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Cardiovascular Imaging Research at the Crossroads

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Cardiovascular (CV) imaging plays a critical role in therapeutic decision making and is performed in more than 10 million patients each year; a large share of the nearly 40 million patients living with CV disease. CV imaging may serve as a valuable component of a patient's evaluation, provided that its enhanced diagnostic findings invoke appropriate and targeted therapies that improve symptom burden and long-term outcomes and are not offset by the upfront procedural and induced costs of care. As well, the overall clinical benefit that imaging imparts to the patient must significantly outweigh any untoward risk, including radiation or procedural complications. Explosive growth in imaging has resulted in a rapid escalation of costs for testing encumbering an estimated $80 billion dollars annually and represents a sizeable portion of cardiologists' income. Concern remains that continued expansion of CV imaging services may further add to the complexity of health care services and magnify the societal burden of health care. The field of CV imaging is beset by high procedural use, high growth rates, and often, a lack of demonstrable quality. The end result of our current health care system and reimbursement models is an over emphasis on volume and throughput, extensive efforts necessary for justification of procedural use, and a broad referral population exceeding guideline-accepted best practices. An inextricable link between imaging markers and outcomes forms a critical nexus that can be used to establish the value of a test, and is now the standard upon which technology will be evaluated by private payers and governmental agencies alike. This new benchmark necessitates high-quality research to compare the effectiveness of CV imaging modalities to elicit improvements in health outcomes; representing a dramatic paradigm shift for the field of CV imaging research. In this review, we will discuss current health policy of CV imaging as well as the future of CV imaging-based comparative effectiveness research.

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Cardiovascular (CV) disease is causative of significant morbidity and mortality in the U.S. and is rapidly expanding in developed and developing countries worldwide (1). In the U.S., CV imaging plays a critical role in therapeutic decision making and is performed in more than 10 million patients

each year; a large share of the ~40 million patients living with CV disease (2,3). CV imaging may serve as a valuable component of a patient's evaluation provided that its enhanced diagnostic findings invoke appropriate and targeted therapies that improve symptom burden and long-term outcomes; yet are not offset by high upfront procedural and induced costs of care. As well, the overall clinical benefit that is imparted to the patient must significantly outweigh any untoward risks associated with imaging, including radiation or procedural complications.

This inextricable link between imaging markers and outcomes forms a critical nexus which can be used to establish the value of a test, and is now the standard upon which technology will be evaluated by private payers and governmental agencies alike (4). This new benchmark necessitates high-quality research to compare the effectiveness of CV imaging modalities to elicit improvements in health outcomes and represents a dramatic paradigm shift for the field of CV imaging research that will be discussed in this review. Further discussion will ensue on the development of evaluative standards to assess quality imaging and the of a new era in pivotal imaging trials comparing health outcomes. Our initial discussion, however, will focus on the current state of CV imaging health policy.

Current Health Policy of CV Imaging

Over the past decade, imaging has become central to discussions on excessive growth and high-cost health care (5,6). Explosive growth in imaging (twice that of other physician services) has resulted in a rapid escalation of costs for testing, encumbering an estimated $80 billion dollars annually and representing a sizeable portion of cardiologists' income (7). Between 2000 and 2007, there was a 70% increase in the rate of growth for imaging services (8). For example, nationwide utilization for myocardial perfusion imaging was 8.54 million studies, with Medicare allowable charges of $1.1 billion dollars in 2007 (9–12). For echocardiography, Medicare allowable charges increased >50% from 2000 to 2005 (13). Imaging growth has yet to be correlated with prevention or postponement of major adverse CV events (11,14).

As illustrated in Figure 1, growth in imaging reached a zenith in 2004 to 2005, with recent declines noted. Reasons for recent declines in imaging utilization are multifactorial, including recent government regulations and increasing physician awareness of appropriate use criteria. For example, the deficit reduction act (DRA) was signed into law in 2005 and affected many domestic entitlement programs, including Medicare. The DRA impacted imaging utilization in 2006 to 2007 with resultant attenuation of growth and declining Medicare allowable charges for imaging services. Despite recent reductions, concerns remain that any expansion of CV imaging services and its associated economic consequences may further add to the complexity of health care services and magnify the societal burden of health care. A recent Government Accounting Office report on imaging growth also contends there is frequent inappropriate and unnecessary testing (15).

In many ways, the field of CV imaging is emblematic of challenges facing all of medicine. The field is beset by high procedural use, high growth rates, and often, a lack of demonstrable quality. The end result of our current health care system and reimbursement models is an overemphasis on volume and throughput, extensive efforts necessary for justification of procedural use, and a capacious referral population exceeding guideline-accepted best practices. In 1 recent analysis, nearly one quarter of referrals to stress myocardial perfusion single-photon emission computed tomography (SPECT) and echocardiography were of uncertain appropriateness or inappropriate (16). The expansion of services has placed CV imaging within the crosshairs of payers and governmental agencies that have been charged with curtailing unnecessary and excessive health care spending. Recently, the Centers for Medicare & Medicaid Services (CMS) physician fee schedule for echocardiography and nuclear imaging was released and included ~40% cuts for 2010 (17). Utilization management efforts including mandatory prior authorization by radiology benefits managers are now standard practice. The realization that continued imaging growth is economically unsustainable has precipitated demands for more robust evidence to support imaging use.

Although minimizing unnecessary imaging is a laudable goal, abolition of all growth is probably not. Given the aging of our population combined with an expanding prevalence of obesity and diabetes (18–20), a certain amount of growth in CV imaging is expected. Quantifying the extent to which worsening population health contributes to increasing imaging utilization will aid in the discrimination of which testing is unnecessary versus which may be justified. Indeed, there is some evidence to suggest that imaging intensity is related to disease burden (21). Evidence also suggests that overtesting does occur; particularly annually or in low-risk patients (22,23). At present, the lack of high-quality evidence has created an environment of uncertainty on the part of referring physicians and guideline writers, leading to wide variability and imprecision in clinical decision making surrounding the use of CV imaging. This lack of evidence demonstrating in whom and when a patient should be referred to or re-evaluated by CV imaging is conducive to developing patterns of inefficiency that are driven by factors external to evidence-based medicine. Definitive evidence establishing that a given CV imaging modality results in improved health status or clinical outcomes can guide referring physicians to make optimal test choices.

At both the societal and patient level, one key process by which to guide future imaging use is the development

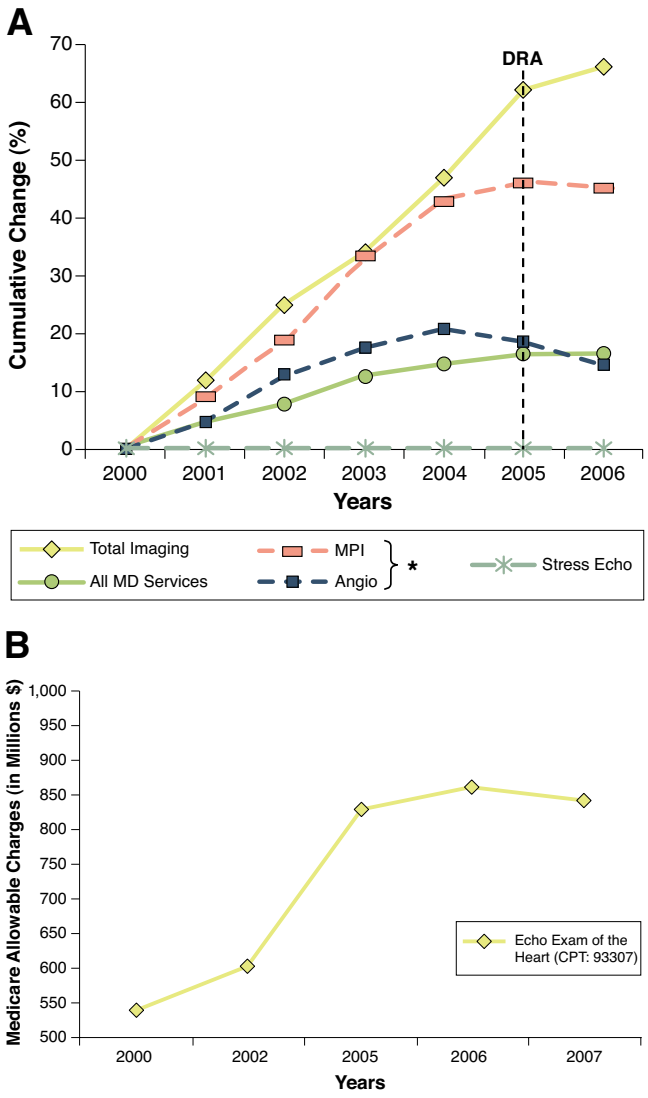

Figure 1. Growth in Imaging as Compared With Other Physician Services From 2000 to 2006

(A) Cumulative changes in cardiac imaging are included on this figure as well as for overall imaging utilization. For cardiac imaging **(dashed lines)**, data for stress myocardial perfusion imaging (MPI), invasive coronary angiography (Angio), and stress echocardiography (Stress Echo) were compiled using Medicare Part B data only. The **dotted black line** at year 2005 signifies the effective date of the Deficit Reduction Act (DRA) where notable declines in imaging utilization have been reported. *Cardiac imaging utilization was derived from the Levin et al. article (9) and includes Medicare Part B utilization data only. Adapted with permission from Iglehart (8) and Levin et al. (9). **(B)** An example of growth and attenuation in imaging charges following the DRA is reported by examining Medicare allowable charges for Current Procedural Terminology (CPT) code: 93307 or Echocardiographic (Echo) Examination (Exam) of the Heart from 2000 to 2007 (13).

of pathways of accountability for imaging practices. The result of this would be a reduction in marked variation in imaging utilization and a greater emphasis on quality. In this regard, high quality evidence on the comparative effectiveness of alternative CV imaging strategies is necessary to guide optimal clinical decision making. Interim steps put forth by the American College of Cardiology (ACC) and American College of Radiology (ACR) now devise procedural and multimodality appropriateness criteria (24–27).

Outcomes Research in CV Imaging

For the practicing clinician, it is essential to understand what defines outcomes research and why it holds a pivotal role in evaluating imaging modalities. The Agency for Health Related Quality defines outcomes research as an examination of the end results of a given health care strategy (28). This term *end result* for CV imaging has historically meant diagnostic or prognostic accuracy. However, "end result" could also mean alterations in patient's symptoms, physical functioning, or quality of life. A critical element of outcomes research is the focus on patient centeredness to provide accountability for the investment in CV imaging (29). For CV imaging, less frequently studied but also important is the role of patient preferences or satisfaction with the ongoing testing received. The use of cost as an end point must be couched within the context of quality or effectiveness, and for that reason it is generally a secondary outcome.

Applying Comparative Effectiveness Research to CV Imaging

Outcomes research broadly refers to the relationship between *processes* of care (e.g., CV imaging) to patient-centered outcomes. More specific types of outcomes research deal with comparing the effectiveness of alternative patient-centered strategies (i.e., comparative effectiveness research [CER]) in order to improve practice and shape health policy (29). The goal of CER is to compare incremental changes in health outcomes for a given strategy, procedure, or therapy (30). The Federal Coordinating Council for CER defined patient-centered CER as ". . . the conduct and synthesis of systematic research comparing different interventions and strategies to prevent, diagnose, treat and monitor health conditions . . . for diverse patient populations" (31).

For CV imaging, this would entail a comparison between 2 or more strategies, including imaging versus nonim-

Table 1. Comparative Effectiveness Research—New Standards and Their Impact on CV Imaging Research

New Standards	Impact
CER entails broad clinical areas impacting large segments of the population	Research assessing comparative modalities for improvements in health outcomes but also testing versus no testing trials to assess the impact of any testing on alterations in outcomes
End point selection: transparency of end points in relation to important clinical outcomes	The admixture of events commonly applied in CV imaging research will require a refocusing toward larger registries sufficiently powered to assess meaningful patient outcomes
Validation methodologies: an important part of comparative effectiveness research is the validation of study findings in ethnically-diverse populations of women and men across varied clinical presentations	There is a lack of methods for validation that require development in CV imaging
Dissemination of study findings to patients, health care providers, and policymakers	The development of standards for disseminating study findings to important stakeholders is critical to improve referral patterns and the quality of imaging-guided care

CER = comparative effectiveness research; CV = cardiovascular.

aging strategies, with the primary end point being an assessment of net improvements in health outcomes. In a recent analysis of the diagnostic imaging literature, the CMS stated that most studies have focused on test characteristics and have not considered health outcomes (32,33). The combination of imaging-guided alterations in patient management with established improvements in outcomes forms the connection whereby CV imaging improves patient outcomes (34).

There are, however, several principles of CER that will require changes to "usual practice" in CV imaging research (35). First, the concept that CER studies address broad clinical questions is fundamental to this type of research. For CV imaging, this would entail evaluation of its additive role in patient management as compared with strategies that employ no testing (i.e., is any imaging warranted?).

Adoption of a CER approach also requires other changes in CV imaging research including: populations studied, choice of end points, validation methodologies, and dissemination of study findings (Table 1) (35). Within CV imaging research, it is common for sample sizes to be small and limited to a few academic centers. Additionally, the choice of end points tends to be a mixture of fatal and morbid complications including subjective outcomes, such as unstable angina or revascularization (36–38). It is imperative for researchers to take time to develop meaningful patient series with rigorously collected, quantitative end points, and that cohorts are broadly representative of patient subgroups and practice settings to ensure generalizability of results. All events should be clearly described in unambiguous terms with regards to what is influencing prognostic modeling. In some cases, this may require independent adjudication of end points, as is routinely performed in clinical trials. Transparency of the relationship between CV imaging abnormalities to prognosis is fundamental to the development of trials or registries of imaging strategies for improving health outcomes (39).

There is, further, a lack of standardization for validation methods in CV imaging research; in particular as it relates to prognostic findings. Validation in larger or diverse patient groups is needed to extend the generalizability of results to broader populations. Finally, there is a mandate for the results of CER to be adequately communicated to patients, health care providers, and policymakers (35). This latter point is fundamental to create optimal referral pathways to and from CV imaging. Optimally, educational platforms for each stakeholder should be linked to track documentation of a positive CER benefit on patient and clinician decision making.

Of concern is that cost containment is a predominant driver for CER. For CV imaging, CER will serve to narrow testing options to modalities with demonstrable quality or value. However, reliance solely on CER to guide health care coverage decisions will render many indications unsupported by high-quality evidence. Moreover, there are clinical areas where large trials or registries may never be performed due to the limited prevalence of affected patients. Accordingly, we anticipate current approaches for defining appropriate CV imaging will remain necessary for many patient indications (24–26).

Levels of Quality Evidence

The development of outcomes evidence plays a critical role in devising strategies for achieving quality of care with CV imaging. Several decades ago, Fryback and Thornbury (40,41) devised hierarchical levels of diagnostic test evidence ranging from technical quality and diagnostic/prognostic accuracy to establishing a test's impact on clinical decision making (Table 2). What these authors further add were 2 higher levels of evidence including patient and societal outcomes. For patient outcomes, achieving this level required that an imaging modality: 1) lengthen or save lives; or 2) improve health status or quality of life. For this assessment of net improvement in health outcomes, comparisons include: a testing versus no testing strategy, or 2 or more test strat-

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Table 2. Fryback and Thornbury Levels of Diagnostic Test Evidence

1) Technical quality: imaging resolution, reliability, repeatability, and validity
2) Diagnostic accuracy: sensitivity, specificity, predictive accuracy
3) Diagnostic impact: impact of a diagnostic test on MD decision making or the ability of a diagnostic test to affect the diagnostic workup
4) Therapeutic impact: impact of a diagnostic test on patient management/affect treatment choices
5) Patient outcomes: ability of a diagnostic test to increase the survival or quality of life
6) Societal outcomes: cost effectiveness analysis

Data from Thornbury et al. (40) and Fryback et al. (41).

egies. Moreover, a higher level also included societal outcomes or incremental cost effectiveness analysis.

Although much work has been completed to understand the diagnostic and prognostic accuracy of CV imaging, the development of evidence assessing patient or societal outcomes is generally not available (42). The introduction of these latter 2 levels, to lengthen or save lives and to improve health status or quality of life, was visionary by Fryback and Thornbury (40,41) and has yet to become a standard for CV imaging research and technology development.

A suggested revision to the CV imaging evidence pyramid is detailed in Figure 2. One may envision that technical improvements or association/correlation studies would provide qualifying evidence for an imaging modality as a potential competitor with existing technology and provide a necessary precondition for CER research. Building on this, we propose the effectiveness pyramid to initiate with evidence on *diagnostic selectivity* including diagnostic accuracy but also an analysis of CV imaging markers and their relationship with CV disease. For all levels within this pyramid, comparative analyses with other modalities or categories of imaging markers (i.e., ventricular function vs. perfusion abnormalities) are required.

Moving upward in this pyramid is the association between imaging risk markers and baseline symptom status (e.g., frequency and stability) as well as downstream symptom changes following therapeutic management alterations. The *prognostic utility* level requires that a given imaging risk marker be incrementally predictive of CV events. It is critical for this level of evidence to provide information on reclassification of risk when compared to: 1) clinical risk estimates; and 2) other competitive imaging or nonimaging markers (43).

The final level of evidence is *optimized test effectiveness strategy*. When compared with prior levels, this level includes CER utilizing randomized controlled trials or registries comparing 2 or more test-guided strategies. For example, it could include comparisons of CV imaging modalities versus no imaging or the impact of 2 different tests on outcomes. Or the effectiveness of an established technique, such as nuclear imaging, may be compared against new technology, such as computed tomography. Importantly, the strategy would unfold beyond the initial episode of care examining the influence of test-therapeutic–linked decision making to near-term improvements in symptoms *and* changes in long-term outcomes. This level of evidence would incorporate patient preferences and satisfaction and consider, not only clinical, but also economic outcomes; such that quality as well as value could be achieved.

Practical Application of CER in Imaging—What Is Needed and How Do We Get There?

Within the field of CER, there is a call for randomized trials and registries to be more relevant to "real world" practice and to include enhanced representation of the ethnically and geographically diverse male and female patient candidate pool (44,45). There are indications that CMS reimbursement may be withheld if study populations do not match the Medicare or at-risk populations (46). Provisional payment may be allowed pending the development of effectiveness evidence in Medicare patients. Moreover, principles of CER deemed by a recent American Heart Association (AHA) statement include studies that encompass broad clinical questions with meaning to large segments of the population (35). Examples of CV imaging application impacting large segments of the population include: 1) the evaluation of suspected CAD; 2) new onset of heart failure; and 3) repeat testing in patients with established CAD (47). The Institute of Medicine reported national priorities to include comparisons of: 1) CV imaging screening strategies (e.g., coronary artery calcium versus carotid intima-media thickness); and 2) coronary computed tomographic angiography versus invasive coronary angiography (48). Should research be pursued in the above indications, data could be available to guide the use of CV imaging impacting health care for millions of patients. A recent commentary stated that the extreme variability in procedural use as well as its rapid growth may be attenuated should there be more precise, high-quality evidence to guide clinical decision making (49). This strongly suggests that the investment in CV imaging CER would be offset by resulting enhancements in efficiency, eliminating variation, and improved health care quality.

Funding for large clinical trials or registries in CV imaging requires a reworking of the current investment levels on the part of public and private agencies, companies, and foundations. Today, clinical trials in CV imaging are, generally, smaller trials (e.g., 300 to 800 patients) or substudies within larger clinical trials (39). These smaller trials have insufficient resources in order to answer larger CER questions on improvements in health outcomes.

Closing the Chasm of Pre- to Post-Approval Requirements for CER

One solution to the current lack of evidence is to require greater research prior to Food and Drug Administration approval; resulting in a wider knowledge

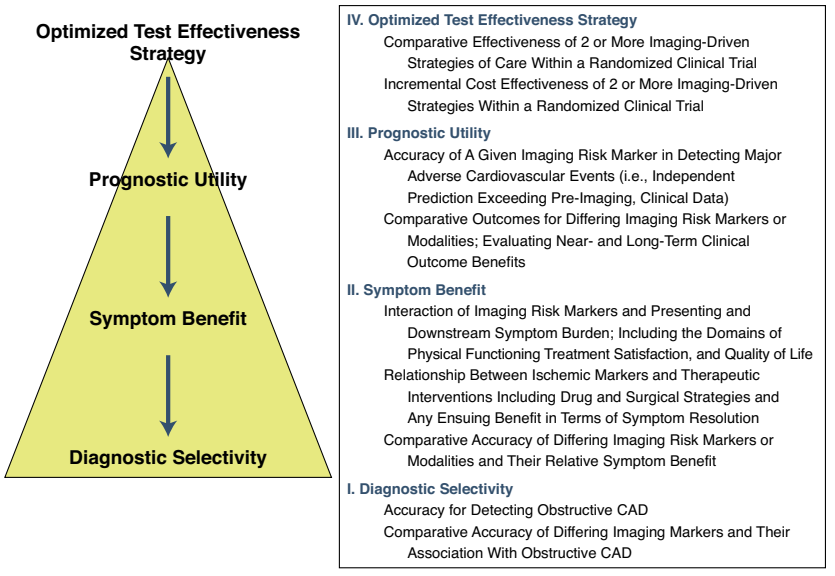

Figure 2. Proposed New Hierarchy of Evidence for CV Imaging

CAD = coronary artery disease.

regarding the relationship between CV imaging and outcomes when a new technology is introduced. The standards for approval, especially for imaging equipment, are insufficient for CER. Improving the quality of pre-approval evidence would result in new devices, radiopharmaceuticals, or drugs entering clinical practice with more well-established outcomes evidence. With a larger body of outcomes evidence upon approval, this new technology could correctly guide current practice towards improved quality health care.

The above strategy remains imperfect as it would protract the approval process delaying the introduction of new technology; rendering U.S. "cutting edge" developments behind that of other countries. Thus, unresolved in our demand for CER is the tension between production of rapid technological advancements in CV imaging and the need for health outcomes data.

Role of Pharmaceutical/Equipment Manufacturers and Payers in Supporting High-Quality, Unbiased CV Imaging Research

Another option for the development of CER trials and registries is funding through pharmaceutical/equipment manufacturers or payers. Companies providing equipment or drugs for CV imaging and third-party payers have yet to make this level of investment in clinical research. Although unusual, a powerful example of success using this funding route is the Advanced Cardiac Imaging Consortium registry supported by Michigan Blue Cross (50). One can only hope that revisions to current funding will ensue on the part of such companies; given recent National Coverage Determination (NCD) from CMS indicating that broader evidence on improvements in clinical outcomes with imaging is required to form the basis for coverage decisions (32,33).

Realistically, CER may require resources exceeding clinical research budgets for many small companies. One solution is the development of multicompany collaborative efforts allowing for the development of larger outcome registries or trials to address this new, clear regulatory requirement. As well, nonprofit organizations representing the interests of a broader industry may play an essential role in collaboration with the scientific community for the development of large-scale, high-quality, carefully designed clinical trials assessing an overall technology. One potential untoward byproduct of this emphasis on CER could be a stifling of technology development and/or refocusing of innovation/discovery toward non-CV areas where these new requirements are not yet mandated.

Research Efforts Aimed at Redesigning the Quality of Imaging Evidence

The gap in knowledge on the relationship between CV imaging and outcomes has recently been recognized by the National Institutes of Health–National Heart, Lung, and Blood Institute (NIH-NHLBI) in its most recent strategic plan (51). The NHLBI plan called for research to optimize diagnostic testing and identify strategies that improve outcomes. Historically, the majority of NIH funding for imaging has been provided for oncologic imaging through the National Cancer Institute. However, the NHLBI plan states that studies are needed to "reduce the inappropriate use of diagnostic tests and treatments" (Challenge 3.1.c), to "evaluate the risks, benefits, and costs of diagnostic tests and treatments in representative populations and settings" (Challenge 3.2.a), and to "establish evidence-based guidelines for prevention, diagnosis, and treatment and identify gaps in knowledge" (Challenge 3.3a) (51).

Similarly, the Medicare Evidence Development & Coverage Advisory Committee recently called for a higher level of outcomes evidence for coronary computed tomographic angiography in a draft NCD (32,33). This draft NCD was groundbreaking by requiring evidence to guide health care coverage, and it is anticipated that similar requirements for high levels of evidence will be the mainstay of CMS policies henceforth. It is envisioned that imaging procedures demonstrating a clear societal benefit or improved patient-centered outcomes would

be less affected by Medicare cuts when compared with other areas with less abundant evidence (32,33).

Role of the ACC, ACR, and Imaging Specialty Societies to Drive High-Quality Imaging Research

The ACC and ACR are leaders in driving health care quality by their guideline and appropriateness criteria statements as well as by their suite of data registries. One such example of a registry that is driving health care quality is the CathPCI Registry run by the ACC National Cardiovascular Data Registry (NCDR). The CathPCI Registry is a national quality improvement program that has helped to shape normative standards for procedural outcomes for patients referred to invasive coronary angiography and interventions (52).

Until recently, the ACC and ACR Imaging Network (ACRIN) have not embarked on similar ventures for CV imaging. It remains feasible that the development of a CV imaging registry could be integrated with other ACC registries and quality improvement programs; dovetailing with existing data collection tools and workflow. Economies of scale would be realized for facilities participating in all of the NCDR registries so that automated links for post-imaging outcomes could be ascertained. A recent proposal has been put forth by the ACC, ACRIN, and the imaging specialty societies to create a national CV imaging registry with the major purpose of accelerating high-quality "real-world" CER in multimodality CV imaging. This vision of the future includes a network of interactive databases that allow for the systematic and automated capture of clinical events and procedures to provide a seamless estimation of "real-world" health outcomes across procedural and diagnostic care (Fig. 3).

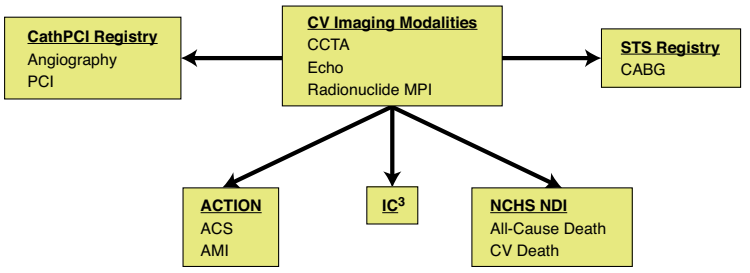

Figure 3. Data Linkages to Facilitate Cost and Clinical Outcome Assessment

CathPCI is a data registry within the American College of Cardiology's National Cardiovascular Data Registry. ACS = acute coronary syndrome; AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CCTA = coronary computed tomographic angiography; CV = cardiovascular; Echo = echocardiography; IC^3 = Improving Continuous Cardiac Care; MPI = myocardial perfusion imaging; NCHS NDI = National Center for Health Statistics National Death Index; PCI = percutaneous coronary intervention.

Conclusions

Charles Dickens once stated: "It was the best of times, it was the worst of times," (53) and perhaps this statement aptly applies to the current state of CV imaging. Although the diverse array of imaging technologies provide detailed anatomic, functional, and molecular information of the heart that is impressive, there remains a large evidence gap between the feasibility of their performance and the clinical and economic value of its use. Given the high rate of CV imaging, there is tremendous pressure to restrain unnecessary or inefficacious growth by refocusing test utilization toward areas of appropriate use. For CV imagers, establishing pathways of appropriate imaging utilization and leading programs of accountability in referral patterns will represent marked steps toward improving current practice.

However, addressing only utilization is insufficient to ensure clinical value with CV imaging. A new, central role for performance of CER will be critical to engage the imaging scientists to focus research to demonstrate imaging strategies that provide the greatest incremental value while concurrently not impeding the development of new technologies that may benefit patients (35). Currently, the ACC, ACR, and CV imaging specialty societies, as well as individual researchers are developing applications for large-scale outcomes projects in CV imaging, including large randomized trials and (national and multinational) registries (47). Several applications have been proposed to the NHLBI to examine CER in CV imaging. Should one of these be funded, this would represent a tremendous step forward in defining a net improvement in health outcome following CV imaging and, perhaps, issue in a new era of imaging megatrials. This latter development is unique to the field of CV imaging, representing a clear demarcation in the quality of clinical research undertaken. Our hopes for the future depend on the development of larger trials and registries so that we can realize the benefit of CV imaging in improving the lives of the millions of patients who undergo testing each year.

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