plaque and estimate plaque burden. The technology is readily available and the imaging relatively straightforward. However, technical advancements are still needed, including methods to reduce radiation exposure and better and more efficient image quantification tools. Similarly, cardiac MRI (with and without contrast) has been shown to identify risk features of aortic and carotid plaque with a relatively low measurement error and a high degree of reproducibility. Appropriately designed clinical trials are needed to identify patient subsets that would demonstrate enhanced risk stratification and altered treatment strategies based on CT and MRI.

What follows are the top priorities where significant progress is needed in the next 5 years:

1. Imaging probe design: Continue with vigorous research and development of new imaging probes (nuclear, MRI, and CT) whose signal intensity accurately reflects key biologic pathways to various aspects of atherosclerosis (eg, inflammation, cell proliferation, and apoptosis) and that can be detected noninvasively. Clearly, post-genomic techniques for target identification and advanced techniques for probe labeling should be used.

2. Instrumentation: Improved sensitivity and resolution (both spatial and temporal) is needed for both human and small animal imaging systems. Emphasis should be placed on hybrid systems, as these will likely be the most successful at meeting the dual challenges of high sensitivity and resolution.

3. Image reconstruction, analysis, and display: Continue development of new reconstruction algorithms to enhance image resolution, alignment, analysis, and display. Such software packages need to be implemented on clinically available workstations and so they can be used routinely to enhance workflow.

4. Develop methods for linkage of information from imaging with genomic, proteomic, and metabolomic data to improve upon conventional risk stratification tools such as the Framingham score and the EuroSCORE.

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**PANEL 2**

**Perfusion Imaging: Adapting to New Technologies**

Co-Chairs: Manuel D. Cerqueira, MD, and Gary V. Heller, MD, PhD

Speakers: Timothy M. Bateman, MD, James A. Case, PhD, and Edward P. Ficaro, PhD

Panelists not listed above: Kim A. Williams, MD, Frank Anstett, MBA, Richard J. Barrett, PhD, Richard L. Comwell, D. Scott Edwards, PhD, Christopher L. Hansen, MD, Robert A. Kovac, Kim McDaniel, and Kamran Rafii

**Improving Diagnostic Accuracy**

Myocardial perfusion imaging (MPI) has attained widespread clinical acceptance as a standard of care for the diagnosis and assessment of coronary artery disease (CAD) in patients with known or suspected disease. The technologic advancements in CT angiography and the continuing improvements in magnetic resonance imaging provide future alternatives to SPECT and PET MPI. This is an opportune time to address the benefits of each modality.

MPI remains the best-validated noninvasive cardiac imaging technique for determining short-term risk and for short-term management decisions. Further improvement in overall diagnostic accuracy can be accomplished in 2 ways: (1) increase sensitivity by improving the detection of patients with left main and multivessel CAD and more accurately identifying single-vessel disease and (2) improve overall image quality, which also translates to improved quantification of myocardial perfusion and flow. The technologic challenge is to accomplish this improvement in image quality while at the same time continuing to increase overall study efficiency and reduce the patient’s radiation exposure to as low as reasonably achievable.

The most direct approach to improving diagnostic accuracy by improving image quality is for more widespread utilization of existing innovations. In SPECT routine clinical use of existing validated attenuation correction, scatter correction, and resolution recovery techniques has been shown to improve diagnostic accuracy. Moreover, new software reconstruction techniques that combine resolution recovery with noise suppression seem to promise greater efficiency with comparable image quality and possibly the same quality with lower radiation exposure. In PET, rubidium 82 MPI appears to
offer improved image quality, better efficiency, and higher accuracy. For PET and SPECT, the interplay between perfusion and CCS (often acquired in the same setting by use of hybrid PET/CT and SPECT/CT devices) is being explored for increasing diagnostic accuracy. A new Food and Drug Administration (FDA)–approved A2a-selective pharmacologic stress agent also shows great promise for improving both efficiency and patient comfort.

**Advancing SPECT/PET Instrumentation**

For nuclear cardiology, SPECT imaging cameras are still largely based on Anger camera technology with thallium-activated sodium iodide crystals and low-energy parallel-hole collimators. Although there are a wide variety of configurations within these SPECT imaging systems, the imaging properties related to imaging resolution, sensitivity, and contrast remain fairly constant between systems and largely unchanged. Current SPECT imaging systems have also been successfully coupled with sealed-source and x-ray transmission imaging systems to correct for patient-specific attenuation correction (absorption and scatter).

**Recent Innovations.** There have been several innovative SPECT and PET technologies that have emerged since 2006. These new technologies include hybrid SPECT/CT imaging systems with multislice diagnostic CT imaging that can acquire CT for attenuation correction, electrocardiography-gated images for assessment of coronary calcium, and CT angiography of the coronary vessels. Recent advances in detector geometries, using larger imaging areas and/or focused or region-centered collimation, have shown significant improvements in primarily count sensitivity, with some improvement in spatial resolution. Advancements in iterative reconstruction algorithms using appropriate modeling for noise and collimation have shown comparable or improved (ie, resolution) image quality compared with conventional reconstruction with a fraction of the required counts.

PET imaging systems are now primarily 3-dimensional systems (ie, no septa) and include multislice CT for attenuation correction, anatomic findings, and CT angiography. Depending on the camera vendor, PET systems can offer high-performance detector crystals, extended fields of view, state-of-the-art iterative reconstruction algorithms, respiratory and electrocardiographic gating, and time-of-flight technology. Most, if not all, of these advancements have resulted in increased count sensitivity and resolution for cardiac imaging.

**Roadmap for implementing innovations.** Diagnostic imaging has become more complicated as accreditation and reimbursement processes can impact the equipment that imaging centers can use. It will become more important for professional societies and their members to work with industry to advance new technologies for routine clinical use. A key component in advancing technologies from concept to clinical use is the validation of these methods to ensure that diagnostic quality is maintained.

**Importance of Measuring MBF**

Another approach to increasing MPI diagnostic accuracy is to clinically integrate the current visual and relative quantitative methods of perfusion assessment with measurements of absolute MBF and coronary flow reserve. Although there have been some reports in the Japanese and Italian literature that these flow measurements are possible with SPECT, most of the experience has been with PET.

There has been considerable investigation of the measurement of MBF by use of cyclotron-generated oxygen 15 water, carbon 11 acetate, nitrogen 13 ammonia, or generator-based Rb-82. These agents have been readily available as part of large-scale academic research programs and, in the case of Rb-82, in some private practice settings. Their short physical half-life restricts utilization to short physical distances from the cyclotron facilities or generator. F-18–labeled perfusion agents currently in phase I development may provide improved flexibility in the delivery to nonacademic imaging centers, but much development is required before it becomes available.

Measurement of MBF should potentially improve the detection and characterization of a significant percentage of patients with obstructive plaques. Moreover, flow measurements may also aid in the detection of less severe plaques, which account for over one half of all myocardial infarctions and sudden cardiac deaths. Thus direct measurement of MBF could provide crucial diagnostic and management data to clinicians in selecting optimal therapies and dosages for individual patients.

Although there are many reports establishing the use of existing software tools to measure MBF and coronary flow reserve, several key changes are needed to bring about widespread clinical adoption. First, automatic software techniques will be needed for measuring the required parameters for calculating MBF. Second, kinetic models will need to be expanded to include estimates of wash-in, washout, and retention models across a broad spectrum of patients. Lastly, clinical insight will be required to incorporate MBF measurements into the clinical decision-making algorithm.
Recommendations

What follows are the top priorities where significant progress is needed in the next 2 years:

1. Address improved validation of new technologies in clinical guidelines
2. Assist industry in developing a roadmap for validation procedures for new technologies
3. Implement stress-only imaging with attenuation correction to reduce protocol time
4. Implement protocols to continue to reduce radiation exposure
5. Explore the full potential of new A2a-selective stressors to improve diagnostic accuracy of perfusion imaging and increase study efficiency and patient comfort
6. Continue to improve instrumentation and reconstruction software for SPECT to optimize cardiac imaging
7. Continue development of instrumentation and software to measure blood flow
8. Provide more correlative data to distinguish PET from SPECT
9. Define the clinical role of PET
10. Update ASNC imaging guidelines for PET
11. Add PET to appropriateness criteria
12. Determine accuracy of MBF measurements
13. Establish in which population MBF is useful

What follows are the top priorities where significant progress is needed in the next 5 years:

1. Make PET more accessible nationally and regionally
2. Improve accreditation requirements based on image quality and instrumentation
3. Develop instrumentation to provide accurate biomarker and molecular imaging
4. Encourage the FDA to accept new surrogate imaging endpoints
5. Generate outcomes data for MBF when established clinically
6. Develop an MBF registry for PET to expand indications in preclinical patients
7. Continue to develop better perfusion tracers

**PANEL 3**

**Multimodality Imaging: How to Integrate Nuclear Cardiology**

Co-Chairs: George A. Beller, MD, and Daniel S. Berman, MD

Speakers: Leslee J. Shaw, PhD, Piotr J. Slomka, PhD, and Jack A. Ziffer, PhD, MD

Panelists not listed above:
Sholom M. Ackelsberg, Dennis A. Calnon, MD, Angela Da Silva, D. Scott Edwards, PhD, Rick Kelly, John J. Mahmarian, MD, Rex Old, Randall C. Thompson, MD, and James Waples

Panel 3 was tasked with discussing the role of nuclear cardiology within the framework of multimodality imaging for the management of patients with cardiovascular disease. Key areas of discussion included the relative importance of integrating nuclear cardiology with other imaging techniques, such as CT or MRI, and meeting the challenges of confronting the clinical dissemination of multimodality imaging, such as determining whether integration is best achieved with sequential or hybrid imaging, the technical challenges of integration, and what evidence is needed to prove the clinical value of integrating these various imaging methods. In the ensuing text is a more complete discussion of these areas and the panel’s recommendations for how to best link specific imaging combinations with clinical scenarios that will result in the improved management of the cardiovascular patient.

**The Case for Integrating Nuclear Cardiology with Other Imaging Technologies**

There is growing, consistent evidence that there may be complementary strengths in integrating various imaging strategies such as nuclear cardiology, CT, and MRI. The results of single-center and multicenter studies of CCTA confirm the robustness of this approach to delineate the anatomic extent of atherosclerosis. However, from the available evidence, it is also clear that this approach limits identification of vessels with dense coronary calcification and, importantly, definition of the hemodynamic significance of coronary stenosis. On the other hand, MPI represents a robust approach to detecting obstructive CAD, quantifying the magnitude of jeopardized myocardium, and assessing the extent of myocardial viability. However, this approach often uncovers only that territory supplied by the most severe stenosis and frequently fails to identify patients with multivessel CAD as being at high risk. It is widely held that balanced reduction of flow in patients with multivessel disease may explain the paradoxical underestimation of clinical risk by a normal scan pattern in high-risk cohorts. The integration of nuclear medicine cameras...
with multidetector CT scanners (eg, hybrid PET/CT and SPECT/CT) provides a unique opportunity to delineate cardiac and vascular anatomic abnormalities and their physiologic consequences in a single setting. However, the practicality of this integration is unclear because of difficulties in determining before the test which patients require both definition of coronary stenosis and assessment of the physiologic significance of stenosis. Nonetheless, the potential usefulness of the combination of CCTA and quantitative MPI during a single study deserves evaluation. From a practical standpoint, hybrid scanning by use of cardiac CT without contrast administration in association with MPI provides an effective method for detection and quantification of the extent of calcified plaque, quantification of vascular reactivity and endothelial health, and assessment of myocardial viability. In the future, hybrid systems may provide the ideal imaging platform to perform cardiovascular molecular imaging, which will require signal-detection schemes with high sensitivity and spatial resolution.

Challenges Confronting the Dissemination of Multimodality Imaging

Sequential versus hybrid imaging. If it is assumed that clinical scenarios exist where multimodality imaging is useful, a logical question is whether a sequential or a combined approach is preferable. In the former situation, different imaging systems would provide the anatomic (eg, CT) and physiologic information (eg, PET or SPECT). In the latter scenario, this would be achieved by use of hybrid systems such as PET/CT or SPECT/CT. Currently, the enthusiasm for hybrid systems is related to their availability (made possible by the widespread use of these systems for oncology) and not by their use in readily identifiable patient subsets with cardiovascular disease. However, there are several theoretic advantages of hybrid imaging that further warrant enthusiasm for their use in cardiovascular imaging. For example, if CCS is obtained from the same data acquisition as during attenuation correction, then radiation dose would be decreased, and the additional information of CCS would be a routine part of MPI examinations. Given the growing body of evidence of the usefulness of combining CCTA with MPI, the ready availability of CT combined with PET or SPECT could increase patient convenience when both studies are required. However, as noted previously, the convenience is outweighed by the difficulty in defining which patients require both examinations, as well as drug interactions (β-blockers or nitroglycerin used in CCTA) influencing the performance of MPI. Nonetheless, future possible applications, such as plaque imaging via molecular imaging techniques, may warrant the need for more exact localization, which is enabled by a hybrid approach.

Accurate image registration. Software solutions have emerged from several vendors to provide fusion of images obtained from different imaging devices, but most of these tools do not provide robust automated algorithms for realignment and manual interaction is required. Furthermore, the cumbersome interactive steps discourage the routine use of multimodality integration and require additional training. There is currently no cardiac software available clinically to perform MRI-MPI cardiac fusion. Similarly, the fusion of echocardiography and MPI is not clinically used, and there is no available clinical software for this purpose.

Need to prove added value. Data are needed to prove added value with multimodality imaging. Despite the promise of serial or hybrid imaging, the current evidence base is weak and largely composed of small patient samples. Data will have to be devised in large, randomized clinical trials or multicenter registries that provide information on the net reclassification of risk—a statistical tool to calculate added value. Akin to the new requirements set forth by the Centers for Medicare & Medicaid Services and Blue Cross/Blue Shield, randomized clinical trials should be designed with the primary endpoint of improved patient outcomes. Moreover, the inclusion of cost-effectiveness analysis should also be a central component of trial design so as to create optimized test efficiency pathways for key patient populations. Whereas most research to date has relied on industry funding, it appears that the National Heart, Lung, and Blood Institute may be expanding funding options to include focused research on cardiovascular imaging, similar to what is current practice within the National Cancer Institute. Finally, future growth in the field of cardiovascular imaging should include trials that focus on the needs of patients worldwide and consider alternative diagnostic pathways in development. Ultimately, research that provides a balance of risk-based information that includes both the physiology (perfusion reserve as well as defect extent and severity) and anatomy (ie, obstructive and nonobstructive atherosclerosis) will prove optimal for determining whether there is a benefit of multimodality imaging with respect to enhanced prognostication and targeted therapeutic intervention.

Recent Accomplishments

Over the last 2 years, there have been a number of scientific publications showing the potentially complementary information obtained from multimodality approaches. Examples include the following:

- Data from multiple single-center studies have suggested that stress MPI provides valuable clinical
Numerous technical advances are needed to improve workflow within the imaging laboratories by use of a multimodality approach. Software packages that allow efficient clinical routine application of multimodality image registration and attenuation-corrected alignment quality control need to be developed and included in the “front end” of the camera/computer system. These packages need to tailored to both sequential and hybrid acquisition schemes.

2. Because 15% to 30% of patients may need multimodality imaging via nuclear and CT methods, there should be continued efforts to identify strategies to reduce radiation exposure. These strategies should be multifactorial, ranging from new hardware design (eg, increased sensitivity) to improved acquisition schemes (eg, CCS and attenuation correction obtained simultaneously) to potentially more efficient clinical protocols (eg, stress-only imaging with attenuation correction).

3. Sequential-imaging randomized control trials are needed to define the appropriate patient groups and clinical situations where nuclear cardiology or CT is the best first test. Moreover, clinical scenarios where a second imaging test is required need to be defined so that “good layering” and “bad layering” practices are identified. Metrics would include outcomes and cost assessed in low-, intermediate-, and high–pretest likelihood risk patients. Funding for these trials would require support from numerous vendors and likely partnering with the NIH. Examples of investigational areas include the following:

- In cases where MPI results are normal, is there a role for further imaging? Does CCS provided added benefit by identifying atherosclerosis, or is CCTA needed to identify severe balanced occlusive disease or noncalcified plaque? Moreover, does aggressive medical therapy alter outcome in the setting of documented atherosclerosis with normal myocardial perfusion?
- In cases where the MPI results are equivocal, what is the role for CCS or CCTA?
- When CCTA findings (eg, stenoses of intermediate severity, image degradation due to artifacts, and presence of coronary calcium) indicate an additional MPI study would be useful, what is the role of stress-only MPI?

Further studies are also needed to clarify the role of multimodality imaging in other cardiovascular patient groups. For example, what is the role of combined neuronal imaging (by use of metaiodobenzylguanidine [MIBG]) and scar imaging (eg, SPECT MPI, FDG PET, MRI, or CT) in identifying patients who would benefit from implantable cardioverter defibrillator placement? Or what is the role of combined anatomic imaging (via MRI, CT, or echocardiography), scar imaging, and dyssynchrony imaging (via echocardiography or SPECT) in identifying patients who will

Recommendations

What follows are the top priorities where significant progress is needed in the next 2 years:

1. Numerous technical advances are needed to improve workflow within the imaging laboratories by use of a multimodality approach. Software packages that allow efficient clinical routine application of multimodality imaging and attenuation-corrected alignment quality control need to be developed and included in the “front end” of the camera/computer system. These packages need to tailored to both sequential and hybrid acquisition schemes.

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4. Further studies are also needed to clarify the role of multimodality imaging in other cardiovascular patient groups. For example, what is the role of combined neuronal imaging (by use of metaiodobenzylguanidine [MIBG]) and scar imaging (eg, SPECT MPI, FDG PET, MRI, or CT) in identifying patients who would benefit from implantable cardioverter defibrillator placement? Or what is the role of combined anatomic imaging (via MRI, CT, or echocardiography), scar imaging, and dyssynchrony imaging (via echocardiography or SPECT) in identifying patients who will

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- In cases where the MPI results are equivocal, what is the role for CCS or CCTA?
- When CCTA findings (eg, stenoses of intermediate severity, image degradation due to artifacts, and presence of coronary calcium) indicate an additional MPI study would be useful, what is the role of stress-only MPI?

4. Further studies are also needed to clarify the role of multimodality imaging in other cardiovascular patient groups. For example, what is the role of combined neuronal imaging (by use of metaiodobenzylguanidine [MIBG]) and scar imaging (eg, SPECT MPI, FDG PET, MRI, or CT) in identifying patients who would benefit from implantable cardioverter defibrillator placement? Or what is the role of combined anatomic imaging (via MRI, CT, or echocardiography), scar imaging, and dyssynchrony imaging (via echocardiography or SPECT) in identifying patients who will
benefit from cardiac resynchronization therapy (CRT)?

What follows are the top priorities where significant progress is needed in the next 5 years:

1. Hybrid equipment needs to be optimized to extend its application beyond the combination of CCTA and MPI. Potentially unique applications of hybrid equipment would include combined MIBG and cine CT imaging, assessing peripheral vascular disease, and in the clinical application, molecular imaging. In the latter case, the clinical role for vascular imaging with PET/CT and FDG needs to be clarified. Furthermore, the potential applicability of PET/MRI should be explored.

2. There is a need to identify the clinical role of absolute quantitative measurements of myocardial perfusion. Such measurements will be key to optimally identifying patients with atherosclerosis documented by CCTA but diffuse microvascular disease as opposed to those with high-risk occlusive disease.

3. The use of hybrid imaging needs to be explored as a means to apply new molecular imaging approaches to develop personalized medicine approaches. Such applications are likely to benefit from the combination of the attributes of PET and SPECT for imaging the molecular targets with the precise anatomic definition of disease provided by the high resolution of CT and MRI.

PANEL 4

Nonperfusion Imaging of the Myocardium

Co-Chairs: Myron C. Gerson, MD, and Vasken Dilsizian, MD

Speakers: Robert Beanlands, MD, Myron C. Gerson, MD, Ernest V. Garcia, PhD, and Albert J. Sinusas, MD

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Metabolic Imaging

Metabolic imaging has played a key role in diagnosis, prognostication, directing therapy, and understanding heart failure, dilated cardiomyopathy, hypertrophic cardiomyopathy, diabetic heart disease, and microvascular disease and in evaluating new therapies. Metabolic imaging can be performed with either PET or SPECT.

Viability. The perfusion/metabolism mismatch pattern on FDG PET imaging is the gold standard for clinically detecting hibernating myocardium. FDG PET metabolic imaging has the advantage that it is FDA approved. FDG PET imaging has shown proven benefit by identifying the potential for recovery of ventricular function and improvement in heart failure symptoms, as well as predicting survival after revascularization. SPECT metabolic imaging with either thallium 201 or technetium 99m tracers is also reliable in detecting myocardial viability, particularly in patients with mildly to moderately impaired left ventricular (LV) dysfunction (left ventricular ejection fraction [LVEF], 25%-50%). SPECT metabolic imaging has the advantage over PET in that there is widespread availability of SPECT cameras in outpatient practices. Moreover, SPECT metabolic imaging does not have the complexity of FDG imaging in the diabetic patient.

Myocardial ischemia. Beyond its proven value for myocardial viability, metabolic switch from fatty acid to glucose has been shown to be a sensitive marker of myocardial ischemia, which persists long after resolution of symptoms and perfusion defects, termed ischemic memory. FDG metabolic imaging with SPECT equipped with a high-energy collimator has the advantage that it can be acquired simultaneously with a SPECT perfusion agent with the FDG “hot imaging” portion not being limited by soft-tissue attenuation generating high-contrast images of ischemia. Because the FDG study is done in fasting conditions, the uptake is heterogeneous and the nonischemic myocardial regions are not seen, so they cannot serve as a reference standard for either visual comparison or relative quantitation.

Fatty acid (iodine 123 beta-methyl-iodophenylpentadecanoic acid) SPECT imaging has the potential for widespread use because of the high availability of SPECT cameras. Moreover, because the ischemic areas appear as “cold spots,” it is more congruent with the experience from perfusion imaging. This attribute allows current quantitative software programs to be easily modified and applied for metabolic imaging. Nevertheless, just like with any new tracer, physicians will have to become familiar with the nuances of a somewhat different normal tracer distribution. Because I-123 has a longer half-life (13 hours) than F-18 (2 hours), it facilitates centralized distribution like a conventional pharmaceutical. Patients with previous myocardial infarction require an additional resting perfusion study with this approach.

Multidetector CT is a competing modality to metabolic imaging for detection of ischemia with the advantage that it can render a quick assessment independent of tracer availability. Despite its high cost, in the emergency department, multidetector CT can be used in a triple–rule out protocol (CAD, pulmonary embolism, and
Neuronal Imaging

Neuronal imaging of the heart can be performed with SPECT and I-123 MIBG or PET and C-11 hydroxyephedrine (HED). The advantage of I-123 MIBG imaging is that it is an easy imaging protocol with favorable dosimetry that uses readily available SPECT instrumentation and relies on experience reported in extensive literature, especially from Europe and Japan.

PET neuronal imaging has the advantage that it allows improved regional myocardial visualization and quantification of the relationship of adrenergic receptor density to the norepinephrine uptake 1 mechanism. This advantage is tempered by the impracticality of using C-11–labeled radiotracers, such as HED, in the clinical setting, because of the 20-minute half-life of C-11. PET neuronal radiotracers with longer half-lives, such as F-18 dopamine or I-124 MIBG, could have wider clinical utility. However, there is still limited use of PET cameras in cardiology practices.

Heart failure. MIBG imaging has been shown to have incremental prognostic value beyond LVEF and clinical variables. Phase III clinical trials have been completed in the United States, and data are being analyzed for FDA submission. It is expected that, once approved, MIBG imaging will be used for (1) selecting patients for transplantation, (2) selecting patients for LV assist devices, and (3) identifying patients with diabetic cardiac neuropathy.

Electrophysiology. Early data using the measurement of the heart-to-mediastinum ratio from MIBG studies have shown promising results for predicting firing of an implanted defibrillator. Similarly, a retrospective European collaborative study has been published confirming the predictive power of I-123 MIBG imaging for total mortality rate and for the combined endpoints of cardiac death, cardiac transplantation, and potentially fatal cardiac arrhythmias. Large clinical studies are also being undertaken to analyze the role of MIBG imaging in heart failure patients with implantable cardioverter defibrillators and to assess the relative roles of myocardial perfusion and innervation in the prediction of sudden cardiac death.

Imaging LV Dyssynchrony

Nuclear imaging such as radionuclide first-pass and multiple gated blood pool imaging has been used to quantify interventricular and intraventricular dyssynchrony based on Fourier phase analysis. For heart failure patients, phase analysis measurements of the variability of regional onset of contraction predict the magnitude of improvement in LVEF, as well as in interventricular and intraventricular synchrony, in response to CRT.

Recently, phase analysis has been developed to allow assessment of LV dyssynchrony by gated SPECT MPI. This technique uses measurements of regional wall thickness changes over the cardiac cycle to calculate the regional onset–of–mechanical contraction phase. Once the onset–of–mechanical contraction phases are obtained 3-dimensionally over the left ventricle, a phase distribution map is formed that represents the degree of LV dyssynchrony. This automatic, reproducible technique has been compared with other echocardiographic methods of measuring LV dyssynchrony and shown promising results in clinical evaluations, particularly in predicting which heart failure patients will respond to CRT.

Imaging LV Remodeling

Emerging evidence is mounting for the role of angiogenesis, matrix metalloproteinases (MMPs), renin-angiotensin-aldosterone system, and caspase/annexin in the progression of LV remodeling after myocardial infarction and/or heart failure.

Investigators are developing approaches for direct imaging of the changes in myocardial collagen associated with remodeling. Others have been developing high-sensitivity MMP-targeted molecular imaging approaches applied in combination with functional imaging methods like cine MRI or cine CT to quantify regional MMP activity and changes in LV deformation and geometry after myocardial infarction. There may also be a role for targeted imaging of angiotensin-converting enzyme or angiotensin or aldosterone receptors within the myocardium by use of radiolabeled angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or aldosterone blockers.

The application of multimodality imaging and targeted molecular imaging approaches should provide unique insights into the role of mechanical forces and activation of MMP and/or the renin-angiotensin-aldosterone system in the processes involved in ventricular remodeling and translate to direct clinical applications that hold both prognostic and diagnostic potential. This multimodality imaging will be facilitated by the availability of hybrid imaging systems (ie, SPECT/CT and PET/MRI).

These imaging approaches have potential clinical applications in 4 general areas:
1. Identifying LV remodeling early: Targeted receptor imaging may identify LV remodeling early in the disease process before transition to interstitial fibrosis and scar formation occurs.

2. Image-guided medical therapy—image-guided approach for early identification of LV remodeling (stages A and B in heart failure): Appropriate selection of therapy, dose, and duration of treatment are some of the advantages of targeted receptor imaging.

3. Efficacy of future treatments: The efficacy of future treatments such as modulators for medical treatment in congestive heart failure, as well as fatty acid oxidation inhibitors (ranolazine) and insulin sensitizers, can be tested with such highly specific receptor imaging.

4. Phenotypic characterization of genetic variables, such as CD36 and peroxisome proliferator–activated receptor: This characterization would facilitate drug development, particularly tailored to individual patients.

These approaches have been successful in oncology, and they reflect current trends in NIH personalized medicine initiatives and are thus worthy of funding.

**Recommendations**

What follows are the top priorities where significant progress is needed in the next 2 years:

1. Generate outcome data showing efficacy of beta-methyl-iodophenyl-pentadecanoic acid in the emergency department.

2. Perform neuronal studies showing greater value of MIBG compared with T-wave alternans, measures of LV dyssynchrony, and magnetic resonance scar for benefit of automatic implantable cardioverter defibrillator implantation. Pay particular attention to patients with LVEF in the range of 30% to 40%.

3. Perform neuronal studies showing greater value of MIBG compared with LVEF, myocardial oxygen consumption (MVO2), and 6-minute walk for selection of patients for transplantation or left ventricular assist device (LVAD).

4. Collaborate with electrophysiology physicians (EP) to develop clinical outcome data for the use of noninvasive measures of dyssynchrony for resynchronization therapy.

5. Advocate for NIH-sponsored requests for proposals (RFPs) for molecular and receptor imaging relating to LV remodeling and heart failure.

What follows are the top priorities where significant progress is needed in the next 5 years:

1. Develop F-18–labeled HED-like and autonomic receptor tracers.

2. Develop translational hardware and software tools to take molecular and receptor imaging applications from the bench to the bedside.

**PANEL 5**

**Cardiovascular Molecular Imaging: Societal Efforts**

*Co-Chairs: Frank M. Bengel, MD, and Robert J. Gropler, MD*

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**Cardiovascular Molecular Imaging**

Molecular imaging is an evolving diagnostic discipline with the broad definition of using targeted and activatable imaging agents to visualize specific molecular targets, pathways, or cellular processes that precede and/or underlie the changes in morphology, metabolism, physiology, and function characteristic of specific diseases. As a consequence, the discipline holds the promise of revolutionizing both biomedical research and patient care. With respect to cardiovascular disease, 4 distinct concepts and/or research areas are beginning to intersect, and their nexus has greatly stimulated the development of cardiovascular molecular imaging (CVMI). First is the ever-burgeoning belief that a greater emphasis must be placed on the diagnosis and treatment of cardiovascular disease at its earliest stages as opposed to its sequelae. Second is the potential of CVMI to facilitate pharmaceutical discovery and development through improved target identification and implementation of more efficient endpoint usage for clinical trial design. Third are the rapid advances in fundamental cardiovascular research, such as in the areas of vascular biology, cellular growth, and metabolism, and tracking and engraftment processes of cardiac stem cells, as well as rapid advances in the “-omics” such as functional genomics, proteomics, and metabolomics. Fourth are the dramatic advances in the
imaging sciences such as in instrumentation, reconstruction algorithms, and contrast agent design.

**Challenges Facing CVMI**

Despite the promise of CVMI, numerous challenges must be overcome for the field to develop and eventually become an essential component of cardiovascular medicine. Some examples include the following:

- Stimulating the collaboration between scientists from diverse backgrounds such as molecular biology, cell biology, physiology, imaging science, and bioinformatics
- Ensuring adequate research funding from federal, nonprofit, and industrial sources to support both the development of new CVMI approaches and their translation to the clinic
- Obtaining FDA approval of new imaging agents and Centers for Medicare & Medicaid Services approval for payment of the CVMI techniques
- Devising and implementing new educational paradigms that encompass the multidisciplinary nature of CVMI for the training of new investigators, practitioners in training, current practitioners, and technologists
- Development and acceptance of new practice models for cardiovascular imagers that account for the increased cost and complexity of performing CVMI

**Efforts of Various Societies to Overcome These Challenges**

The importance of molecular imaging both in general and with respect to the cardiovascular system has been recognized by numerous societies that have devoted significant resources to advancing the field. Examples from the American Society of Nuclear Cardiology (ASNC), Society of Nuclear Medicine (SNM), Radiological Society of North America (RSNA), and Academy of Molecular Imaging (AMI) are highlighted as follows:

- **ASNC** ([http://www.asnc.org/](http://www.asnc.org/)): The society first initiated its efforts in CVMI in 1997, promoting the field primarily through extensive educational efforts and providing research funding to investigators in the field. Educational efforts have included extensive and diverse publications in the *Journal of Nuclear Cardiology*, such as basic reviews of the principles of molecular biology as it pertains to cardiovascular imaging and bench-to-bedside review articles highlighting key advances in various aspects of CVMI, as well as original articles in the field. In addition, ASNC has routinely included CVMI research advances as part of its annual meeting as well as the biennial International Congress of Nuclear Cardiology meeting of which ASNC is a cosponsor. Both meetings provide the opportunity to present CVMI topics to an international audience. In 2005 the Nuclear Cardiology Foundation was established to advance the field of nuclear cardiology. Both ASNC and, more recently, the Nuclear Cardiology Foundation have provided 3 to 6 awards per year to postdoctoral fellows and junior faculty performing research in the field. In addition, the Nuclear Cardiology Foundation provides 3 pilot and feasibility grants to permit investigators pursuing high-risk/high-reward research to obtain preliminary data in order to successfully compete for more extensive funding from federal and nonfederal sources. In addition, ASNC has sponsored or cosponsored several symposia designed to improve interactions between scientists and stimulate interest by funding agencies in the field, with the NIH Cardiovascular Molecular Imaging Symposium held in May 2004 being but one example.
- **SNM** ([http://www.snm.org/](http://www.snm.org/)): The SNM is advancing molecular imaging through a 5-year bench-to-beside campaign. It is a strategic plan that encompasses diverse communications, funding, education, advocacy, and translational activities. Spearheading these efforts is the Molecular Imaging Center of Excellence. Examples of improved communications include the launching of a community molecular imaging Web site ([http://www.molecularimagingcenter.org/](http://www.molecularimagingcenter.org/)), a quarterly newsletter discussing current issues and monthly references, and daily e-mail services that bring the latest research and news, as well as the *Journal of Nuclear Medicine* providing both extensive reviews and original articles related to molecular imaging. Funding initiatives includes several predoctoral, postdoctoral, and junior faculty research awards in the field. From an educational perspective, the SNM continues to highlight molecular imaging during its mid-winter and annual meetings, is developing online training modules, and is providing funding for experts to speak on a wide array of molecular imaging topics to interested parties. From an advocacy standpoint, the SNM integrates new non-nuclear and broader molecular imaging issues into its portfolio of government relations issues. An example of an outreach activity is the Molecular Imaging Center of Excellence reaching out to other organizations using member “ambassadors” to identify areas of common interest and identify future collaborative educational and outreach activities such as the upcoming American Heart Association/SNM Joint Session: Molecular Imaging—State of the Art 2008 Symposium to be held at this year’s Annual Scientific Sessions of the American Heart Association. Finally, the SNM supports innovations in translational
research, including dedicated industry/academic/government summits and issue-focused workshops.

- RSNA (http://www.rsna.org/): In 2005, the RSNA, recognizing the importance of molecular imaging and molecular medicine to the future of health care, formed the Molecular Imaging Committee (MIC). Its membership includes many of the pre-eminent scientists and clinicians in the field. The MIC monitors the evolving science and clinical application of molecular and functional imaging, designs and implements programs to integrate molecular imaging science and scientists into appropriate RSNA programs/products, and makes recommendations to the RSNA Board of Directors regarding needed actions, policies, and issues to consider in achieving its vision for the future as it relates to the science and practice of biomedical imaging. From an educational perspective, the MIC has cosponsored a number of national meetings on molecular imaging such as the 2-day RSNA/SNM/Society for Molecular Imaging Pre-conference Symposium, entitled “Imaging in Molecular Medicine.” In 2007 the RSNA Refresher Course Committee, in conjunction with the MIC, instituted a 1-week refresher course entitled “Essentials of Molecular Imaging for Clinical Radiologists.” The MIC also conducted a 1-day vertical course symposium, entitled “Molecular Imaging: Introduction and Overview.” Each of these high-profile courses highlighted CVMI in addition to other clinical applications of molecular imaging. The RSNA, through its Research and Education Foundation, offers research grants to medical students, residents, fellows, and faculty in departments of radiology, radiation oncology, and nuclear medicine. To date, the Research and Education Foundation has sponsored just over 700 grants, many of which have addressed cutting-edge issues in molecular imaging.

- AMI (http://www.ami-imaging.org/): This society is an international organization composed of 4 independent councils representing all aspects of molecular imaging. The councils are the Institute for Clinical PET (ICP), the Society of Noninvasive Imaging in Drug Development (SNIDD), the Institute for Molecular Imaging Sciences (IMIS), and the Institute for Molecular Technologies (IMT). By working together, the 4 councils have an opportunity to advance the field of molecular imaging and increase the utilization of molecular imaging tools as both diagnostics and biomarkers. Strategically, AMI efforts fall into 2 broad categories: (1) continuing efforts to support molecular imaging probe approval and reimbursement and (2) facilitating molecular imaging biomarker discovery, development, and acceptance. The focus of the ICP is to drive the use of molecular imaging in clinical practice. The ICP was central to the establishment of the National Oncology PET Registry, which represents an evidence-based approach to demonstrating that FDG-PET imaging has a significant impact in the management of patient care. Following up on this success, the ICP will look for other opportunities to fund key clinical trials aimed at increasing the use of molecular imaging. Education is also a key feature of the ICP mission, with an emphasis on providing adequate training for scientists and clinicians around clinical trial design and translational research for novel molecular imaging probes. The application of imaging technologies to drug development is the primary focus of SNIDD, with an emphasis on imaging education. The IMIS focuses on the basic science and technology surrounding molecular imaging. Education is a fundamental mission of this group and, when combined with the educational missions of both the ICP and SNIDD, demonstrates the strength of the AMI. The IMT provides a forum for the manufacturing organizations in the molecular imaging industry to discuss areas of common interest and to interact with the expertise represented in the other councils. The AMI has an annual meeting that is held during the World Molecular Imaging Congress, whose founding members are the AMI, the Society for Molecular Imaging, the European Society of Molecular Imaging, and the Federation of Asian Societies for Molecular Imaging.

**Recommendation**

CVMI has the potential to revolutionize the management of cardiovascular disease through the characterization of disease before morphologic and functional changes occur and by facilitating the implementation of advances in molecular diagnostics and therapeutics. However, to date, the visibility of CVMI in the scientific community to funding agencies and to industry has been limited when compared with oncologic or neurologic applications of molecular imaging. CVMI, as with molecular imaging in general, is inherently multidisciplinary, and because of the need for translation of discoveries from bench to bedside, it is also inherently interdisciplinary. CVMI falls within the purview of numerous imaging societies, each with different skill sets and constituencies. As a consequence, the most efficient and likely successful efforts to move the field forward will require a coordinated multi-societal effort. To this end, the panel recommends the formation of an independent inter-societal council composed of representatives from societies with an interest in CVMI. The goal of the council is to stimulate communication between the various stakeholder societies and to forge consensus in order to facilitate overcoming the many challenges to the field
detailed previously and thus, translate the current promise of CVMI into a clinical reality:

- **Philosophy**: Inclusiveness would be the philosophy of the council encouraging participation by all interested stakeholder societies. Indeed, it would be hoped that all fields representing the many aspects of CVMI research and development such as target identification, probe development, instrumentation design, preclinical evaluation, clinical validation, and clinical application studies would be represented. Key to the success of the council would be that members of the council would be empowered to represent their individual societies.

- **Goals**: The council should initially focus on the alignment of key issues related to education, advocacy, and training. In the case of education, key target audiences will include the individual societies, federal and nonfederal funding agencies, industry, appropriate federal regulatory bodies, and the public. Interweaved with education will be advocacy involving similar groups but with emphasis on the potential benefits of promising preclinical compounds, the need for research funding, and the facilitation of processes to enhance translation to the clinic of promising CVMI techniques. The council should likely play a key role in devising paradigms for the training of scientists, whether they represent the physical, biologic, or clinical sciences, who wish to develop research programs in CVMI. In addition, the council should also provide key insights into the training of physicians who will use CVMI techniques in clinical practice.

- **Governance**: By definition, the council will operate independently of any individual society. It is envisioned that there would be equal representation and perhaps a rotating chairperson to further ensure the independence of the council. More specific details regarding the governance and operational aspects of the council would be decided by the council.

- **First steps**: To initiate the process of forming this council, each society represented at this meeting will present this report to their representative boards for approval. Once approved, each board will identify 2 representatives to the council. Subsequently, other stakeholder societies with an interest in CVMI will be contacted and invited to join the council. Planning to organize the first meeting of the council should take place by late fall of 2008.