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Outcomes Research in Cardiovascular Imaging

Report of a Workshop Sponsored by the National Heart, Lung, and Blood Institute

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In July of 2008, the National Heart, Lung, and Blood Institute convened experts in noninvasive cardiovascular imaging, outcomes research, statistics, and clinical trials to develop recommendations for future randomized controlled trials of the use of imaging in: 1) screening the asymptomatic patient for coronary artery disease; 2) assessment of patients with stable angina; 3) identification of acute coronary syndromes in the emergency room; and 4) assessment of heart failure patients with chronic coronary artery disease with reduced left ventricular ejection fraction. This study highlights several possible trial designs for each clinical situation.

Cardiovascular imaging is a source of innovation and controversy for the health care community. Cardiologists and radiologists are now capable of obtaining high quality images that describe myocardial function and perfusion, define risk of major clinical events, and show coronary anatomy without need for invasive instrumentation (1). At the same time, there is concern that the rapid dissemination of cardiovascular imaging is a prime example of a costly technology that is enthusiastically embraced without appropriate supporting scientific evidence (2,3).

During the past 5 years, medical imaging has grown substantially, with Medicare Part B costs alone increasing from $6.89 billion in 2000 to $14.11 billion in 2005 (105%) of which an estimated one-third is cardiovascular (3,4). In addition, there is inconsistent use, with some areas of the country having utilization rates 10 times those of others (5). There is no clear explanation for the rapid growth; it cannot be ascribed entirely to aging of the popu-

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lation, changing disease rates, or improved outcomes (3,4). The "value" of imaging in terms of improved health outcomes or reduced cardiovascular events remains subjective, with limited evidence, often generated with flawed research methodology (6,7). There are also concerns that imaging can cause harm (8,9), that there are few rigorous regulatory controls, and that utilization is at least in part driven by self-referral (10) and, in some cases, even direct-to-consumer advertising (11).

A commonly cited model for efficacy in imaging describes 6 hierarchical tiers of evidence: 1) technical efficacy; 2) diagnostic accuracy; 3) diagnostic thinking; 4) therapeutic efficacy; 5) patient outcome; and 6) societal efficacy (12–14). A recently convened American College of Cardiology–Duke University think tank on imaging quality in cardiovascular medicine (15), noted that imaging research has primarily focused on diagnostic and prognostic accuracy, with little work directed at determining the direct impact of imaging on patient outcomes. As a result, among 745 recommendations for cardiovascular imaging in American College of Cardiology and American Heart Association guidelines, only 1% are based on Level of Evidence: A (16). In contrast, in cancer medicine, randomized trials have been completed or are under way for assessing the ability of imaging technologies to prevent major clinical events due to breast (17) or lung cancer (18).

Trial Design Considerations

Methodology. Though it may seem logical that diagnosing disease with "better" imaging tests will yield better outcomes, there are reasons why this may not be so. For example, some disease detected by sensitive technologies in fact reflects subclinical disease that if left alone would never become clinically manifest (19). This was discovered during large-scale studies of mass screening for neuroblastoma in children (20). Another unintended consequence of advanced imaging may be the detection of "nontarget" findings, such as noncalcified lung nodules, that may not have clinical relevance but require additional testing and/or procedures. Therefore, a number of scientists have argued that a preferred way to definitively determine whether or not any new diagnostic test improves outcomes is through properly designed randomized trials using clinical events as outcomes (21). However, there are a number of major methodological difficulties in designing and implementing randomized trials in which imaging tests themselves are the target of randomization (6). Effects, by definition, have to be indirect as tests do not directly affect clinical status. Instead we must presume that they lead clinicians and patients to modify behavior, which hopefully will lead to fewer clinical events.

Several issues represent important considerations when planning trials to determine if imaging can affect outcomes.

Comparison group. The initial consideration is whether one is testing a strategy of performing an imaging test versus not performing any imaging, or whether a comparison is desired between distinct imaging modalities. As an example of the latter design, 103 patients with chronic coronary artery disease (CAD) and left ventricular (LV) dysfunction being considered for revascularization (22) were randomized to either single-photon emission computed tomography (SPECT), myocardial perfusion imaging (MPI) or positron emission tomography (PET) for determination of viability. The imaging information was provided to clinicians for decision making blinded with regard to the imaging modality (with polar maps showing areas of ischemia, infarction, and the like) and patients were followed for 2- to 3-year outcomes. There was no difference in event-free survival between the 2 groups, suggesting that the use of either imaging modality to inform revascularization decisions results in similar outcomes. An ongoing study that represents the "imaging versus no imaging" approach is the WOMEN (What is the Optimal Method for Ischemia Evaluation in WomeN?) study, in which women with suspected CAD are randomized to an initial evaluation strategy of SPECT MPI versus an initial exercise electrocardiography (ECG) testing strategy, with the end point of 2-year negative predictive value for outcome events (23). These studies demonstrate that it is feasible to subject imaging modalities to the same rigorous comparisons that are standard for therapeutics.

End points. An area of substantial uncertainty in the evaluation of imaging outcomes is the appropriate end points for use in trials. Ideally, end points would involve important natural history outcomes such as death, cardiac death or composites of cardiac death, and nonfatal cardiovascular events including myocardial infarction (MI). However, the many decisions made "downstream" from the imaging results have a highly significant effect on outcomes, such that the imaging results themselves are only 1 of many influences on outcomes, and thus challenging to isolate. This has led to considerations of other end points occurring over a shorter time horizon, including such metrics as cost-to-diagnosis, cost-to-predict event, cost-to-prevent nonfatal events, and behavior change with risk factor modification.

Efficacy versus effectiveness. *Efficacy* refers to the performance characteristics of a test under ideal conditions performed and interpreted by experts. *Effectiveness* refers to test performance under "real-life" conditions (24). An efficacious test does not necessarily translate into an effective test, and ideally imaging modalities would be subject to both types of analysis. Stowers et al. (25) reported SPECT imaging efficacy in a small study of 46 emergency department (ED) patients randomized to resting SPECT perfusion imaging or conventional clinical strategy. Length of stay and costs were lower in the imaging strategy arm. Effectiveness of rest perfusion imaging was studied in the ERASE Chest Pain (Emergency