

Cardiac Nuclear Imaging

Final Evidence Report

August 12, 2013

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FINAL APPRAISAL DOCUMENT

CARDIAC NUCLEAR IMAGING

August 12, 2013

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ACKNOWLEDGEMENTS

ICER would like to thank the following individuals for their expert opinions as well as review of our evidence report:

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EXECUTIVE SUMMARY

Introduction

Coronary artery disease (CAD) is among the most common chronic conditions in the U.S., affecting over 16 million adults (Roger, 2012). Due to its prevalence, and because several options (e.g., surgery, medication) exist to reduce CAD-related morbidity and mortality, accurate diagnosis and/or risk stratification of CAD is critical. Currently the definitive standard for diagnosis is invasive coronary angiography. Because angiography primarily documents the anatomic presence of significant stenosis rather than identifying the "culprit" lesions likely to cause an adverse cardiovascular event (Stone, 2011), a growing number of non-invasive tests have been developed to identify CAD lesions significant enough to affect the flow of blood to the heart (i.e., myocardial perfusion) (Berman, 2006). These functional tests are typically performed under exercise- or pharmacologically-induced stress to determine whether blood flow deteriorates when the stressor is introduced.

The most common tests of cardiac function include the stress-electrocardiogram (EKG or ECG), or treadmill test (ETT), which measures cardiac activity via electrical signals, and the echocardiogram (ECHO), which uses ultrasound to measure abnormalities in heart wall motion using 2-dimensional imagery. ETT has fallen out of favor for use in patients at higher risk of CAD, however, as it has relatively low sensitivity in these patients (Bax, 2007), while stress-ECHO has been found to lack precision in detecting single-vessel versus multi-vessel disease and may produce suboptimal imagery in obese patients, those with chronic respiratory conditions, and patients with chest deformities or pre-existing myocardial damage (Kim, 2007).

To address some of these concerns, "nuclear imaging tests" have been developed to provide perfusion data in a broader spectrum of patients. The most longstanding of these is single photon emission computed tomography (SPECT), which uses a radioactive tracer and gamma camera to obtain 3-dimensional images of tracer uptake; areas of poor uptake are associated with abnormal levels of perfusion (Carlisle, 2008). Positron emission tomography (PET) scanners are also used with a radiotracer, and are felt by some to provide better image resolution in heavier patients and those with dense breast tissue (Rahmim, 2008). So-called "hybrid" modalities have also been introduced to visualize both perfusion abnormalities and anatomic lesions using CT or MRI imagery in addition to nuclear testing.

There are trends in the use of cardiac nuclear imaging tests that are currently points of controversy, however. For one, the use of nuclear imaging for cardiovascular testing has grown substantially in recent years (IMV Medical Information Division, 2011). In addition,

questions have been raised about the appropriateness of nuclear imaging in certain populations. A substantial decrease in the prevalence of abnormal findings on such tests has been observed over time (Rozanski, 2013), due in part to greater recognition and treatment of cardiac risk factors but also to possible changes in referral patterns. This combination of substantial growth in utilization of cardiac nuclear imaging and declining rates of "positive" test results raises questions about the populations and indications for which such testing is appropriate. All nuclear imaging and other noninvasive tests for CAD also differ in terms of their risks, cost, and availability. To investigate these issues, the Washington Health Care Authority has commissioned a comprehensive evaluation of the evidence on the comparative clinical effectiveness and comparative value of cardiac nuclear imaging tests.

Appraisal Scope

This appraisal sought to compare the available evidence on the impact of cardiac nuclear imaging and comparator tests on patient outcomes, treatment decisions, risks of testing, and resource utilization and costs. Target populations included patients for whom CAD is suspected as an underlying cause of symptoms, those who are asymptomatic but nonetheless at higher risk of CAD (e.g., patients with diabetes), and patients with known CAD who receive nuclear imaging tests for prognostic purposes such as risk stratification, treatment selection, and/or follow-up monitoring. Key questions included the following:

- 1) How do SPECT, PET, and relevant hybrid imaging modalities compare to other noninvasive functional tests (e.g., stress-ECHO, ETT) in their ability to guide the management and improve the outcomes of:
 - A. Patients at low-to-intermediate risk of CAD who have symptoms suggestive of myocardial ischemia? (diagnosis)
 - B. Patients at high risk of CAD who have symptoms suggestive of myocardial ischemia? (diagnosis)
 - C. Asymptomatic patients at high risk of CAD due to existing comorbidities? (diagnosis)
 - D. Patients with known CAD who have changes in symptoms? (diagnosis)
 - E. Patients with known CAD who have no changes in symptoms? (prognosis)
- 2) What are the risks associated with these tests, including contrast and radiotracer reactions, patient anxiety, and radiation exposure?
- 3) What is the impact on the comparative benefits and risks of these tests of differences in:
 - A. Patient age, sex, race or ethnicity, and comorbidities (e.g., obesity)

- B. Clinical setting (e.g., emergency department vs. outpatient)
- C. Selection of test by primary care vs. specialty physician
- D. Scan vendor, type of assessment (i.e., quantitative vs. qualitative), type of radioisotope, and type of stressor (e.g., adenosine, exercise)
- 4) What are the costs and the incremental cost-effectiveness of these testing options when used within patient populations that vary by underlying prevalence of CAD and other patient characteristics?

For the purposes of this evaluation, low, intermediate, and high CAD risk were defined based on the Diamond-Forrester model of pretest probability (Diamond, 1979), based on age, gender, and type of chest pain; these equate to probability ranges of <10%, 10-90%, and >90% respectively. These ranges should be considered in context, however, as they have been promulgated in large part to identify "intermediate-risk" patients for whom non-invasive testing is likely to be most valuable; whether the actual range in the physician's mind is 10-90% or 30-70% is not considered to be as important (Fihn, 2012). There are also other pretest probability and risk classification systems used in CAD; we abstracted the method used to define risk from each study where reported (see Section 7).

It is also the case that Diamond-Forrester and other pretest probability models tend to overestimate actual CAD prevalence, particularly in women, as chest pain symptoms are less accurate predictors of obstructive CAD in women than in men (Shaw, 2006). Our decision-analytic model relied on assumed levels of CAD prevalence to generate estimates of test accuracy; we therefore selected levels of CAD prevalence that would approximate populations with low, intermediate, and high pretest probability of disease (see Section 8).

We focused attention on evidence for cardiac nuclear imaging tests (SPECT, PET, and relevant hybrid modalities) and the common testing options to which they have been compared (ETT and ECHO) in randomized controlled trials (RCTs) or cohort studies; the latter design was accepted if multiple testing options were compared in separate groups of patients or performed in the same patient population. Case series of a single nuclear imaging test were not abstracted for effectiveness data but were accessed for information on potential risks and other relevant concerns (e.g., extracardiac findings).

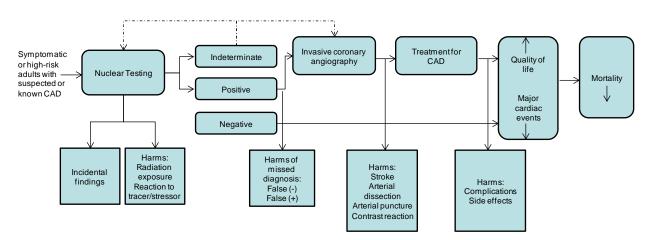
Information on test accuracy (e.g., sensitivity/specificity, positive/negative predictive values) was not a primary focus of this evaluation, as the "reference standard" for CAD diagnosis has historically been anatomic evidence of significant artery stenosis (typically \geq 70%) on invasive coronary angiography. The use of angiography as the gold standard for *functional* tests such as those under consideration here has been called into question, however, as the mere presence of stenosis has been found to correlate poorly with that of "functionally significant" lesions, especially at moderate levels (e.g., 50-70%) (Tonino, 2010).

Where available, however, we analyzed any diagnostic accuracy data involving the use of an independent *functional* reference standard such as "fractional flow reserve" (FFR) and summarized recent systematic reviews using anatomic reference standard for context.

While all potential risks of testing were recorded, the primary focus of attention was on adverse effects requiring medical attention (where such designations were available). In addition, because radiation exposure is an area of increasing interest and controversy, we abstracted these data where recorded. Finally, while not technically a risk, all cardiac imaging tests have the potential for "extracardiac" findings – that is, issues of potential concern outside the heart, which may in turn result in follow-up testing and invasive treatment that may be unnecessary in some cases.

Analytic Framework

The analytic framework for this review is shown in the Figure below. Note that the figure is intended to convey the conceptual links involved in evaluating outcomes of cardiac nuclear imaging tests and their alternatives, and is not intended to depict a clinical pathway through which all patients would flow. This framework also does not represent the clinical pathways as they were constructed for the decision analytic model.



Analytic Framework: Cardiac Nuclear Imaging

The evidence hierarchy for diagnostic imaging differs from that for treatment, as RCTs are often not feasible and key patient outcomes of interest may lie many years in the future following the use of a test. In the early 1990s, Fryback and Thornbury developed an influential hierarchy of evidence specifically for imaging tests (Fryback, 1991). The hierarchy is presented in Table ES1 on the following page.

Diagnostic Imaging Evidence Hierarchy Level	Example of Outcome Measures
1. Technical Efficacy	Interpretable scan resolution, inter-reader and inter-laboratory reliability of test results
2. Diagnostic Accuracy	Sensitivity/specificity vs. gold standard test or vs. some other standard
3. Diagnostic Impression	Change in presumptive diagnosis following introduction of new test results
4. Diagnostic Action	Initiation or cessation of treatment; impact on use of additional diagnostic studies
5. Patient Outcomes	Mortality, rates of major cardiovascular events, side effects of treatment driven by test results

Table ES1. Evidence hierarchy for diagnostic imaging.

Source: Fryback and Thornbury, Medical Decision Making, 1991

Study Quality

6. Societal Outcomes

We used criteria published by the U.S. Preventive Services Task Force to assess the quality of RCTs and comparative cohort studies, using the categories "good", "fair", or "poor". Guidance for quality rating using these criteria is presented below (AHRQ, 2008).

Cost-effectiveness of testing

- **Good:** Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.
- **Fair:** Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done for RCTs.
- **Poor:** Studies will be graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

Quality of diagnostic accuracy studies was assessed using the revised Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2), which assesses risk of bias and level of study applicability in 4 distinct domains: patient selection, index test, reference standard, and flow and timing (Whiting, 2011). The QUADAS-2 does not produce a single summary score, but rather ratings for each domain that describe whether the level of concern regarding bias and applicability is low, high, or unclear. Study quality was not assessed for case series.

Data from all retrieved studies were included in evidence tables regardless of study quality. However, the focus of attention in presentation of results was primarily on good- or fairquality studies.

Data on costs and potential cost-effectiveness were obtained from published studies as well as from a newly-developed decision-analytic model that simulated and compared multiple diagnostic pathways in patients with symptoms suggestive of myocardial ischemia, as described in the "Comparative Value" section of this summary.

Evidence on Comparative Clinical Effectiveness (KQ 1)

Overview of Evidence and Quality Assessment

Limited RCT evidence was available comparing nuclear imaging tests to alternative strategies. Five RCTs were identified that met study entry criteria, all of which measured the impact of testing on patient outcomes (i.e., level "5" on the Fryback and Thornbury hierarchy). These included a multicenter outpatient trial comparing SPECT screening vs. no screening in 1,123 asymptomatic patients with diabetes (Young, 2009); a study comparing SPECT with ETT in 772 women across 43 cardiology practices with suspected CAD who had low-to-intermediate pretest probability of disease (Shaw, 2011); a comparison of SPECT with ETT in 457 patients seen at a hospital chest pain clinic, most of whom had intermediate-to-high pretest likelihood of CAD (Sabharwal, 2007); a study of 898 primarily high-risk patients referred for angiography at a tertiary cardiothoracic center who were randomized to receive SPECT, ECHO, CMR, or direct referral to angiography (Sharples, 2007); and a randomized comparison of the interaction of imaging modality (SPECT vs. PET) and patient gender on outcomes (Mullani, 2000). This latter study was rated poor quality due to treatment group imbalances and lack of standardized outcome measurement. The remainder of the RCTs were rated good- or fair-quality.

The evidence base for comparative cohort studies varied by patient population. No such studies were identified in purely asymptomatic populations. In fact, of the cohort studies identified, one-thirds were in "mixed" populations comprised of asymptomatic and symptomatic patients, those with suspected and known CAD, and/or a relatively even distribution of low, intermediate, and high CAD risk. Among symptomatic populations, a greater number of studies were performed in higher-risk individuals (5 vs. 4 for low-to-intermediate risk), while 4 studies were available in patients with known CAD. Sixteen

cohort studies assessed the impact of testing on patient outcomes (level 5), 9 measured the effects of imaging on downstream testing and treatment (level 4), and one assessed the impact of testing on diagnostic impression (level 3).

The majority of comparative studies were comparisons of SPECT-based strategies to alternative testing approaches. Only 3 studies involved the use of PET, and 2 assessed the impact of hybrid testing; none of these were good- or fair-quality randomized studies. Twelve cohort studies involved the use of multiple tests in a single population, while 9 compared the results of imaging strategies in multiple comparator groups.

The evidence on the impact of cardiac nuclear imaging on patient outcomes, downstream testing and treatment decisions, and health-related quality of life is summarized in Table ES2 on the following page. Findings are also discussed by population in the sections that follow.

Table ES2. Summary Evidence Table: Impact of SPECT, PET, and hybrid imaging modalities on patient management and outcomes.

Study Information	Comparators	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Direction of Effect	Comments
	MORTALITY AND RISK OF CARDIOVASCULAR EVENTS							
Asymptomatic, high-risk	individuals							
SPECT (N=1,123) RCT=1 Mean follow-up: 4.8 yrs		Low	N/A	Direct	N/A	++ Low	No differences	>short-term revasc for SPECT
PET	NO Screening	LOW	IN/ A	Direct	No Studies	LOW	No unierences	
Hybrid					No Studies			
Symptomatic patients at	low-to-intermediat	te CAD risk						
Mean follow-up: 2.2 yrs	ECHO (1), stress	Medium	Inconsistent	Direct	Imprecise	+++ Moderate	No differences vs. ECHO; mixed evidence vs. ETT	
PET					No Studies			
Hybrid					No Studies			
Symptomatic patients at SPECT (N=4,279) RCT=1; CC=4 Mean follow-up: 2.3 yrs	ETT (1), PET or CCTA (1), ECHO	Medium	Inconsistent	Direct	Imprecise	+++ Moderate	Superior to ETT; no difference vs. ECHO; mixed evidence vs. PET/CCTA	
PET (N=1,703) CC=1 Follow up: 3 mo	SPECT or CCTA (1)	Medium	N/A	Direct	N/A	+ Insufficient		Mixed evidence on revasc
· · · · · · · · · · · · · · · · · · ·	Matched vs. unmatched images (1)	High	N/A	Indirect	N/A	+ Insufficient		Matched images superior to unmatched for revasc

Study Information	Comparators	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Direction of Effect	Comments
Known CAD								
SPECT (N=5,098) CC=2 Mean follow-up: 4 yr	sequence (1), by	High	Inconsistent	Indirect	Imprecise	+ Insufficient		SPECT reduced revasc when after angiography
PET					No Studies			
Hybrid					No Studies			
Mixed Populations								
SPECT (N=5,439) RCT=2; CC=2; SA=4 Mean follow-up: 2.5 yr	(2), PET (2), CMR	Medium	Inconsistent	Direct	Imprecise	+++ Moderate	Mixed evidence vs. ECHO; superior to ETT; mixed evidence vs. PET	
PET (N=2,471) RCT=1; CC=1 Mean follow-up: 11 mo		Medium	Inconsistent	Direct	Imprecise	++ Low	PET superior to SPECT for revasc; no other differences	
	unmatched images (1)	High	N/A	Indirect	N/A	+ Insufficient		Matched images superior to unmatched for revasc
DOWNSTREAM TESTIN	NG AND CLINICA	AL DECISIO	N-MAKING					
Asymptomatic, high-risk	individuals							
SPECT (N=1,123) RCT=1 Mean follow-up: 4.8 yr	Ũ	Low	N/A	Direct	N/A	++ Low	Mixed evidence	SPECT > for angiography referral; no screening > for add'1 stress tests
PET		No Studies						
Hybrid					No Studies			

Study Information	Comparators	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Direction of Effect	Comments
Symptomatic patients at	low-to-intermedia	te CAD risk			- <u>-</u>			•
SPECT (N=772) RCT=1 Follow-up: 2 yr		Low	N/A	Direct	N/A	++ Low	Mixed evidence	>repeat testing for SPECT; > crossover for ETT
PET					No Studies			·
Hybrid					No Studies			
Symptomatic patients at	high CAD risk							
SPECT (N=2,160) RCT=1; CC=1 Mean follow-up: 1.1 yr	CCTA (1)	Low	Inconsistent	Direct	Imprecise	++ Low	Superior to ETT; mixed evidence vs. PET and CCTA	
PET (N=1,703) CC=1 Follow up: 3 mo	SPECT or CCTA (1)	Medium	N/A	Direct	N/A	+ Insufficient		PET >SPECT for angiography referral; no differences in medication use
	unmatched images (1)	High	N/A	Indirect	N/A	+ Insufficient		Matched >unmatched for angiography referral
Known CAD			-					
SPECT		No Studies						
PET (N=100) SA=1 Mean follow-up: 9 mo	before/after PET	High	N/A	Direct	N/A	+ Insufficient		>use of med mgmt after PET
Hybrid					No Studies			

Study Information	Comparators	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Direction of Effect	Comments
Mixed Populations		_						
SPECT (N=1,037) RCT=1; SA=1 Mean follow-up: 1.5 yr	(1), angiography	Medium	Inconsistent	Direct	Imprecise	++ Low	No difference vs. ECHO, CMR, or angiography; superior w/ and w/o ETT vs. ETT alone	ETT comparison based on hypothetical referral rate
PET (n=2,261) CC=1 Mean follow-up: 1 yr		Medium	N/A	Direct	N/A	+ Insufficient		PET superior for angiography referral
Hybrid					No Studies		·	
HEALTH-RELATED QU	ALITY OF LIFE							
Asymptomatic, high-risk	individuals					No studi	es	
Symptomatic patients at	low-to-intermedia	te CAD risk						
SPECT (N=772) RCT=1 Follow-up: 2 yr	ETT	Low	N/A	Direct	N/A	++ Low	No differences	General QoL and SAQ
PET			•		No Studies	1	l	I
Hybrid					No Studies			
Symptomatic patients at	high CAD risk					No Studies		
Known CAD						No Studies		
Mixed populations	Mixed populations							
	ECHO (1), CMR (1), angiography (1)	Low	N/A	Direct	N/A	++ Low	No differences	SAQ, SF-36, EQ-5D
PET		No Studies						
Hybrid		No Studies						

Asymptomatic Patients at High Risk of CAD

The one available study assessing the impact of cardiac nuclear imaging in asymptomatic, high-risk patients found no difference between SPECT screening and no screening in mortality or cardiovascular events, although many patients in both groups received subsequent stress testing for clinical reasons over approximately 5 years of follow-up (Young, 2009). SPECT screening did increase the short-term rates of referral for angiography and revascularization vs. no screening.

Symptomatic Patients at Low-to-Intermediate Risk of CAD

<u>Correlation of Imaging Study Findings with Mortality and Cardiovascular Events</u> Rates of mortality and MACE events did not generally differ between imaging modalities in available studies. Patients in the WOMEN study, an RCT of 772 women randomized to SPECT or ETT-based testing strategies (Shaw, 2011) were at very low CAD risk. Adverse cardiovascular events were relatively infrequent (17 events in 772 women over 2 years of follow-up); among these, only one death was reported. The rates of all major adverse cardiovascular events at 2 years were 1.7% and 2.3% for ETT and rest/stress SPECT respectively, but this difference was not significant (Hazard Ratio [HR]: 1.3; 95% CI: 0.5, 3.5; p=.59). The rate of revascularization also did not statistically differ between groups.

The long-term prognostic value of exercise SPECT (²⁰¹Thallium), exercise ECHO, ETT, and clinical parameters was measured in a single cohort of 248 patients (mean age, 56 years; 76% male) who were followed for a mean of 3.7 years (Olmos, 1998). A total of 64 MACE events occurred during follow-up. In multivariate analyses examining the incremental impact of (1) clinical + ETT data; (2) data in (1) + rest ECHO data; (3) data in (1) + exercise ECHO data; and (4) data in (1) + exercise SPECT data on predicting MACE events, the area under the curve did not statistically differ between the SPECT and ECHO models (0.78 and 0.77 respectively), but was significantly (p<.05) higher than the base model (0.68) or the rest ECHO model (0.72).

Chang and colleagues evaluated the impact on all-cause mortality of normal findings on stress-only vs. stress/rest SPECT (Tc-99m sestamibi or tetrofosmin) protocols in nearly 17,000 low-to-intermediate risk patients (mean age, 59 years; 44% male) followed for a median of 4.5 years (Chang, 2010). Annualized unadjusted mortality rates were statistically-significantly greater in the stress/rest group (2.92% vs. 2.57% for stress-only, p=.02); however, this difference was no longer apparent after multivariate adjustment for differences in baseline characteristics. The authors conclude that a stress/rest protocol may be unnecessary in lower-risk individuals. It should be noted that these protocols employed CT-based attenuation correction, however, which is not yet in wide use with SPECT. Potential cost savings from performing stress-only protocols would need to be weighed against additional costs for equipment and investigation of extracardiac findings in such a setting.

Downstream Testing and Clinical Decision-Making

The impact of testing on downstream resource utilization and clinical decisions was evaluated only in the WOMEN study (Shaw, 2011). Over 2 years of follow-up, repeat testing with the same modality was more frequent in the SPECT group vs. ETT (9% vs. 3%), although this difference was not statistically tested. However, 18% of women randomized to ETT crossed over to SPECT during follow-up. The overall rate of referral to angiography was higher in the ETT group (9.0% vs. 5.5% for SPECT, p<.0001). Changes in the use of nitrates, beta-blockers, and antidepressant therapies during follow-up did not differ between the two arms in the study.

Health-related Quality of Life

The impact of testing on HrQOL also was examined only in the WOMEN study (Shaw, 2011). General QoL and life satisfaction were assessed using categorical rating scales, while functional status was assessed using the Seattle Angina Questionnaire (SAQ), a 19-item instrument assessing physical limitations, treatment satisfaction, disease perception, and anginal symptoms (Spertus, 1995). Similar proportions of women in each treatment group reported "excellent" or "very good" QoL as well as "best" or "average" life satisfaction, with no statistical differences between groups. There were also no statistically-significant differences between ETT and SPECT groups in relation to changes in any of the SAQ subscales.

Symptomatic Patients at High Risk of CAD

<u>Correlation of Imaging Study Findings with Mortality and Cardiovascular Events</u> In high risk populations, some differences in event rates by modality were apparent. An RCT of ETT vs. SPECT in 457 intermediate-to-high risk patients focused primarily on the period between testing and diagnosis, but did report on the rate of revascularization, which occurred more frequently in the ETT group (18% vs. 11% for SPECT, not statistically tested) (Sabharwal, 2007). In the "SPARC" registry, a study comparing short-term outcomes of PET, SPECT and coronary CT angiography (CCTA), revascularization rates at 90 days did not materially differ between PET and SPECT, regardless of whether findings were mildly or moderately-severely abnormal (Hachamovitch, 2012).

Schinkel and colleagues assessed the prognostic value of both dobutamine ECHO and dobutamine SPECT (Tc99m-sestamibi) in 301 patients (mean age unreported; 56% male) who were unable to exercise and were at intermediate-to-high risk of CAD; patients were followed for a mean of 7.3 years (Schinkel, 2004). Event-free survival was significantly better for patients with normal vs. abnormal findings on both tests, and did not differ statistically between tests. In multivariate models based on clinical data, stress testing, and imaging results, abnormal findings on either SPECT or ECHO were the strongest predictors of both cardiac death (HR [95% CI]: 4.4 [1.2, 21.0] and 3.4 [1.2, 12.0] for SPECT and ECHO respectively) and cardiac events (3.1 [1.1, 8.9] and 2.6 [1.1-6.2] respectively).

Finally, information from an evaluation of fused stress-rest Tc-99m tetrofosmin SPECT with CCTA in 335 patients (mean age, 61 years; 67% male) who were at primarily intermediateto-high risk of CAD was used to correlate matched and unmatched test results with MACE events (Pazhenkottil, 2011). Patients were followed for a median of 2.8 years. A total of 69 MACE events occurred in 47 patients; annual rates were 21.0%, 7.8%, and 2.2% for patients with matched (abnormal) findings, unmatched findings, and normal findings on both tests respectively (p<.005). In multivariate analyses controlling for patient characteristics and CAD risk factors, matched findings were the strongest predictor of unfavorable outcome (HR: 3.80; 95% CI: 1.76, 8.21; p=.002).

Downstream Testing and Clinical Decision-Making

Two studies reported on the effects of testing on downstream resource use and/or clinical decisions. Of the 207 patients randomized to ETT in the Sabharwal RCT, a total of 146 (71%) were referred for further testing (47% to angiography and 23% to stress ECHO) (Sabharwal, 2007). In contrast, further testing was requested in only 16% of patients randomized to SPECT, all of which were angiography procedures (p<.0001 for the comparison). ETT also appeared to generate more false-positives for significant CAD. Only 38% of ETT patients referred to angiography were revascularized, vs. 66% of SPECT patients so referred (p<.05).

In the SPARC registry, referral for angiography occurred in a greater percentage of PET patients (11.1% vs. 4.3% for SPECT; p<.001). In multivariate analyses controlling for patient characteristics, comorbidities, and testing location, imaging modality was significantly and positively correlated with referral to angiography for PET (OR: 5.0; 95% CI: 1.0, 24.4) in comparison to SPECT. Neither PET nor SPECT were associated with significant medication changes.

Health-Related Quality of Life

There were no studies in symptomatic, high-risk individuals that reported on the impact of cardiac nuclear imaging tests on HrQoL.

Known CAD

<u>Correlation of Imaging Study Results with Mortality and Cardiovascular Events</u> Bourque and colleagues conducted a comparative cohort study comparing the rate of revascularization in 2,951 patients (median age 65 years, 73% male) with known CAD and left ventricular dysfunction and (1) who had been tested with SPECT before referral for angiography; (2) were tested with SPECT only after a positive angiography; or (3) had no SPECT before or after angiography (Bourque, 2004). The rate of revascularization differed significantly (p=.001) among groups, with the lowest rate of 35.8% seen in postangiography SPECT patients, 45.6% in patients who had SPECT neither before nor afterward.

Downstream Testing and Clinical Decision-Making

In a study by Siegrist and colleagues, 100 consecutive patients (mean age, 60.9 years; 72% male), 79% of who had known CAD, underwent adenosine rest-stress PET (¹³N-ammonia) perfusion testing (Siegrist, 2008). Physicians were first queried on proposed patient management strategies without PET perfusion data; actual patient management was measured 4 weeks after PET. Proposed patient management was altered in 78% of patients. Most prominently, conservative medical management was initially proposed in 28% of patients; after PET testing, 76% were managed this way in actuality. In addition, use of angiography to guide treatment via PTCA was proposed in 6%, but was performed in 20% after PET testing.

Health-Related Quality of Life

There were no studies in patients with known CAD that reported on the impact of cardiac nuclear imaging tests on HrQoL.

We did not identify *any* comparative studies evaluating the impact of serial nuclear imaging in asymptomatic patients with known CAD.

Mixed Populations

The largest number of studies was available for populations that did not fit neatly into the categories described above. They represented a true "mix" of patients based on relatively uniform distributions by risk or pretest probability, presence or absence of symptoms, and/or inclusion of patients with known vs. suspected CAD. A total of 10 studies were identified, including a fair-quality RCT comparing SPECT to ECHO, CMR, and direct referral to angiography (Sharples, 2007), the aforementioned good-quality prospective cohort study comparing PET to both matched internal and external SPECT control groups (Merhige, 2007), and an RCT comparing the interaction of imaging modality (PET vs. SPECT) and patient gender on outcomes (Mullani, 2000). This latter study was rated poor quality, however, because of imbalance in treatment groups and lack of standardization in outcome measurement, and so is not reported in detail here. Another poor-quality study evaluated outcomes in patients undergoing rest-only vs. rest-stress SPECT (Abdoul-Enein, 2003).

Six additional studies examined the effects of multiple imaging tests performed in a single patient population. These included 3 studies comparing SPECT and ECHO (Basic, 2006; De Lima, 2003; Hoque, 2002), and one each comparing SPECT with ETT (Muzzarelli, 2010), SPECT with ETT and angiography (Pattilo, 1996), and findings from hybrid SPECT and CCTA (Fiechter, 2012).

Given the heterogeneity of patient populations and comparisons for this category, study descriptors and findings with respect to mortality and cardiovascular events are summarized in Table ES3 on page 17.

<u>Correlation of Imaging Study Results with Mortality and Cardiovascular Events</u> Data on mortality and cardiovascular events were available in 8 studies. The <u>Cost-Effectiveness of Functional Cardiac Testing</u> (CeCAT) Trial was an RCT comparing multiple diagnostic strategies – rest-adenosine stress SPECT (Tc-99m sestamibi), ECHO (dobutamine stress), adenosine stress CMR, and direct referral to angiography – among 898 primarily high-risk patients (mean age, 62 years; 70% male) with known or suspected CAD and stable symptoms of ischemia who were referred to a tertiary center in the UK for angiography and were followed for 18 months (Sharples, 2007). In this study, the number of total, cardiac, and noncardiac deaths did not statistically differ by imaging modality. When compared with the referent angiography group, the number of nonfatal adverse cardiac events did not differ for SPECT or CMR, but was statistically-significantly higher for ECHO (relative risk [RR]: 1.95; 95% CI: 1.23, 3.08; p=.012). When the number of *patients* reporting adverse cardiac events was compared, however, no significant differences were observed.

Findings from the Merhige study comparing PET and SPECT were somewhat mixed. No differences in cardiovascular mortality or the rate of MI were observed between groups. (Merhige, 2007). However, the rates of CABG (3.4% vs. 7.8%, p<.01) and any revascularization (6.0% vs. 11.4%, p<.01) were statistically-significantly lower for PET vs. the internal SPECT control group. The rate of any revascularization was also significantly lower in comparison to the external SPECT control group (6.0% vs. 13.0%, p<.0001).

Study	Design	CAD Risk	% w/ Symptoms	% Known CAD	Comparison	Main Findings
Sharples 2007 (n=898)	RCT	High: 69%	NR	NR	SPECT vs. ECHO/MRI/ angiography	SPECT ↑ vs. ECHO for readmission
Merhige 2007 (n=2,261)	Comparative Cohort	NR	NR	49	SPECT vs. PET	PET ↑ for CABG/total revasc
Basic 2006 (n=51)	Single Cohort	NR	100	NR	SPECT vs. ECHO	No differences
De Lima 2003 (n=126)	Single Cohort	Intermediate to High	NR	58	SPECT vs. ECHO	No differences
Hoque 2002 (n=206)	Single Cohort	NR	100	NR	SPECT vs. ECHO	SPECT ↑ for MI/angina, ECHO ↑ for mortality/CHF
Fiechter 2012 (n=62)	Single Cohort	NR	50	NR	SPECT/CCTA	Matched results ↑for revasc
Pattilo 1996 (n=732)	Single Cohort	NR	100	NR	SPECT vs. ETT vs. angiography	SPECT ↑ETT and angiography

Table ES3. Correlation of cardiac nuclear imaging with mortality and cardiovascular events in mixed populations (good- and fair-quality studies only).

NOTE: \uparrow indicates (a) reduced rates of mortality or adverse CV events; or (b) better ability to predict mortality or adverse CV events

The 3 single cohorts comparing the prognostic ability of SPECT and ECHO generally showed comparable results for both tests. No statistical differences between imaging modalities in event rates or event-free survival were observed in 2 studies (Basic, 2006; De Lima, 2003). In the third, an evaluation of exercise stress ECHO vs. exercise stress SPECT (²⁰¹Thallium) in 206 symptomatic veterans who received both tests (Hoque, 2002) and were followed for up to 10 years, moderate-to-large ischemia on ECHO was the strongest independent predictor of overall mortality (RR: 6.2; p<.0001), cardiovascular death (RR: 17.6; p=.01), congestive heart failure (RR: 17.4; p=.0005), or sudden death (RR: 26.8; p=.003). The presence of moderate-to-large fixed defects on SPECT was the strongest independent predictor of nonfatal MI (RR: 8.1; p=.0002) and unstable angina (RR: 3.0; p=.005). Pattilo and colleagues assessed the predictive capability of functional data from ETT, exercise stress SPECT (²⁰¹Thallium), and the "Gensini score" from angiography evaluation in 732 patients (mean age, 59 years; 71% male) who were followed for a mean of 3.5 years

(Pattilo, 1996). Abnormal results on SPECT and the Gensini score were significantly ($p \le .01$) associated with poorer event-free survival, while ETT data were not. Analyses of the receiver operator curve (ROC) for events indicated that SPECT was the strongest independent predictor of events (0.67 vs. 0.61 and 0.46 for Gensini score and ETT, p < .05).

Downstream Testing and Clinical Decision-Making

A total of 3 good- or fair-quality studies examined the impact of cardiac nuclear imaging on further testing and clinical decision-making. In the CeCAT trial, the proportions of patients in the SPECT, ECHO, and CMR groups who were referred to angiography ranged between 75-80% and did not statistically differ between groups (Sharples, 2007); in addition, decisions on further invasive or medical management were also similar.

The rate of referral to angiography in the Merhige comparison of PET and SPECT was statistically-significantly lower for PET (13%) in comparison to both the internal and external SPECT groups (31% and 34% respectively, p<.0001). The rate of angiography-negative results was also significantly lower for PET vs. internal SPECT controls (5.2% vs. 15.6%, p<.0001).

Finally, a hypothetical referral rate to angiography was assessed in 955 patients (mean age 61 years; 70% male) undergoing ETT and rest-exercise stress SPECT (²⁰¹Thallium/Tc-99m sestamibi) (Muzzarelli, 2010). Algorithms using ETT data alone, SPECT data alone, and a combination of the 2 tests were applied. An estimated 27% of patients would have been referred to angiography based on ETT results alone, vs. 13% for SPECT data alone and 12% using both ETT and SPECT data (p<.01 for both comparisons to ETT alone). Findings were similar when compared among patients without known CAD.

Health-Related Quality of Life

HrQoL was assessed in the CeCAT trial using the Seattle Angina Questionnaire, the SF-36, and the EuroQol EQ-5D instruments (Sharples, 2007). While some statistically-significant differences were noted in certain subscales at particular timepoints, improvements in HrQoL were clinically comparable across testing groups for all measures.

Diagnostic Accuracy

A total of 8 studies were available that examined the accuracy of cardiac nuclear imaging tests in relation to a functional reference standard. As described previously, this is currently believed to be a more accurate method to determine whether a defect noted on non-invasive imaging relates to CAD that is functionally-significant – that is, likely to be the cause of an adverse cardiovascular event if not treated. Details on these studies are provided in Table ES4 on the following page. Meta-analysis of these data was not attempted for the evidence review due to heterogeneity in patient populations and the threshold for positivity, but was conducted to inform sensitivity analyses in the economic model.

Study	Test	CAD Risk	Stressor	Reference Standard	Sensitivity	Specificity
DeBruyne 2001 (n=107)	SPECT	100% Prior MI	Adenosine	FFR <0.75	82%	87%
Melikian 2010 (n=67)	SPECT	100% Known CAD	Adenosine	FFR <0.80	66%	50%
Oraby 2002 (n=38)	SPECT	NR	Dipyridamole	ECHO	58%	100%
Yanagisawa 2002 (n=165)	SPECT	70% Prior MI	Dipyridamole	FFR <0.75	90% (DM+) 71% (DM-)	70% (DM+) 74% (DM-)
Yanagisawa 2004 (n=245)	SPECT	100% Known CAD	Adenosine	FFR <0.75	83% (DM+) 79% (DM-)	75% (DM+) 83% (DM-)
Danand 2013 (n=120)	PET PET/CCTA	High	Adenosine	FFR ≤0.80 or Stenosis ≥50%	76% 76% (H)	83% 92% (H)
Kajander* 2010 (n=107)	PET PET/CCTA	30-70%	Adenosine	FFR ≤0.80 or Stenosis ≥50%	95% 95% (H)	91% 100% (H)

Table ES4. Diagnostic accuracy in PET and SPECT studies using a functional reference standard.

DM: Diabetes mellitus; H: Hybrid PET/CCTA test

*A second publication using the same population showed sensitivity of 74% and specificity of 73% when analyzed using relative uptake vs. absolute blood flow

It should be noted that, in the Danand and Kajander studies, the reference standard included either a functional *or* anatomic measure, and so their applicability to a construct of accuracy to detect important ischemia is limited.

Historical Evidence Using Anatomic Reference Standards

As described previously, recent research has raised questions about the use of anatomic data on angiography to confirm findings of functional tests such as ECHO, SPECT, and PET. There is nevertheless a large body of evidence evaluating the accuracy of non-invasive functional tests using visualization of coronary arteries as the reference standard. One of the most widely-cited meta-analyses compared the diagnostic accuracy of exercise ECHO and exercise SPECT based on 44 studies (Fleischmann, 1998). Pooled sensitivity of the 2 tests was similar (85% and 87% for ECHO and SPECT respectively), but pooled

specificity was rated higher for ECHO (77% vs. 64% for SPECT, p<.05). However, substantial heterogeneity in study populations, imaging protocols, and SPECT radiotracers was noted for this sample; subsequent reanalysis with controls for heterogeneity found no statistical differences between the tests (Kymes, 2000).

Methods to assess diagnostic accuracy have also evolved, and feature newer techniques designed to capture the natural correlation between sensitivity and specificity (Reitsma, 2005). A recent meta-analysis using newer bivariate methods found that ECHO was slightly more sensitive than SPECT (87% vs. 83% respectively), while SPECT was somewhat more specific (77% vs. 72% for ECHO) (de Jong, 2012). An additional bivariate metaanalysis using a much larger set of 113 SPECT studies found greater sensitivity (88%) and similar specificity (76%) (Parker, 2012), although other commentators have noted that the older SPECT studies included in this review were subject to "verification bias" (i.e., use of the reference standard only in test-positive or other selected individuals) (de Jong, 2012), which tends to inflate sensitivity and may also reduce specificity (Knottnerus, 1987). The Parker meta-analysis also included estimates of diagnostic accuracy from 9 PET studies (pooled estimates of 93% and 81% for sensitivity and specificity respectively) (Parker, 2012). Finally, a third recent meta-analysis estimated diagnostic performance from 114 SPECT and 15 PET studies (Jaarsma, 2012). SPECT sensitivity was similar to that reported elsewhere (88%), but specificity was somewhat lower (61%). Sensitivity and specificity for PET was estimated to be 84% and 81% respectively. It should be noted, however, that the Jaarsma analysis did not use modern meta-analytic techniques, instead meta-analyzing sensitivity and specificity as separate variables.

Other Outcomes

Extracardiac Findings

With the enhanced imagery available for many noninvasive tests, incidental findings outside of the area of interest can be problematic given the additional resources required for investigation (Stone, 2006). The reported rate of incidental extracardiac findings is very low with nuclear imaging tests given the limited field of detection, however; most available studies are limited to case reports of mediastinal masses (Kim, 2002; Hawkins, 2007; Paull, 2000). One recent study compared the rate of such findings between CCTA and SPECT in 479 patients; extracardiac findings requiring further investigation were detected in 7% of CCTA patients but in no SPECT patients (p=.0001) (Cheezum, 2011). Another analysis examined images of 2,155 patients undergoing SPECT studies, 6 (0.3%) of whom had extracardiac findings requiring follow-up. Four of the 6 patients had malignancies requiring further treatment (Gratz, 2008). We identified no PET studies reporting extracardiac findings.

While SPECT itself is associated with a low rate of extracardiac findings, the increasing use of CT for attenuation correction may result in increased detection of these findings. In a cohort study assessing prevalence of extracardiac findings from 582 SPECT/CT studies, a

total of 400 (68.7%) included noncardiac findings, 196 (33.7%) of which were felt to be potentially relevant (Husmann, 2009).

Equivocal/Indeterminate Results

While equivocal or indeterminate findings are possible with any diagnostic test, these results are rarely published. A recent systematic review of nearly 1,200 diagnostic accuracy studies found that only 35% reported the presence of inconclusive results (Shinkins, 2013). Inconclusive results were reported in only one of the available studies in our sample. In the CeCAT trial comparing SPECT with ECHO, CMR, and angiography, rates of equivocal findings were 4.0%, 6.6%, 6.6% and 2.0% respectively (Sharples, 2007).

Risks of Testing (KQ 2)

Patients appear to be at minimal immediate risk from cardiac nuclear imaging tests in and of themselves, although harms data are reported in only a small number of comparative studies. The risks that are reported are related primarily to the stressor employed (i.e., exercise or pharmacologic stress).

Comparative Data on Testing Risks

Only 2 studies in our sample compared adverse effects of multiple testing modalities. In the WOMEN study that randomized patients to ETT or exercise SPECT, no statisticallysignificant differences between groups were noted in rates of chest pain, dyspnea, or fatigue after testing (Shaw, 2011). In the CeCAT trial comparing SPECT, ECHO, CMR, and angiography specific reasons for failed tests were recorded (Sharples, 2007). Failure to complete the test due to adverse effects occurred in 4 ECHO patients (1.8%), due to vasovagal reactions, blood pressure changes and dyspnea; no patient failed to complete SPECT due to adverse effects. Findings from comparative studies are summarized in Table ES5 on page 23.

Adverse Effects by Stressor

Information on adverse effects attributed to specific stressors was obtained from 15 studies. Of these, 4 were RCTs involving SPECT, comparing binodenoson vs. adenosine stressors (Udelson, 2004), an accelerated vs. conventional protocol for dobutamine (Leão Lima, 2008), adenosine, dobutamine, and arbutamine stress (Wright, 2001), and 2 different infusion durations for adenosine (Treuth, 2001). Another 5 studies were comparative cohort studies, 2 of which featured comparisons of exercise vs. pharmacologic stress (Kabasakal, 1996; Chaptini, 2010). Regardless of the comparisons made, events were typically described as nonserious and resolved once the stressor infusion ended.

Reported ranges of adverse effects by category and type of stressor are summarized in Table ES6 on page 24. Rates were similar across pharmacologic agents. Limited data suggest lower rates of adverse effects for exercise vs. pharmacologic stress in the 2 studies making this comparison, although statistical comparisons were not available for all event types.

Study Information	Comparators	Adverse Effect	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Direction of Effect	Comments
SPECT vs. Co	mparator								
N=772 RCT=1	ETT vs. SPECT w/ no stressor (1)	Chest pain	Low	N/A	Direct	N/A	++ Low	No difference	
		Dyspnea	Low	N/A	Direct	N/A	++ Low	No difference	
N=898 RCT=1	Echo/MRI/ angiography vs. SPECT w/adenosine (1)	Chest pain	Low	N/A	Direct	N/A	++ Low	No difference	

 Table ES5. Summary evidence table: Risks of SPECT, PET, and hybrid imaging.

ETT: exercise treadmill test; N: number; N/A: not applicable; RCT: randomized controlled trial; SPECT: single photon emission computed tomography

Range (# studies reporting)	Exercise	Adenosine	Arbutamine [†]	Binodenoson [†]	Dobutamine	Dipyridamole	Regadenoson
Arrhythmias	NR	0-5% (4)	NR	3-4% (1)	1-39% (3)	NR*	NR
Chest Pain	3% (1)	0-46% (6)	77% (1)	21-47% (1)	12-62% (4)	NR*	13% (1)
Dyspnea	16% (1)	3-59% (6)	NR	16-58% (1)	6-12% (2)	NR*	12% (1)
Flushing/ Chills	0% (1)	3-68% (6)	35% (1)	17-40% (1)	0-54% (4)	NR*	NR
GI Effects	0-6% (2)	6-7% (2)	NR	NR	0-8% (3)	11% (1)	2% (1)
Headache/ Dizziness	NR	18-23% (2)	NR	NR	5-14% (3)	NR*	7% (1)
Hyper-/ Hypotension	NR	NR	NR	0% (1)	1-3% (2)	NR*	NR

Table ES6. Reported risks of cardiac nuclear imaging, by adverse effect type and stressor.

NOTE: Binodenoson rates ranged by dose in 1 study.

*Side effects requiring medical intervention occurred in 24-53% of patients receiving dipyridamole in 2 comparative studies vs. adenosine (p<.001 for greater side-effect rate vs. adenosine) *Not commercially available in U.S.

Radiation Exposure

Potential adverse health effects associated with radiation exposure are important factors to consider in the evaluation of cardiac nuclear imaging tests, particularly because patients may already be exposed to radiation at other points along the diagnostic pathway (e.g., CCTA, angiography), cumulative radiation dose may be substantial in patients receiving serial imaging studies, and imaging alternatives such as ECHO and CMR exist that do not involve radiation. Radiation dose is a measure of ionizing energy absorbed per unit of mass, expressed as units of Gy (Gray) or mGy; it often is quoted as an equivalent "effective" dose to major organs in the scanned area, in units of Sv (Sievert) or mSv. For x-rays, the radiation type produced by CT scanners, 1 mSv = 1 mGy. To place the effective radiation dose received from SPECT and PET in context, the effective doses based on varying test protocols and radiotracers are listed in Table ES7 on the following page, based on data presented in guidelines from the American Society of Nuclear Cardiology and other sources (Di Carli, 2011).

Protocol	MPI: Average Effective Dose (mSv)*	CT w/Attenuation Correction: Average Effective Dose (mSv)†	Average Total Effective Dose (mSv)
1-Day 99m-Tc SPECT	9.9 - 11.4	0.5	10.9 – 12.4
2-Day 99mTc SPECT	12.8 - 15.7	0.5	13.8 - 16.7
²⁰¹ Thallium/99mTc SPECT	29.3	0.5	30.3
Stress-only 99mTc SPECT	7.1 - 8.0	0.5	8.1 - 9.0
¹³ N-ammonia PET	2.2	0.5	2.7
⁸² Rubidium PET	3.7	0.5	4.2

Table ES7. Myocardial perfusion with SPECT and PET: average effective radiation doses

Adapted from DiCarli, 2011.

* Estimated per American Society of Nuclear Cardiology Guidelines; Senthamizhchelvan, 2010 & 2011.

† CT attenuation based on typical protocol. Attenuation correlation for SPECT based on separate rest and stress scans.

CT: computed tomography; MPI: myocardial perfusion imaging; mSv: millisievert; PET: positron emission tomography; SPECT: single photon emission computed tomography

Dose ranges for SPECT and PET have also been placed alongside typical doses from other tests and exposures to radiation in the graphic on the following page.

Radiation Exposure Scenario	Approximate Effective Dose (mSv)
Chest x-ray	0.02
Round-trip flight, New York-Seattle	0.06
Low-dose CT colonography	0.5-2.5
Lumbar spine x-ray	1.3
Head CT	2.0
Single-screening mammogram (breast dose)	3.0
Annual background dose caused by natural radiation	3.0/yr
ССТА	2.0-14.0
Cardiac PET Imaging	2.0-14.0
Invasive coronary angiography	5.0-7.0
Adult abdominal CT scan	10.0
Cardiac SPECT Imaging	7.0-30.0
Typical dose to A-bomb survivor at 2.3 km distance from ground zero Hiroshima	13.0
Annual radiation worker annual exposure limit	50.0/yr
Annual exposure on international space station	170.0/yr

Sources: Brenner, 2005; FDA

[http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm115329.htm]; ICER CCTA systematic review; Van Gelder 2004, Mettler 2008, Shuman 2008; Earls 2008; Husmann 2008 [2].

While exposure to ionizing radiation at these levels is associated with potential increase in cancer risk, the latency period for the development of such cancers may range from 10 to 40 years for solid tumors depending on the age and sex of the patient being tested (Gerber, 2009). The intended use of cardiac imaging tests then becomes a critical consideration. For example, the clinical tradeoff may be clearly in favor of imaging in the case of a symptomatic patient with known 3-vessel CAD or at very high CAD risk, with survival on medical therapy expected to be 50% or less within 5 years (Gerber, 2010); in other populations, such as stable patients undergoing serial imaging or in asymptomatic individuals, the tradeoff may be less certain.

Differential Effectiveness/Safety for Key Patient Subgroups (KQ 3)

We sought information on the *comparative* impact of cardiac nuclear imaging tests vs. alternative testing strategies in these subgroups. Results are summarized by subgroup category in the sections that follow, as well as in the summary evidence table ES8 beginning on the following page.

Patient Age, Sex, Race or Ethnicity, and Comorbidities

A single comparative cohort study was available that assessed all-cause mortality for stressonly vs. stress-rest SPECT (n=16,854) in specific subgroups over a mean of 4.5 years of follow-up (Chang, 2010). On a univariate basis, stress-rest protocols were associated with a statistically-significantly higher mortality rate in older (age >65) individuals, men, patients with a BMI <30 kg/m², and patients with diabetes. However, after multivariate adjustment for baseline characteristics, no statistically-significant differences remained.

While not part of our sample of studies comparing diagnostic modalities, several large cohort studies and meta-analyses have assessed the performance of SPECT in certain patient subgroups. For example, several studies have found that SPECT's diagnostic and prognostic performance is similar for women and men (Berman, 2003; Iskandar, 2013). Comparable results have also been found in several large ECHO studies (Wake, 2007; Arruda-Olson, 2002). A meta-analysis of risk-stratification studies in over 13,000 patients age >65 years found that both stress SPECT and stress ECHO accurately risk-stratified patients vs. ETT (Rai, 2012). A multicenter cohort study of approximately 1,100 patients found that SPECT results were predictive of cardiac events in both Caucasian and African-American patients (Alkeylani, 1998).

Table ES8. Summary evidence table: Differential effectiveness and/or safety of cardiac nuclear imaging in key subgroups.

Study Information	Comparator Sub-groups	Risk of Bias	Consistenc y	Directne ss	Precision	Strength of Evidence	Direction of Effect	Comments			
Mortality and Cardiovascular Events											
Patient Demographics: Sex											
SPECT (N=16,854) CC=1 Mean follow-up: 4.5 yrs	Stress vs. stress rest (1) Subgroups: Men vs. women	Medium	N/A	Direct	N/A	+ Insufficient		No differences after multivariate adjustment			
Patient Demographics: Age											
SPECT (N=16,854) CC=1 Mean follow-up: 4.5 years	Stress vs. stress rest (1) Age(<65 vs. >65)	Medium	N/A	Direct	N/A	+ Insufficient		No differences after multivariate adjustment			
Patient Demographics: (Patient Demographics: Comorbidities										
SPECT (N=16,854) CC=1 Mean follow-up:4.5 years	Stress vs. stress rest (1) Subgroups: Obesity (<30 kg/m ² vs. >30 kg/m ²), Diabetes	Medium	N/A	Direct	N/A	+ Insufficient		No differences after multivariate adjustment			
Clinical Setting											
SPECT (N=16,854) CC=1 Mean follow-up:4.5 years	Stress vs. stress rest (1) Subgroups: Inpatient vs. outpatient	Medium	N/A	Direct	N/A	+ Insufficient		No differences after multivariate adjustment			

Study Information	Comparator Sub-groups	Risk of Bias	Consistenc v	Directne ss	Precision	Strength of Evidence	Direction of Effect	Comments			
Scan Vendor, Tracer Type, Stressor Type											
SPECT (N=20,819) CC=3 Mean follow-up:1.5-4.5 years	Tetrofosmin vs. sestamibi (2) Subgroups: Tetrofosmin vs. sestamibi	Medium	Consistent	Direct	Precise	+++ Moderate	No difference s				
	Stress vs. stress and rest (1) Subgroups: Exercise vs. pharmacologic stress	High	N/A	Direct	N/A	+ Insufficient		No differences after multivariate adjustment			
Diagnostic Accuracy		1	1	1		-	T				
SPECT Cohort=2 N=410 Mean follow up: NR	Diabetes, Hypertension	High	Inconsisten t	Direct	Imprecise	++ Low	Mixed evidence	Better accuracy among pts w/diabetes in 1 of 2 studies; no differences for hypertension			

CC: comparative cohort; N: Number; N/A: Not applicable; NR: Not reported; SPECT: single photon emission computed tomography

Analyses comparing patients with and without diabetes suggest that, while diabetes is a predictor of mortality for any nuclear imaging result, SPECT testing provides incremental prognostic information in patients with and without diabetes alike (Berman, 2003; Kang, 1999). Multiple studies have found that SPECT is feasible and has comparable diagnostic and prognostic performance in normal-weight, overweight, and obese patients (Gimelli, 2012; Berman, 2006; Kang, 2006). Finally, a meta-analysis SPECT and ECHO studies in hypertensive patients showed diagnostic accuracy similar to that observed in all patients with suspicion of CAD (Gargiulo, 2011).

Clinical Setting

In the previously-described comparison of stress-only vs. stress-rest SPECT (Chang, 2010), mortality was initially statistically-significantly higher in stress-rest patients in an inpatient setting. After multivariate adjustment, however, no significant differences remained.

Limited additional data are available explicitly comparing the performance of SPECT by setting. One study evaluating the potential benefit of an emergency department chest pain clinic estimated that unnecessary hospitalizations would be reduced in 30% of patients and inappropriate discharges avoided in 6% through the use of a selective SPECT protocol (Abbott, 2001).

Selection of Test by Primary Care vs. Specialty Physician

No study in our sample assessed the impact of ordering specialty on patient outcomes, clinical decision-making, or costs. There are, however, several studies that have assessed the impact of specialty on whether ordered cardiac SPECT studies meet published appropriate use criteria (AUC). In a multicenter assessment of an online SPECT appropriateness classification system, Hendel and colleagues found that the rate of inappropriate studies was statistically-significantly higher among noncardiologists (19.5% vs. 13.2% for cardiologists, p<.0001). Similar findings have been observed in several single-center studies (Gupta, 2011; Druz, 2011; Mehta, 2008). Of note, most inappropriate ordering of SPECT perfusion studies appears to have occurred in women, younger patients, and/or those without symptoms.

Scan Vendor, Type of Assessment, Type of Radioisotope, and Type of Stressor No study in our sample assessed the impact of scan vendor or qualitative vs. quantitative assessment on patient outcomes, clinical decision-making, or costs.

Most of the studies evaluating differences according to stressor type focused on rates of adverse effects of pharmacologic testing (see "Risks of Testing" on page 105). Chang's evaluation of stress-only vs. stress-rest SPECT found no statistically-significant effects on mortality with subgroups defined by exercise vs. pharmacologic stress on either a univariate or multivariate-adjusted basis (Chang, 2010).

Two studies examined the impact of different SPECT radiotracers on outcomes. In one, a total of 1,818 patients (median age, 63 years; 66% male) underwent exercise or pharmacologic stress SPECT with Tc-99m sestamibi or Tc-99m tetrofosmin at Duke

University Medical Center (Borges-Neto, 2004). Patients were followed for a mean of 1.5 years, during which no statistically-significant differences were observed between groups in the rates of overall mortality, cardiovascular mortality, or the composite endpoint of cardiovascular mortality or nonfatal MI.

Adams et al. compared mortality outcomes among 2,147 patients with known CAD (median age, 67 years; 55% male) undergoing pharmacologic stress SPECT with either Tc-99m sestamibi or Tc99m tetrofosmin who were followed for a median of 4 years (Adams, 2007). During follow-up, a total of 704 all-cause deaths (493 cardiovascular-related) were reported. There was no significant difference in either overall or cardiovascular mortality between radiotracer groups on both an unadjusted and multivariate-adjusted basis.

Analysis of Comparative Value (KQ 4)

Published Evidence

Limited evidence is available that directly measured and compared the economic impact of non-invasive testing strategies for CAD. For example, no such studies were available among asymptomatic or symptomatic patients at high risk of CAD. Three of the RCTs in our sample included costs. In one, an RCT of ETT vs. SPECT in 772 women at low-tointermediate risk of CAD in 43 cardiology practices across the U.S. (Shaw, 2011), total mean costs of testing over 2 years were higher in the SPECT arm (\$643 vs. \$338, p<.001), as the higher costs of initial SPECT testing outweighed the increased costs of downstream testing in the ETT arm. In another 2-year RCT conducted in 457 primarily intermediate-risk patients in the UK, however, downstream testing costs were substantially higher in the ETT arm, leading to significantly higher total costs from randomization to diagnosis using National Health Service (NHS) estimates (\$1,244 v \$743 for SPECT, p<.001). The final RCT compared costs of initial and repeat testing, treatment, and adverse events over 18 months of follow-up for mixed-risk patients randomized to SPECT, ECHO, CMR, or direct referral to angiography (Sharples, 2007). Direct referral to angiography was the lowest-cost strategy. Incremental costs (relative to angiography) were similar for the SPECT and CMR strategies (~\$650), but were twice as high for patients in the ECHO group (~\$1,250) due to a higher rate of hospital readmissions.

Economic evidence for PET was limited to 2 studies. In one, an evaluation of planned vs. actual management before and after PET perfusion testing in 100 patients with known CAD (Siegrist, 2008), savings from reduced need for angiography were greater than the incremental costs of PET testing and revascularization, leading to overall savings of \$240 per patient. In the other, a matched comparative cohort analysis of PET and SPECT (Merhige, 2007), mean costs of all diagnostic testing were approximately \$2,500 in both groups, but greater requirements for revascularization at 1 year led to higher total costs in the SPECT group (\$5,937 vs. \$4,110 for PET).

Decision-Analytic Model

Because evidence is limited comparing the short-term clinical consequences and costs for all relevant non-invasive strategies for CAD diagnosis, we developed a decision-analytic model to provide additional information. The target population involved men and women with suspected or known CAD who had stable symptoms of myocardial ischemia (i.e., atypical or typical chest pain or other symptoms such as dyspnea). As previously described, models of CAD pretest probability often overestimate actual CAD prevalence seen in clinical practice. As CAD prevalence was required for our model to estimate the results of diagnostic testing (e.g., identifying true negatives vs. false positives), we chose levels of prevalence that would approximate constructs of low, intermediate, or high "risk". These levels of prevalence were 10%, 30%, and 50-70% respectively.

As noted previously, evidence of test accuracy to detect *functionally-significant* ischemia is quite limited and not available for all testing strategies of interest. We were therefore required to use anatomic reference standard data to depict test results.

Model outcomes and costs were estimated over a 90-day period, as we believed there would be little utility in extrapolating long-term outcomes from point-in-time testing. For example, some patients with false-negative test results will suffer a major clinical event or die because of the missed diagnosis, while others will have their symptoms recur, will present again for testing, and will be correctly diagnosed. Any attempt to estimate the distribution of future behavior for such patients would be highly speculative.

Based on expert clinical input, we developed 7 different strategies, alone and in combination, to capture a wide range of management approaches:

- 1. ECHO, followed by invasive coronary angiography if ECHO is positive or inconclusive
- 2. ETT, followed by angiography if ETT is positive or inconclusive
- 3. SPECT, followed by angiography if ETT is positive or inconclusive
- 4. PET, followed by angiography if ETT is positive or inconclusive
- 5. ETT, followed by ECHO if ETT is positive or inconclusive, followed by angiography if the ECHO is positive or inconclusive
- 6. ETT, followed by SPECT if ETT is positive or inconclusive, followed by angiography if the SPECT is positive or inconclusive
- 7. ETT, followed by PET if ETT is positive or inconclusive, followed by angiography if the PET is positive or inconclusive

Choice of Outcomes

In the interest of transparency, a cost-consequence analysis was conducted in which diagnostic and economic outcomes are presented in disaggregated form. Key outcomes obtained from the decision model included:

- 1) numbers of true positive non-invasive test results per 1,000 population tested;
- 2) numbers of false positive non-invasive test results per 1,000 population tested;
- 3) numbers of true negative non-invasive test results per 1,000 population tested;
- 4) numbers of false negative non-invasive test results per 1,000 population tested;
- 5) numbers of patients referred for angiography per 1,000 population tested;
- 6) numbers of angiography-negative results per 1,000 population tested (i.e., truenegative and false-positive results from non-invasive testing);
- 7) numbers of angiography-related deaths per 1,000 population tested;
- 8) numbers exposed to radiation per 1,000 population tested;
- 9) numbers of incidental extracardiac findings requiring follow-up per 1,000 population tested; and
- 10) total (90-day) costs per patient

Model Inputs

We derived model estimates of diagnostic accuracy largely from 2 recently published systematic reviews that employed modern bivariate meta-analytic techniques. The bivariate meta-analysis by de Jong and colleagues provided the sensitivity and specificity values for ECHO and SPECT (de Jong, 2012). We derived the sensitivity and specificity of PET from a second bivariate meta-analysis (Parker, 2012). Diagnostic accuracy values for ETT were derived from the CE-MARC study (Greenwood, 2013). Data on inconclusive results are rarely reported in diagnostic accuracy studies; we opted instead to obtain these data from available RCTs in our study sample (Table 11). The probability of mortality with angiography was derived from a Report from the CathPCI Registry of the National Cardiovascular Data Registry in the United States, 2010 through June 2011 (Dehmer, 2012), and was calculated as a cumulative risk for all angiographies performed within a given strategy.

Note that accuracy estimates, even those from bivariate analyses, are based on use of anatomic data from angiography as the reference standard. As noted in our systematic review, only a small number of studies have assessed the accuracy of the tests of interest in comparison to a functional reference standard, which precluded our use of such data in primary analyses. We nevertheless included pooled estimates of accuracy for PET and SPECT using FFR-based reference standards in sensitivity analyses.

Direct costs were considered from the payer perspective; reimbursement rates from the Washington Health Care Authority were used. Estimates of direct costs included professional and technical fees as well as facility charges for the initial noninvasive

diagnostic test and those for any subsequent noninvasive diagnostic test and/or invasive coronary angiography costs. While we displayed the number of patients for whom extracardiac findings requiring follow-up would be observed, we did not model the costs, benefits, or risks of identifying such findings, as available data are extremely sparse with respect to the costs and consequences of such findings. We assumed that SPECT, ETT, and ECHO would be done with exercise stress, while PET would be conducted under pharmacologic stress. The costs of stress modalities are included in the estimated costs for each test, as are radiotracer costs for PET and SPECT.

Key Assumptions

Listed in Table ES9 below are assumptions made in designing the model for this evaluation in order to preserve model transparency and simplicity. Our model was based to some degree on past decision models evaluating short-term diagnostic and economic outcomes of myocardial perfusion testing for CAD (Walker, 2013; Institute for Clinical and Economic Review, 2009; Kim, 1999).

Table ES9. Key model assumptions.

It is assumed that all patients are fit enough to undergo exercise stress (use of pharmacologic stress for PET is a function of the device)

All patients are able to complete each test (exercise patients achieve target heart rate, stressor infusion is successful, there are no technical failures)

Angiography is assumed to have sensitivity and specificity of 100% for detection of CAD (i.e., the "gold" standard)

The studies included in the underlying meta-analyses are similar enough in terms of study and patient characteristics to compare across diagnostic strategies

Summary Model Results

Table ES10 on the following page depicts the results for 1,000 adults with an underlying prevalence of CAD of 50%. The columns represent the results if all patients had undergone each strategy.

It can be seen that there are important trade-offs to consider when comparing these strategies. For example, PET alone has the highest number of true positives at 464 and the lowest number of false negatives at 34 among all strategies. ETT \rightarrow PET has the highest number of true positives and lowest number of false positives among all 2-test strategies. However, PET (and SPECT) also carry radiation exposure risks for all patients. PET also has the highest cost per patient, with a cost of \$5,074 per patient evaluated.

In comparing ECHO and SPECT, SPECT as a single-test strategy produces 21 more false negative results but 33 fewer false positive results. SPECT results in radiation for all patients, compared to 60% of patients who begin evaluation with ECHO. ECHO requires

follow-up for incidental extracardiac findings in 57 patients, however, vs. 8 for SPECT. ECHO is also less expensive overall by approximately \$450 per patient tested. When combined with ETT in a 2-test strategy, SPECT still produces more false negatives and fewer false positives, but the differences with ECHO are much less, on the order of 13-15 patients per 1,000 evaluated.

			-				
		ETT	SPECT	PET	ETT → ECHO	ETT → SPECT	ETT → PET
True Positive, non-invasive	437	365	416	464	320	305	340
False Positive, non-invasive	163	194	130	111	64	51	43
True Negative, non-invasive	336	305	370	389	436	449	457
False Negative, non-invasive	61	133	82	34	178	193	158
Referred for angiography	603	562	549	578	386	358	386
Angiography negative results	163	194	130	111	64	51	43
Angiography related deaths	4	3	3	3	2	2	2
Exposed to radiation	603	562	1000	1000	386	562	562
Incidental findings requiring f/u	57	0	8	8	32	5	5
Total costs/patient [excluding all f/u costs, \$)	2538	1883	2987	5074	1737	1996	3204

Table ES10: Results from	patients with	high risk	(50%) of CAD
	1	0	()

ECHO: echocardiogram; ETT: exercise treadmill testing; PET: positron emission tomography; SPECT: single photon emission computed tomography

Value judgments are required to evaluate the trade-offs in the outcomes of these different testing approaches. Some of these judgments include: whether false positives are more important than false negatives; the relative importance of differences in diagnostic accuracy and the costs of competing testing strategies; and the importance of radiation exposure.

Because the underlying CAD prevalence varies in different patient populations, we present Tables ES11, ES12 and ES13 on the following pages depicting the result of the identical testing strategies for a population with 10%, 30% and 70% CAD prevalence. Comparing these results to the basecase analysis demonstrates the importance of the underlying

prevalence on the relative balance of false negatives, false positives, rates of referral to angiography, and costs. For example, among a patient population with a CAD prevalence of 10%, the difference in false negatives between SPECT and ECHO almost vanishes (4 per 1,000). In contrast, the difference in false positives between SPECT and ECHO in a population with 50% CAD prevalence was 33 per 1,000 but is increased to 60 per 1,000 when the underlying prevalence of CAD is only 10%. The relative differences in angiography referral, patients exposed to radiation, and costs also shift, emphasizing again the importance of value judgments to comparisons of the clinical and economic outcomes of these different testing strategies as simulated in this model.

Sensitivity Analyses

We also conducted a number of sensitivity analyses in which we varied the sensitivity and specificity estimates for the different tests, analyzed outcome using a "very low" prevalence of underlying CAD (2%), and conducted probabilistic sensitivity analyses that took into account the estimated variability in our estimates. Results of these analyses can be found in Appendix E of this report.

	ЕСНО	ETT	SPECT	PET	ETT → ECHO	ETT → SPECT	$\begin{array}{c} \text{ETT} \rightarrow \\ \text{PET} \end{array}$
True Positive	87	73	83	93	64	61	68
False Positive	293	350	233	199	115	91	78
True Negative	605	548	665	700	785	808	822
False Negative	12	27	16	7	36	39	32
Referred for angiography	383	425	319	294	180	153	147
Angiography negative results	293	350	233	199	115	92	78
Angiography related deaths	2	3	2	2	1	1	1
Exposed to radiation	383	425	1000	1000	180	425	425
Incidental findings requiring f/u	57	0	8	8	24	4	4
Total costs/patient [excluding all f/u costs, \$)	1865	1464	2284	4206	1011	1191	2021

Table ES11: Results from patients with low risk (10%) of CAD.

ECHO: echocardiogram; ETT: exercise treadmill testing; PET: positron emission tomography; SPECT: single photon emission computed tomography

	ЕСНО	ETT	SPECT	PET	ETT → ECHO	ETT → SPECT	ETT → PET
True Positive	262	219	250	278	192	183	204
False Positive	228	272	182	155	89	71	61
True Negative	471	426	517	544	610	629	639
False Negative	36	80	49	20	107	116	95
Referred for angiography	493	494	434	436	283	256	266
Angiography negative results	228	272	182	155	90	71	61
Angiography related deaths	3	3	3	3	2	2	2
Exposed to radiation	493	494	1000	1000	283	494	494
Incidental findings requiring f/u	57	0	8	8	28	4	4
Total costs/patient [excluding all f/u costs, \$)	2201	1674	2636	4640	1374	1594	2613

Table ES12: Results from patients with intermediate risk (30%) of CAD.

ECHO, echocardiogram, ETT, Exercise treadmill testing; PET= Positron Emission Tomography; SPECT= Single Photon Emission Computed Tomography

			-				
	ECHO	ETT	SPECT	PET	ETT→ ECHO	ETT → SPECT	ETT → PET
True Positive	611	510	582	649	449	427	476
False Positive	98	117	78	66	38	30	26
True Negative	202	183	222	233	262	269	274
False Negative	85	186	114	47	249	270	221
Referred for angiography	713	631	664	720	490	460	505
Angiography negative results	98	117	78	66	38	31	26
Angiography related deaths	4	4	4	4	3	3	3
Exposed to radiation	713	631	1000	1000	490	631	631
Incidental findings							
requiring f/u	57	0	8	8	36	5	5
Total costs/patient							
[excluding all f/u costs, \$)	2874	2092	3339	5507	2100	2399	3796

Table ES13: Results from	patients with high	risk (70%) of CAD.
	r	

ECHO, echocardiogram, ETT, Exercise treadmill testing; PET= Positron Emission Tomography; SPECT= Single Photon Emission Computed Tomography

Strengths and Limitations

There are a number of strengths of this study. First, clinical inputs were derived from systematic reviews that were based largely on recently-published underlying studies (2000 and onward if possible) and used statistical approaches that incorporated the correlation between sensitivity and specificity (i.e., bivariate models). Other decision models and economic evaluations in this area were based on accuracy estimates from meta-analyses that did evaluated sensitivity and specificity as distinct variables and/or included older studies of technically obsolete forms of nuclear imaging tests (Hayashino, 2004; Kim, 1999). Second, our analysis followed a transparent and accepted methodology and largely adheres to the International Society of Pharmacoeconomics and Outcomes Research Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement (Husereau, 2013). Third, wherever possible, the model used costing data reflective of the Washington Health Care Authority experience. Finally, detailed sensitivity analyses were performed to examine the robustness of results to variation in model parameters and assumptions.

Despite its strengths, this analysis has certain limitations that warrant discussion. First, and perhaps most importantly, available data were insufficient to design a model based on detection of functionally-important ischemia. As with previous decision models, we were required to rely on estimating test accuracy based on anatomic angiography findings. As described previously, the correlation between anatomic evidence of stenosis and presence of functionally-important ischemia is quite weak. However, it is also the case that use of anatomic data from angiography still informs a substantial percentage of treatment decisions, even in the presence of functional data from non-invasive tests (Chan, 2011).

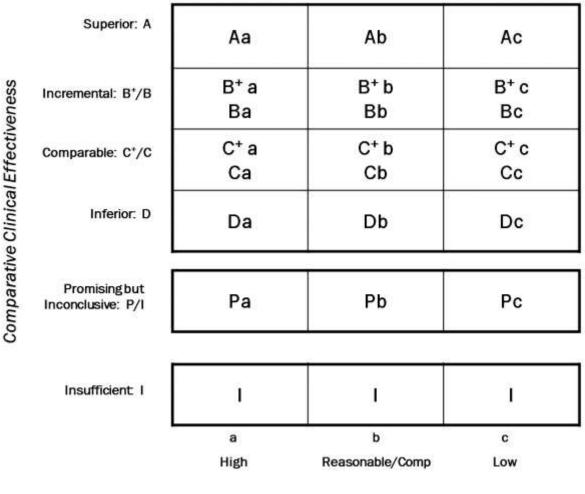
Even with a focus on anatomic reference standards, we were unable to identify a single systematic review and meta-analysis which considered all of our treatment strategies simultaneously, used recently published data, and was based on a bivariate statistical model. Therefore, we were forced to use different sources for different treatments. We did conduct detailed sensitivity analyses to adjust for potential heterogeneity across data sources, as well as to use alternative estimates of test accuracy, however.

Second, the results of studies on diagnostic test accuracy for CAD are often reported as a 2×2 classification matrix (Shinkins, 2013). This is problematic because restricting test results to be either positive or negative fails to represent the complete reality of how they are used in clinical practice, where there is a probability that the test is inconclusive and different clinical decisions may in fact be made on the basis of whether results are "mildly, moderately, or severely" abnormal (Shinkins, 2013). To account for this issue, we were forced to derive estimates for the probability of inconclusive tests from alternative sources.

Third, to enhance transparency we adopted a simplistic decision model which does not account for the severity of CAD. We opted for this simplistic approach because we had limited data to populate sensitivity, specificity, and the probability of inconclusive results for all of the strategies when the decision model was stratified by severity of CAD. Nevertheless, the model is adaptable and does allow one to consider disease severity if robust data become available to populate these parameters (see Figure D2 in Appendix D). This simplistic approach also precluded us from incorporating all of the permutations of testing that may occur in clinical practice, such as use of pharmacologic stress in patients unable to exercise and/or in those who do not achieve target heart rate, and restarting the test (or referral to another test) due to technical failure or problematic image acquisition. Even if data on these concerns were available for all of the testing strategies of interest, however, it is likely that their inclusion would have affected the magnitude of our findings rather than their direction.

ICER Integrated Evidence Ratings

The ICER integrated evidence rating matrix is shown below; a detailed explanation of the methodology underpinning this rating system can be found beginning on page 43. Separate ratings are provided for cardiac nuclear imaging tests by population; the ratings and rationale are described on the following pages. As noted previously, a significant proportion of the evidence involved "mixed" populations of patients at varying levels of CAD risk, symptoms, and whether or not CAD is known to be present. Rather than develop a separate set of ratings for these patients, we have used findings from studies in mixed populations to inform ratings in specific populations.



ICER Integrated Evidence Rating ™ Comparator X vs. Reference Technology Y

Comparative Value

Asymptomatic, High-Risk Individuals

- SPECT vs. No Screening: Cc
- SPECT vs. ETT or ECHO: I
- PET vs. any Alternative: I
- Hybrid vs. any Alternative: I

Rationale for ICER Rating

There were no comparative studies identified that compared PET or hybrid technologies to any screening alternative in asymptomatic individuals at high risk of CAD. Similarly, there were no studies comparing SPECT to ETT- or ECHO-based screening strategies. Therefore, we consider the evidence "Insufficient" to make a determination regarding these comparisons.

We identified a single study comparing SPECT-based one-time screening to no screening, an RCT of 1,123 asymptomatic patients with diabetes who were followed for 5 years (Young, 2009). No differences were noted between groups in mortality or major cardiovascular events, even though a higher rate of short-term revascularization was seen in the SPECT arm. Even though our determination is largely based on this single RCT, its size and duration lend greater certainty to our estimate of comparative net health benefit. Therefore, we rated the comparative clinical effectiveness of SPECT vs. no screening to be "Comparable". While not explicitly part of our model, the use of SPECT screening does introduce additional cost (for both initial and downstream testing) for outcomes that are essentially functionally equivalent. We therefore rated the comparative value of SPECT vs. no screening to be "Low".

Symptomatic Individuals at Low-to-Intermediate CAD Risk

- SPECT vs. ETT: C+c
- SPECT vs. ECHO: Cb
- PET vs. any Alternative: I
- Hybrid vs. any Alternative: I

Rationale for ICER Rating

The entire body of evidence in this population suggests that SPECT provides incremental diagnostic and prognostic information over ETT at the higher end of the low-to-intermediate risk spectrum. However, in lower-risk populations such as those in the

previously-described RCT comparing SPECT with ETT in women (Shaw, 2011), no material differences are seen. Given this increased level of uncertainty about the precision of our estimate of comparative net health benefit across the spectrum of risk, we therefore rated the comparative clinical effectiveness of SPECT in this population to be "Comparable or Better". However, our modeling results suggest that, based on HCA payment figures, SPECT is a more costly strategy than ETT when used as an initial test (despite higher numbers of false-positive results for ETT), and a 2-test strategy of ETT before SPECT may provide additional cost savings. For these reasons, we rated the comparative value of SPECT vs. ETT to be "Low".

In contrast, findings from multiple studies comparing SPECT and ECHO in low-tointermediate-risk patients indicate similar diagnostic and prognostic performance, giving us enough certainty to rate the comparative clinical effectiveness as "Comparable". Findings from prior economic evaluations and our own model also suggest comparable costs to diagnose a patient with CAD, resulting in our value rating of "Reasonable/Comparable". As with asymptomatic individuals, there were insufficient data to rate the performance of PET or hybrid modalities in patients at low-to-intermediate CAD risk.

Symptomatic Individuals at High CAD Risk

- SPECT vs. ETT: B+b
- SPECT vs. ECHO: Cb
- PET vs. any Alternative: I
- Hybrid vs. any Alternative: I

Evidence from a single-center RCT suggests that, in patients at higher risk of CAD, SPECT reduces unnecessary referral to angiography (and therefore potential revascularization) in comparison to ETT. Because these data come from a single study, we used an "Incremental or Better" rating for comparative clinical effectiveness to reflect uncertainty in this estimate. While 90-day costs in our model remain higher for SPECT, the rate of false-negatives is substantially higher for ETT-based strategies. We did not estimate the costs of these outcomes but in our judgment there is a reasonable balance between higher SPECT test costs and the costs that would ensue from false-negative results. We therefore have assigned a comparative value rating of "Reasonable/Comparable". As in lower-risk individuals, both the comparative clinical effectiveness and comparative value of SPECT vs. ECHO were felt to be "Comparable". Evidence was insufficient to evaluate the performance of PET or hybrid modalities in comparison to any alternative.

Known CAD*

- SPECT vs. ETT: I
- SPECT vs. ECHO: Cb
- PET vs. any Alternative: I
- Hybrid vs. any Alternative: I

*All comparisons "Insufficient" for asymptomatic patients with known CAD

There were no studies comparing SPECT to ETT in populations comprised entirely of patients with known CAD, and only a single older cohort study suggesting benefits of SPECT over ETT in mixed populations (Pattilo, 1996). We therefore rated the comparative clinical effectiveness of SPECT vs. ETT to be "Insufficient". We did the same for comparisons of hybrid testing approaches. While there was some evidence available suggesting that PET information was associated with changes in patient management (Siegrist, 2008) and that PET reduced rates of downstream testing and revascularization vs. SPECT (Merhige, 2007), the evidence base was limited to nonrandomized comparative studies. Comparative clinical effectiveness was therefore rated "Insufficient" in this instance as well.

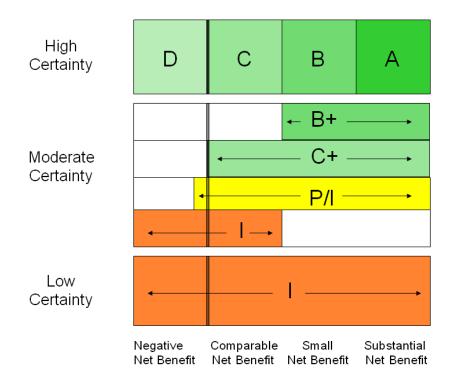
With regard to SPECT vs. ECHO, data from a single RCT suggested that use of ECHO resulted in greater numbers of hospital readmissions for chest pain vs. SPECT, although it was acknowledged that SPECT is the more established modality in this setting and the higher readmission rate for ECHO was related to the complicated clinical courses of a few patients (Sharples, 2007). Other cohort studies in mixed populations of suspected and known CAD indicated similar performance between these modalities. Overall, we felt the evidence base robust enough to provide high certainty of "Comparable" comparative clinical effectiveness in this patient population between SPECT and ECHO. Although we did not explicitly model this population, the comparative value of SPECT vs. ECHO was expected to be similar to that observed in symptomatic populations (i.e., "Reasonable/Comparable").

Finally, as noted previously, these ratings are applicable to patients with known CAD who have changes in symptoms, as we did not identify any comparative studies evaluating the impact of nuclear imaging in *asymptomatic* patients with known CAD. Therefore, all modality comparisons would be rated "Insufficient" for this population.

Methodology: ICER Integrated Evidence Rating[™]

Comparative Clinical Effectiveness

The ICER Integrated Evidence Rating[™] combines a rating for comparative clinical effectiveness and a rating for comparative value. The clinical effectiveness rating arises from a joint judgment of the level of certainty provided by the body of evidence and the magnitude of the net health benefit -- the overall balance between benefits and harms. This method for rating the clinical effectiveness is modeled on the "Evidence- Based Medicine (EBM) matrix" developed by a multi-stakeholder group convened by America's Health Insurance Plans. This matrix is depicted below:



Comparative Clinical Effectiveness

A = *"Superior"* - High certainty of a substantial (moderate-large) net health benefit

B = "Incremental" - High certainty of a small net health benefit

C = *"Comparable"-* High certainty of a comparable net health benefit

D="Negative"- High certainty of an inferior net health benefit

B+=*"Incremental or Better"* – Moderate certainty of a small net health benefit, with high certainty of at least incremental net health benefit

C+="*Comparable or Better*" - Moderate certainty of a comparable net health benefit, with high certainty of at least comparable net health benefit

P/I = "*Promising but Inconclusive*" - Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit

I = "*Insufficient*" – Either moderate certainty that the best point estimate of comparative net health benefit is comparable or inferior; or any situation in which the level of certainty in the evidence is low

Certainty

The vertical axis of the matrix is labeled as a degree of certainty with which the magnitude of a technology's comparative net health benefit can be determined. This operational definition of certainty thus is linked to but is not synonymous with the overall validity, consistency (i.e., similar magnitude and direction of findings across studies), and directness (i.e., head-to-head comparisons, direct measurement of key rather than surrogate outcomes) of the body of evidence available for the assessment. ICER establishes its rating of level of certainty after deliberation by the Evidence Review Group, and throughout ICER follows closely the considerations of evidentiary strength suggested by the Effective Health Care program of the Agency for Health Research and Quality (AHRQ) (www.effectivehealthcare.org) and the GRADE working group (www.gradeworkinggroup.org).

General Characteristics of Evidence Providing Different Levels of Certainty:

High Certainty

- Mostly high-quality, larger studies
- Conducted in representative patient populations
- Direct comparisons available
- Address important outcomes or validated surrogate outcomes
- Long-term data on benefits/risks available
- Consistent results
- Future studies unlikely to change conclusions

Moderate Certainty

- Mix of study quality
- Cannot estimate net benefit with good precision, based on limitations including:
 - Weak study design or conduct
 - Inconsistent findings
 - Indirect evidence only
 - Limited applicability of results
 - Evidence of reporting bias
 - Future studies may result in modest shifts in estimates of net health benefit

Low Certainty

- Mostly poor-quality, smaller studies
- Evidence insufficient to estimate net benefit at all

- Flaws in evidence base make it impossible to determine if intervention inferior, comparable, or superior to comparator
- High likelihood that new evidence would substantially change conclusions regarding net benefit

Net Health Benefit

The horizontal axis of the comparative clinical effectiveness matrix is "net health benefit." This term is defined as the balance between benefits and harms, and can either be judged on the basis of an empiric weighing of harms and benefits through a common metric (e.g., Quality Adjusted Life-Years, or "QALYs"), or through more qualitative, implicit weightings of harms and benefits identified in the ICER appraisal. Either approach should seek to make the weightings as explicit as possible in order to enhance the transparency of the ultimate judgment of the magnitude of net health benefit:

- *Negative:* the intervention produces a net health benefit inferior to that of the comparator
- *Comparable:* the intervention produces a net health benefit comparable to that of the comparator
- *Small:* the intervention produces a small positive net health benefit relative to the comparator
- *Substantial:* the intervention produces a substantial (moderate-large) positive net health benefit relative to the comparator

Whether judged quantitatively or qualitatively, there are two general situations that decision-making groups face in judging the balance of benefits and harms between two alternative interventions. The first situation arises when both interventions have the same types of benefits and harms. For example, two blood pressure medications may both act to control high blood pressure and may have the same profile of toxicities such as dizziness, impotence, or edema. In such cases a comparison of benefits and harms is relatively straightforward. However, a second situation in comparative effectiveness is much more common: two interventions present a set of trade-offs between overlapping but different benefits and harms. An example of this second situation is the comparison of net health benefit between medical treatment and angioplasty for chronic stable angina. Possible benefits on which these interventions may vary include improved mortality, improved functional capacity, and less chest pain; in addition, both acute and late potential harms differ between these interventions. It is possible that one intervention may be superior in certain benefits (e.g. survival) while also presenting greater risks for particular harms (e.g. drug toxicities). Thus the judgment of "net" health benefit of one intervention vs. another often requires the qualitative or quantitative comparison of different types of health outcomes.

Since net health benefit may be sensitive to individual patient clinical characteristics or preferences there is a natural tension between the clinical decision-making for an individual and an assessment of the evidence for comparative clinical effectiveness at a population level. ICER approaches this problem by seeking, through the guidance of its scoping committee, to identify a priori key patient subpopulations that may have distinctly different net health benefits with alternative interventions. In addition, the ICER appraisal will also seek to use decision analytic modeling to identify patient groups of particular clinical characteristics and/or utilities which would lead them to have a distinctly different rating of comparative clinical effectiveness.

The exact boundary between small and moderate-large net benefit is subjective and ICER does not have a quantitative threshold. The rating judgment between these two categories is guided by the deliberation of the Evidence Review Group. It is also worth noting that there are two variants of these categories available: "comparable or better" and "incremental or better". While these categories also must take into consideration the level of certainty in the point estimate, they are of great utility when considering a new or emerging intervention. For example, some new medications may be structurally identical to existing alternatives but with simpler dosing schedules or more convenient drug delivery, suggesting clinical performance that is at least as good as, and perhaps incrementally better than, existing treatments. In other situations, a new intervention may offer a distinct advantage over existing alternatives, but the true level of incremental benefit (i.e., small vs. substantial) is not yet known.

Comparative Value

There are three categories of value: high, reasonable or comparable, and low. The ICER rating for comparative value arises from a judgment that is based on multiple considerations. ICER does not employ a single measure of cost-effectiveness for assignment of comparative value, nor does it rely on a formal threshold for determination of the level of value. Instead, comparative value is informed by multiple measures of potential economic impact, including:

- Impact on service use (e.g., tests, hospitalizations)
- Cost to reduce adverse outcomes (e.g., cost per hospitalization averted)
- Cost to achieve clinical success (e.g., cost per curative outcome)
- Cost per life year gained
- Cost per quality-adjusted life year (QALY) gained
- Budget impact per 1,000 diseased individuals
- System issues (e.g., manpower tradeoffs to invest in new technology)

The advantages for evaluating the full list of economic measures are twofold. First, the importance of these measures varies for individual stakeholders. For example, payers may be most interested in expressions of the clinical value achieved for the additional investment provided (e.g., cost per QALY, cost per event averted), while integrated health systems may ascribe most importance to measures of budgetary or system impact, and

patients may be most interested in differential rates of downstream testing or other service use. Second, sole reliance on traditionally-accepted measures of cost-effectiveness such as cost per QALY may mask important considerations in evaluating whether to adopt a new technology. Cost-effectiveness findings may appear to be "reasonable" based on widelyused thresholds (e.g., \$50,000 per QALY gained), when in reality the incremental investment required is for an imperceptible clinical gain.

ICER has developed a method for presenting multiple measures of economic impact together in a format known as the Comparative Value Evidence Table (CVET), which allows for visualization of economic measures important to each healthcare stakeholder. Wherever feasible, the CVET has been designed for interactive modification of certain economic model parameters and visualization of how findings might change. Uncertainty in model results is also explored through "sensitivity analyses" — analyses of the robustness of the economic model to changes in certain probabilities and/or costs. Assignment of comparative value is made based on the performance of the technology in question across all of these measures, in consultation with the ICER Evidence Review Group. An example of the summary table from the CVET can be found below.

ICER Comparative Value Evidence Table	e (CVET)		
Measure	Technology A	Technology B	Difference (B-A)
1. Service Impact			
Tests	27.4	17.9	(9.5)
Visits	31.6	24.8	(6.8)
Hospitalizations	0.0	1.0	1.0
Hospital days	0.0	3.0	3.0
Days of missed work	4.7	5.9	1.2
Pathway Total	63.7	52.6	(11.1)
2. Cost-Consequences			
\$ to Prevent 1 Case of X		\$210,000	
\$ per Cure		\$350,000	
3. Cost per Life-Year Saved		N/A	(equivalent survival)
4. Cost per QALY Gained		\$1,050,000	
% of Cost/QALY <\$100,000		2.63%	
SA 1: Surg Compl. 50% of Basecase		\$547,000	
SA 2: ED 50% of Basecase		\$442,000	
5. Budget Impact (per 1,000, 2 years)		\$1,425,000	
6. Fixed Budget Tradeoffs		19.0	Nurse FTEs @ \$75K each
5		11.4	MD FTEs @ \$125K each

Details on the methodology underpinning the design and presentation of cost-effectiveness analyses within ICER appraisals are available on the ICER website at <u>www.icer-review.org</u>.

Integrated Ratings

The ICER Integrated Evidence Rating[™] combines the individual ratings given for comparative clinical effectiveness and comparative value. The overall purpose of the integrated ratings is to highlight the separate considerations that go into each element but to combine them for the purposes of conveying that clinical benefits provided by technologies come at varying relative values based on their cost and their impact on the outcomes of care and the health care system.

	Superior: A	Aa	Ab	Ac
eness	Incremental: B⁺/B	B⁺ a Ba	B ⁺ b Bb	B⁺c Bc
I Effectiv	Comparable: C*/C	C⁺ a Ca	C ⁺ b Cb	C⁺ c Cc
e Clinica	Inferior. D	Da	Db	Dc
Comparative Clinical Effectiveness	Promisingbut Inconclusive: P/I	Ра	Pb	Pc
	Insufficient I	1	1	I
	L	a High	b Reasonable/Comp	c Low

ICER Integrated Evidence Rating ™ Comparator X vs. Reference Technology Y

Comparative Value

APPRAISAL REPORT

Final Scope

Coronary artery disease (CAD) is among the most common chronic conditions in the U.S., affecting over 16 million adults. This appraisal focuses on multiple non-invasive nuclear imaging tests used for diagnosis, prognosis, or monitoring in patients with suspected or known CAD. The final scope of this appraisal, described using the Populations, Interventions, Comparators, Outcomes, Timeframe, and Study Designs (PICOTS) format (Counsell, 1997), is described in detail in the sections that follow. Three general populations were specified as of interest for this evaluation:

- Patients with symptoms suggestive of myocardial ischemia who are at low, intermediate, or high risk of CAD;
- Patients without symptoms but considered at higher risk of CAD due to one or more risk factors (e.g., diabetes); and
- Patients with known CAD who are candidates for prognostic testing to guide treatment selection and/or conduct post-procedure or post-event monitoring

Tests of interest included single photon emission computed tomography (SPECT) and positron emission tomography (PET), as well as newly-emerging hybrid modalities (e.g., PET/CT). Comparator tests included the other widely-available tests employed to provide information on inducible myocardial ischemia, stress electrocardiogram (EKG) and stress echocardiogram (ECHO).

Objective and Methods:

The objective of this report is to appraise the comparative clinical effectiveness and comparative value of cardiac nuclear imaging tests. To support this appraisal we report the results of a systematic review of published randomized controlled trials, systematic reviews, and observational studies as well as the findings from a *de novo* decision analysis.

Key Questions:

1) How do SPECT, PET, and relevant hybrid imaging modalities compare to other noninvasive functional tests (e.g., stress-ECHO, ETT) in their ability to guide the management and improve the outcomes of:

A. Patients at low-to-intermediate risk of CAD who have symptoms suggestive of myocardial ischemia? (diagnosis)

B. Patients at high risk of CAD who have symptoms suggestive of myocardial ischemia? (diagnosis)

C. Asymptomatic patients at high risk of CAD due to existing comorbidities? (diagnosis)

D. Patients with known CAD who have changes in symptoms? (diagnosis)

- E. Patients with known CAD who have no changes in symptoms? (prognosis)
- 2) What are the risks associated with these tests, including contrast and radiotracer reactions, patient anxiety, and radiation exposure?
- 3) What is the impact on the comparative benefits and risks of these tests of differences in:
 - A. Patient age, sex, race or ethnicity, and comorbidities (e.g., obesity)
 - B. Clinical setting (e.g., emergency department vs. outpatient)
 - C. Selection of test by primary care versus specialty physician
 - D. Scan vendor, type of assessment (i.e., quantitative vs. qualitative), type of radioisotope, and type of stressor (e.g., adenosine, exercise)
- 4) What are the costs and the incremental cost-effectiveness of these testing options when used within patient populations that vary by underlying prevalence of CAD and other patient characteristics?

Risk Groups:

For the purposes of this evaluation, low, intermediate, and high CAD risk were defined based on the Diamond-Forrester model of pretest probability (Diamond, 1979), based on age, gender, and type of chest pain; these equate to probability ranges of <10%, 10-90%, and >90% respectively. These ranges should be considered in context, however, as they have been promulgated in large part to identify "intermediate-risk" patients for whom non-invasive testing is likely to be most valuable; whether the actual range in the physician's mind is 10-90% or 30-70% is not considered to be as important (Fihn, 2012). There are also other pretest probability and risk classification systems used in CAD; we abstracted the method used to define risk from each study where reported (see Section 7).

It is also the case that Diamond-Forrester and other pretest probability models tend to overestimate actual CAD prevalence, particularly in women, as chest pain symptoms are less accurate predictors of obstructive CAD in women than in men (Shaw, 2006). Our decision-analytic model relied on assumed levels of CAD prevalence to generate estimates of test accuracy; we therefore selected levels of CAD prevalence that would approximate populations with low, intermediate, and high pretest probability of disease (see Section 8).

1. Background

The Condition

Coronary artery disease (CAD) is among the most common chronic conditions in the U.S., affecting over 16 million adults (Roger, 2012). CAD is estimated to cause over 1 million acute coronary events and over 400,000 deaths in this country each year (Roger, 2012).

Due to its prevalence, and because several options (e.g., surgery, medication) exist to reduce CAD-related morbidity and mortality, accurate diagnosis and/or risk stratification of CAD is critical. Currently the definitive standard for diagnosis is invasive coronary angiography. There are risks associated with angiography, however, such as infection, artery trauma, and heart arrhythmias. For this reason non-invasive diagnostic methods have been explored to document the presence of CAD. In addition, because angiography primarily documents the anatomic presence of significant stenosis rather than identifying the "culprit" lesions likely to cause an adverse cardiovascular event (Stone, 2011) a growing number of non-invasive tests have been developed to identify CAD lesions significant enough to affect the flow of blood to the heart (i.e., myocardial perfusion) (Berman, 2006). These functional tests are typically performed under exercise- or pharmacologically-induced stress to determine whether blood flow deteriorates when the stressor is introduced.

The most common tests of cardiac function include the stress-electrocardiogram (EKG or ECG), or treadmill test (ETT), which measures cardiac activity via electrical signals, and the echocardiogram (ECHO), which uses ultrasound to measure abnormalities in heart wall motion using 2-dimensional imagery. ETT has fallen out of favor for use in patients at higher risk of CAD, however, as it has relatively low sensitivity in these patients (Bax, 2007), while stress-ECHO has been found to lack precision in detecting single-vessel versus multi-vessel disease and may produce suboptimal imagery in obese patients, those with chronic respiratory conditions, and patients with chest deformities or pre-existing myocardial damage (Kim, 2007).

To address some of these concerns, "nuclear imaging tests" have been developed to provide perfusion data in a broader spectrum of patients. The most longstanding of these is single photon emission computed tomography (SPECT), which uses a radioactive tracer and gamma camera to obtain 3-dimensional images of tracer uptake; areas of poor uptake are associated with abnormal levels of perfusion (Carlisle, 2008). Positron emission tomography (PET) scanners are also used with a radiotracer, and are felt by some to provide better image resolution in heavier patients and those with dense breast tissue (Rahmim, 2008). So-called "hybrid" modalities have also been introduced to visualize both perfusion abnormalities and anatomic lesions using CT or MRI imagery in addition to nuclear testing.

There are trends in the use of cardiac nuclear imaging tests that are currently points of controversy, however. For one, their use in the U.S. has grown substantially, from

approximately 7 million in 1999 to 11 million in 2005 (IMV Medical Information Division, 2011). Secondly, the appropriateness of testing has been called into question due to declining rates of abnormal test results. Data from a long-term evaluation of SPECT findings at a large academic medical center found that the prevalence of abnormal test results declined from 40.9% during the period 1991-1995 to only 8.7% in 2006-2009 (Rozanski, 2013). In addition to risk factor management and medication use, a change in the threshold for testing (i.e., greater referral of patients with milder intensity and/or duration of symptoms, or direct referral to angiography in patients with severe symptoms) was hypothesized by the authors as a possible explanation for this decline (Rozanski, 2013).

The combination of substantial growth in utilization of cardiac nuclear imaging and declining rates of "positive" test results raises questions about the populations and indications for which such testing is appropriate. All nuclear imaging and other non-invasive tests for CAD also differ in terms of their risks, cost, and availability. To investigate these issues, the Washington Health Care Authority has commissioned a comprehensive evaluation of the evidence on the comparative clinical effectiveness and comparative value of cardiac nuclear imaging tests.

Washington State Agency Experience: 2009-2012

Figure 1a. Cardiac Nuclear Imaging Procedures – PEBB** Paid Amounts, 2009-2012

Agency/Year	20091	2010	2011	2012	4 year Overall Total ²	Average Annual % Change	
PEBB** Average Annual Mbrs	210,501	213,487	212,596	212,684		0.3%	
Non-emergent care							
Patients	4,510	4,115	3,940	3,826	13,727	-5.6%	*
Encounters ²	4,866	4,405	4,194	4,145	17,610	-5.4%	*
Total Paid	\$3,569,485	\$2,483,458	\$2,502,694	\$2,277,985	\$10,833,622	-13.1%	*
Average Paid/Encounter ³	\$734	\$564	\$597	\$550	\$615		
Average Paid, Primary ⁴	\$1,232	\$991	\$1,083	\$1,036	\$1,304		
Avg Encounters/Patient (95% upper limit)	1.1 (1.8)	1.1 (1.7)	1.1 (1.7)	1.1 (1.9)	1.3 (2.7)		
Max Encounters / Patient	7	5	5	7	12		
Emergent care							
Patients (Emergent care)	130	94	99	140	462	6.1%	*
Encounters (Emergent care)	130	95	100	142	467	6.6%	*
Total Paid, (Emergent care)	\$139,953	\$75,200	\$62,828	\$91,430	\$369,411	-5.9%	*
Average Paid, (Emergent)	\$1,581	\$1,125	\$1,220	\$1,116	\$1,289		

See table notes on following page.

Figure 1b. Cardiac Nuclear Imaging Procedures – Medicaid Paid Amounts, 2009-2012

Agency/Year	2009 ¹	2010	2011	2012	4 year Overall Total ²	Average Annual % Change	
Medicaid FFS*** Population	463,966	474,676	473,356	477,727		1.0%	
Non-emergent care							
Patients	2,331	1,796	2,313	1,959	7,841	-3.9%	*
Encounters ²	2,483	1,908	2,450	2,073	8,914	-4.1%	*
Total Paid	\$811,951	\$746,114	\$933,608	\$639,626	\$3,131,299	-5.6%	*
Average Paid/Encounter ³	\$327	\$391	\$381	\$309	\$351		
Average Paid, Primary ⁴	\$332	\$441	\$543	\$494	\$438		
Average Encounters/Patient (95% upper limit)	1.1 (1.7)	1.1 (1.7)	1.1 (1.7)	1.1 (1.8)	1.1 (2.2)		
Max Encounters / Patient	5	6	6	6	11		
Emergent care							
Patients (Emergent care)	61	48	54	45	208	-9.2%	*
Encounters (Emergent care)	61	48	54	46	209	-8.6%	*
Total Paid, (Emergent care)	\$27,665	\$22,821	\$32,329	\$13,904	\$96,719	-11.6%	*
Average Paid, (Emergent)	\$454	\$475	\$599	\$302	\$463		

See table notes on following page.

Agency/Year	2 009 ¹	2010	2011	2012	4 year Overall Total²	Average Annual % Change	
L&I Annual Claims	125,611	122,712	121,043	121,660		-1.1%	
Non-emergent care							
Patients	145	118	98	82	429	-16.4%	*
Encounters	151	123	105	87	466	-15.9%	*
Total Paid	\$187,232	\$118,810	\$100,913	\$77,500	\$484,456	-24.2%	*
Average Paid/Encounter ³	\$1,240	\$966	\$961	\$891	\$1,040		
Average Encounters/Patient (95% upper limit)	1(1.4)	1(1.4)	1.1(1.6)	1.1(1.5)	1.1(1.7)		
Max Encounters / Patient	2	2	2	2	3		
Emergent care							
Patients (Emergent care)	6	4	3	1	14	-40.9%	*
Encounters (Emergent care)	6	4	3	1	14	-40.9%	*
Total Paid, Emergent	\$6,784	\$3,723	\$2,980	\$1,066	\$14,553	-42.4%	ĸ
Average Paid (Emergent)	\$1,131	\$931	\$993	\$1,066	\$1,039		

Figure 1c. Cardiac Nuclear Imaging Procedures - L&I Paid Amounts, 2009-2012

Figure 1 Notes:

*Average % Change adjusted for population.

**Public Employee Benefits

***Fee For Service

¹ Imaging code definitions changed significantly between 2009 and 2010 – higher charges in 2009 may be a billing artifact and are therefore not useful for cost projection

²Patients who receive treatment in multiple years are counted only once in the "4 Yr Overall" total.

³ Encounter amounts include directly related charges on the day of service, such as radiopharmaceuticals, pharmaceutical stressors and contrast materials. Procedures were excluded for diagnoses related to congenital heart and valvular defects (see code list at end of Agency Experience section for specific included and excluded diagnoses). Cardiac Imaging procedures included are SPECT, 2 Dimensional Planar Imaging (2D PI), Myocardial PET, Cardiac MRI, and CT Heart. The PET, CT and MRI usage data is included due to combination imaging described in the topic intervention scope and constitute a minor proportion of the total (3.7% of PEBB encounters, 1.4% of Medicaid encounters, and <1% of L&I encounters).

⁴ Primary average excludes imaging payments where the agency is secondary to another payer – therefore it is more representative for cost projection.

Number of Images	Number of Patients (n=13727)	Average Days Between Imaging Procedures
2	2200	492.8
3	604	373.2
4	180	306.4
5	41	236.6
6	16	217.4
7	6	170.8
8	1	100.3

Figure 1d. Repeated procedures: PEBB 2009-2012

Figure 1e. Repeated procedures: Medicaid 2009-2012

Number of Images	Number of Patients (n=7841)	Average Days Between Imaging Procedures
2	562	328.0
3	77	273.6
4	24	172.6
5	11	123.9
6	5	110.1
7	2	67.4
8	6	137.8
11	1	64.9

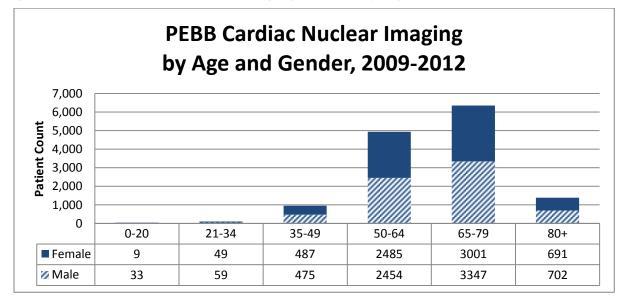
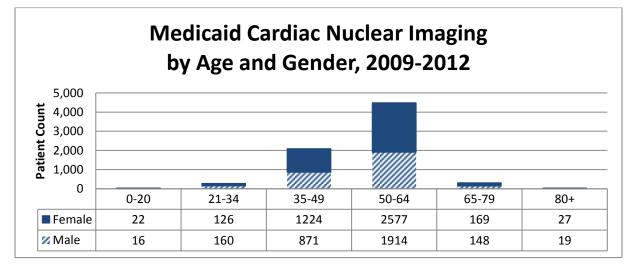
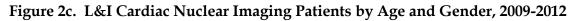
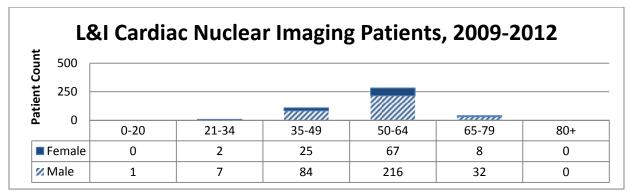


Figure 2a. PEBB Cardiac Nuclear Imaging Patients by Age and Gender, 2009-2012

Figure 2b. Medicaid Cardiac Nuclear Imaging Patients by Age and Gender, 2009-2012







Per Procedure Avg Allowed Charges, PEBB Primary Payer only	PEBB SPECT (n=7609)	PEBB 2D PI (n=412)	PEBB Cardiac MRI (n=153)	PEBB CT Heart (n=121)	PEBB Myocardial PET (n=19)	
Breakdown 1						
Professional Services	\$558	\$96	\$264	\$33	\$152	
Facility/Other	\$800	\$443	\$1,072	\$137	\$2,983	
Breakdown 2	Breakdown 2					
Procedure	\$927	\$463	\$1,336	\$170	\$3,135	
Stress Test	\$277	\$7	\$0	\$0	\$0	
Radiopharmaceuticals	\$153	\$60	\$0	\$0	\$0	
Avg Allowed/Procedure	\$1,358	\$539	\$1,336	\$170	\$3,135	

Figure 3a. PEBB Cardiac Nuclear Imaging Average Allowed Amounts, 2009-2012

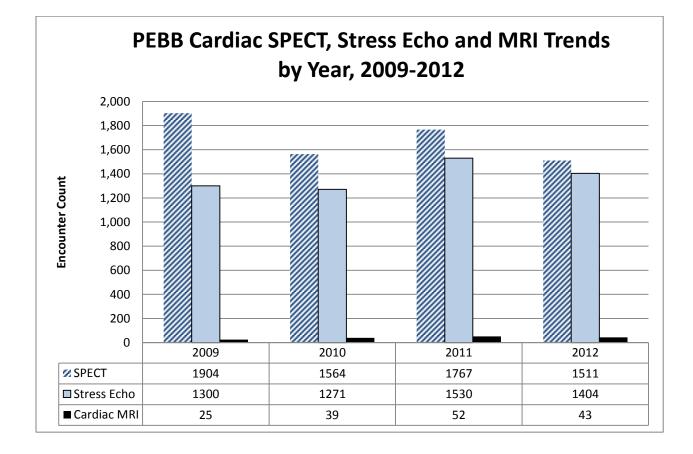
Figure 3b. Medicaid Cardiac Nuclear Imaging Average Allowed Amounts, 2009-2012

Per Procedure Avg Allowed Charges, Medicaid Primary Payer only	Medicaid SPECT (n=6482)	Medicaid 2D PI (n=687)	Medicaid Cardiac MRI (n=87)	Medicaid CT Heart (n=9)	Medicaid Myocardial PET (n=6)
Breakdown 1					
Professional Services	\$115	\$48	\$59	\$28	\$214
Facility/Other	\$362	\$163	\$328	\$0	\$1004
Breakdown 2					
Procedure	\$351	\$204	\$387	\$28	\$1,218
Stress Test	\$104	\$0	\$0	\$0	\$0
Radiopharmaceuticals	\$22	\$7	\$0	\$0	\$0
Avg Allowed/Procedure	\$477	\$211	\$387	\$28	\$1,218

Figure 3b. L&I Cardiac Nuclear Imaging Average Amounts, 2009-2012

L&I Per Procedure Avg Charges	L&I SPECT (n=456)	L&I 2D PI (n=6)
Breakdown 1		
Professional Services	\$624	\$173
Facility/Other	\$431	\$147
Breakdown 2		
Procedure	\$698	\$302
Stress Test	\$168	\$0
Radiopharmaceuticals	\$189	\$18
Avg Allowed/Procedure	\$1,055	\$320

Note: L&I use of other imaging procedures was very low: 2 procedures each for CT Heart and Cardiac MRI.





Related Medical Codes

Туре	Code	Description	Category
CD9 Dx	Couc	Description	category
	393	Chronic rheumatic pericarditis	Exclude
	394	Rheumatic diseases of mitral valve	Exclude
	395	Rheumatic diseases of aortic valve	Exclude
	396	Rheumatic diseases of mitral and aortic valves	Exclude
	397	Rheumatic diseases of other endocardial structures	Exclude
	398	Other rheumatic heart disease	Exclude
	402.0-	Hypertensive heart disease	Include
	402.9		
	411.0	Postmyocardial infarction syndrome	Include
	411.1	Intermediate coronary syndrome (impending infarction, preinfarction angina,	Include
		preinfarction syndrome, unstable angina	
	411.8	Other coronary symptoms	Include
	411.81	Acute coronary occlusion without myocardial infarction	Include
	411.89	Other - coronary insufficiency (acute) and subendocardial ischemia	Include
	413.0	Angina decubitus (nocturnal angina)	Include
	413.1	Prinzmetal angina (variant angina pectoris)	Include
	413.9	Other and unspecified angina pectoris (NOS, cardiac, equivalent, of effort,	include
		angina syndrome, status anginosus, stenocardia, syncope anginosa)	
	428.0	Congestive heart failure, unspecified	Include
	428.1	Left heart failure	Include
	428.2	Systolic hear failure, unspecified	Include
	428.21	Acute	Include
	428.22	Chronic	Include
	428.23	Acute on chronic	Include
	428.3	Diastolic heart failure, unspecified	Include
	428.31	Diastolic heart failure, acute	Include
	428.32	Diastolic heart failure, chronic	Include
	428.33	Acute on chronic	Include
	428.4	Combined systolic and diastolic heart failure, unspecified	Include
	428.41	Acute	Include
	428.42	Chronic	Include
	428.43	Acute on chronic	Include
	428.9	Heart failure, unspecified (cardiac failure, NOS, heart failure NOS, myocardial	Include
		failure NOS, weak heart	
	429.0	Myocarditis, unspecified	Exclude
	429.1	Myocardial degeneration	Exclude
	429.2	Cardiovascular disease, unspecified	Include
	429.3	Cardiomegaly	Include
	429.4	Functional disturbances following cardiac surgery	Include
		Cardiac insufficiency following cardiac surgery or due to prosthesis	
		Heart failure following cardiac surgery or due to prosthesis	
	420 5	Postcardiotomy syndrome, Postvalvulotomy syndrome	Evely 1
	429.5	Rupture of chordae tendineae	Exclude
	429.6	Rupture of papillary muscle	Exclude

Tuno	Code	Description	Catagory
Туре	Code	Excludes: congenital defects of heart, coronary aneurysm , disorders of	Category
		papillary muscle, postmyocardial infarction syndrome , rupture of chordae	
		tendineae	
	429.71		Evoludo
	-	Acquired cardiac septal defect	Exclude
	429.79	Other	Include
	420.0	Mural thrombus (atrial) (ventricular) acquired, following myocardial infarction	Fueluele
	429.8	Other ill-defined heart diseases	Exclude
	429.81	Other disorders of papillary muscle	Exclude
		Papillary muscle:	
	420.02	atrophydegenerationdysfunctionincompetenceincoordinationscarring	
	429.82	Hyperkinetic heart disease	Exclude
	429.83	Takotsubo syndrome, Broken heart syndrome, Reversible left ventricular	Include
		dysfunction following sudden emotional stress, Stress induced	
		cardiomyopathy	
		Transient left ventricular apical ballooning syndrome	
	429.9	Heart disease, unspecified (heart disease organic NOS, morbus cordis NOS	Include
	786.50	Chest pain, unspecified	Include
	997.1	Cardiac failure in the immediate post-operational period	Exclude
СРТ	75557	Cardiac magnetic resonance imaging for morphology and function without	MRI
		contrast material;	
	75559	with stress imaging	MRI
	75561	Cardiac magnetic resonance imaging for morphology and function without	MRI
		contrast material(s), followed by contrast material(s) and further sequences;	
	75563	with stress imaging	MRI
	75565	Cardiac magnetic resonance imaging for velocity flow mapping (List separately	MRI
		in addition to code for primary procedure)	
	75571	CT Heart (added 2010)	СТ
	75572	CT Heart imaging (function) (added 2010)	СТ
	75573	CT Heart imaging and function (added 2010)	СТ
	78451	Myocardial perfusion imaging, tomographic (SPECT) (including attenuation	SPECT
		correction, qualitative or quantitative wall motion, ejection fraction by first	
		pass or gated technique, additional quantification, when performed); single	
		study, at rest or stress (exercise or pharmacologic)	
	78452	Myocardial perfusion imaging, tomographic (SPECT) (including attenuation	SPECT
		correction, qualitative or quantitative wall motion, ejection fraction by first	
		pass or gated technique, additional quantification, when performed); multiple	
		studies, at rest and/or stress (exercise or pharmacologic) and/or redistribution	
		and/or rest reinjection	
	78453	Myocardial perfusion imaging, planar (including qualitative or quantitative	2D CNI
		wall motion, ejection fraction by first pass or gated technique, additional	
		quantification, when performed); single study, at rest or stress (exercise or	
		pharmacologic)	
	78454	Myocardial perfusion imaging, planar (including qualitative or quantitative	2D CNI
	, 5 , 5 4	wall motion, ejection fraction by first pass or gated technique, additional	
		The model of the second of the second s	1
		quantification, when performed); multiple studies, at rest and/or stress	
°PT	78459	quantification, when performed); multiple studies, at rest and/or stress (exercise or pharmacologic) and/or redistribution and/or rest reinjection	PFT
СРТ	78459	quantification, when performed); multiple studies, at rest and/or stress	PET

Туре	Code	Description	Category
		stress (exercise and/or pharmacologic), wall motion study plus ejection	
		fraction, with or without additional quantitative processing	
	78473	multiple studies, wall motion study plus ejection fraction, at rest and stress	2D CNI
		(exercise and/or pharmacologic), with or without additional quantification	
	78481/3	Cardiac blood pool imaging (planar), first pass technique; single study, at rest	2D CNI
		or with stress (exercise and/or pharmacologic), wall motion study plus	
		ejection fraction, with or without quantification (single/multiple)	
СРТ	78491	Myocardial imaging, positron emission tomography (PET), perfusion; single	PET
		study at rest or stress	
СРТ	78492	multiple studies at rest and/or stress	PET
	78499	Unlisted cardiovascular procedure, diagnostic nuclear medicine	Unknown
СРТ	93015	Cardiovascular stress test using maximal or submaximal treadmill or bicycle	Stress test
		exercise, continuous electrocardiographic monitoring, and/or	reported with
		pharmacological stress; with supervision, interpretation and report	CNI or other
	93016	supervision only, without interpretation and report	u
	93017	tracing only, without interpretation and report	u
	93018	interpretation and report only	"
	93350	Echocardiography, transthoracic, real-time with image documentation (2D),	Comparator
		includes M-mode recording, when performed, during rest and cardiovascular	Stress ECHO
		stress test using treadmill, bicycle exercise and/or pharmacologically induced	
		stress, with interpretation and report	
	93351	including performance of continuous electrocardiographic monitoring, with	Comparator
	55551	supervision by a physician or other qualified health care professional	Stress ECHO
	93000/	Electrocardiogram, routine ECG with at least 12 leads; with interpretation and	Comparator
	05/10	report (comparator with stress test only – 93015/16/17/18)	ECG
	93454/5/	Angiography 2011 forward	Comparator
	6		Comparator
HCPCS	A9500	Radiopharmaceuticals	Contrast
IICF CJ	A9502	hadiopharmaceuticais	Contrast
	A9502 A9505		
	A9505 A9526		
	A9555		
	A9560		
	J0150/2	Injection, adenosine for diagnostic use, 6 or 30 mg (not to be used to report	Pharma
	J1245	any adenosine phosphate compounds and other pharmaceutical stressors)	stressors
	J1250	Dipyridamle	
	J0280	Dobutamine	
	J0461	Aminophylline (halt Rx stress)	
	J2785	Atropine	
	Ļ	Regadenoson	
Super-		Cross walk for 2009	Pre-2010 CNI
ceded	78451	78464/78478/78480	Pre-2010 CNI
СРТ	78452	78465/78478/78480	Pre-2010 CNI
	78453	78460	Pre-2010 CNI
	78454	78461	Pre-2010 CNI
	78460-5	Superceded by 78451-78454 in 2010, needed for 2009 data	CNI Pre-2010
	78460	Myocardial perfusion imaging; (planar) single study, at rest or stress (exercise	CNI Pre-2010
	/0.00	and/or pharmacologic), with or without quantification	0

Туре	Code	Description	Category
	78461	Myocardial perfusion imaging; multiple studies (planar), at rest and/or stress (exercise and/or pharmacologic), and redistribution and/or rest injection, with or without quantification	CNI Pre-2010
	78464	Myocardial perfusion imaging, tomographic (SPECT) (including	CNI Pre-2010
	78465	Myocardial perfusion imaging, tomographic (SPECT), multiple studies (including attenuation correction when performed), at rest and/or stress (exercise and/or pharmacologic) and redistribution and/or rest injection, with or without quantification	CNI Pre-2010
	78478	Myocardial perfusion study with wall motion, qualitative or quantitative study	CNI Pre-2010
	78480	Myocardial perfusion study with ejection fraction.	CNI Pre-2010
	75552-6	Deleted heart MRI codes for 2008, not needed	Deleted 2008
	0144T	Cardiac CT (through 2009)	CT Pre-2010
	0151T	Cardiac CT (through 2009)	CT Pre-2010
	93501 93508 93539/ 40/45/46	Angiography prior to 2010	Comparator Pre-2010

2. The Alternative Diagnostic Strategies

Multiple testing modalities are available for the diagnosis and/or risk stratification of patients with suspected or known CAD. The most common options, all of which are performed with concurrent electrocardiography (EKG), include exercise stress testing utilizing a treadmill (ETT) or a bicycle, visualization of wall motion and other aspects of cardiac function using echocardiography (ECHO), and myocardial perfusion imaging with single-photon emission computed tomography (SPECT). Both ECHO and SPECT can be performed under either exercise or pharmacologic stress (see "Pharmacologic Stressors" on page 55).

Newer diagnostic options include positron emission tomography (PET) or hybrid imaging combining SPECT or PET with coronary computed tomography angiography (CCTA). Although not a focus of this appraisal, the use of CCTA alone for CAD diagnosis or prognosis is also discussed in the sections that follow, as is the use of emerging technologies such as CT perfusion and cardiac magnetic resonance imaging (CMR).

Nuclear Perfusion Testing

SPECT and PET allow radiologists and cardiologists to evaluate myocardial perfusion and blood flow in 3-D imagery using radioactive tracers and specialized scanners. Studies may be conducted under stress and at rest, providing for baseline evaluation of cardiac perfusion with comparison to the heart's capabilities during increased activity. Unless stenoses are severe (e.g. >90% narrowing), perfusion defects may only be evident under exercise-induced or simulated stress (Sharples, 2007). However, stress-only studies may be conducted in low-to-intermediate risk patients as normal results would potentially eliminate the need for a rest study (Bourque, 2011). Cardiovascular stressors include pharmacologic agents, a treadmill or a bicycle (Banerjee, 2012). Following intravenous injection, the radiotracer will begin to degrade, releasing energy which is recorded by the scanner (Brigham and Women's Hospital, 2012). While SPECT and PET technologies have been available for more than 30 years, the use of PET perfusion testing has increased in the last 10 years as image resolution has improved (Bourque, 2011; Cerqueira, 2010; Bengel, 2009). Patients undergoing these tests fast overnight with avoidance of caffeine prior to the scan (Dilsizian, 2009). Following the imaging procedure, patients increase their fluid intake to flush the tracers from the body. While adverse events from the tracers are uncommon, patients may experience bleeding and pain at the injection site or an allergic reaction to the radioactive tracer (Mayo Foundation, 2011). All nuclear imaging tests (as well as invasive angiography) also expose the patient to radiation. Features of the individual tests are described in further detail below.

SPECT

The two most common radiotracers utilized in SPECT imaging are technetium-99m-based agents (sestamibi and tetrofosmin) and ²⁰¹Thallium. SPECT tests may be done under

exercise or pharmacologic stress (see below). While the actual imaging time occurs over 20 minutes, patients undergoing rest-stress protocols are typically present for 3-4 hours, with the stress imaging taking place approximately 1 hour following the rest study (Brigham and Women's Hospital, 2012). Two-day protocols may be followed as well, allowing for precise dosing of radioactivity (Sharples, 2007).

Important technical considerations with the use of SPECT include EKG gating, which allows for measurement of radiotracer uptake during specific phases of heart rhythm to reduce heart motion artifacts and limit radiation dose, as well as processing protocols for image and data reconstruction. Attenuation correction is often employed to reduce artifacts from absorption of radiotracers into body tissues such as the diaphragm or scatter loss of critical activity outside the detector field of view (Dilsizian, 2009). This may be done via additional CT scanning or through an adaptation of the gamma camera used for SPECT itself.

PET

Radiotracers used in PET imaging for evaluation of myocardial blood flow include ⁸²Rubidium and ¹³N-ammonia, both of which are readily available (Beanlands, 2010). Because these tracers have very short half-lives, pharmacologic rather than exercise stress is utilized with PET; as with SPECT, rest/stress studies are conducted in 1 or 2-day protocols (Beanlands, 2010). Scans may take approximately 30 – 60 minutes (Brigham and Women's Hospital, 2012).

As with SPECT, important technical considerations for PET images include the use of EKG gating and various corrections taken to assist with image reconstruction.

Hybrid Imaging

The use of SPECT/PET along with CCTA technology provides physicians with both myocardial perfusion data and anatomical information, assessed in the span of a single visit by the patient (Flotats, 2011). The combined imaging procedure may take up to 45 minutes (Delbeke, 2006). Imaging is often done sequentially, with the scan order dependant on the pretest likelihood of CAD (George, 2012). The resulting images are then "fused" to provide a single report to the clinician. Image fusion is a technically demanding process, however, and thus far hybrid imaging is in use only at selected research centers (Bourque, 2011).

Pharmacologic Stressors

Medications intended to simulate cardiovascular stress are utilized in nuclear perfusion imaging and in patients incapable of participating in an exercise test or with functional instability (Akinpelu, 2011). Available agents include adenosine, dipyridamole, dobutamine, and regadenoson. Adenosine, regadenoson and dipyridamole are cardiac vasodilators, leading to increased myocardial blood flow with modest increases in heart rate and decreases in blood pressure (Henzlova, 2009). In contrast to more common agents such as adenosine or dipyridamole, which are given as continuous infusions, regadenoson is administered as a single injection, allowing for more efficient completion of the test (Akinpelu, 2011). Side-effect rates are similar across these agents; however, as a newer agent, regadenoson is more costly (~\$270 per infusion vs. \$5-\$45 for other agents) (RedBook, 2013).

Prior to testing, caffeine intake is restricted, and cardiac medications such as beta-blockers and nitrates may be withheld to avoid any interference with testing (Akinpelu, 2011). Following the induced stress test, patients are monitored up to 1 hour for adverse events such as dizziness and abnormal heart rhythms (Akinpelu, 2011). Other side effects may include headache, flushing and chest pain (Henzlova, 2009).

Dobutamine is a second-line agent, commonly used in patients who cannot tolerate vasodilators. It works to stimulate the heart rate, blood pressure as well as the contractility of the heart muscle (Henzlova, 2009). Given as a continuous infusion, side effects may include chest pain, palpitations, and shortness of breath (Henzlova, 2009).

Exercise Treadmill Testing (ETT)

Also known as a stress test, the ETT provides information to a cardiologist about cardiac electrical activity during physical exertion (Mayo Foundation, 2011). Cardiovascular stress is induced by patients walking on a treadmill or using a stationary bicycle (Banerjee, 2012). Patients are monitored for changes in blood pressure, heart rhythm and the emergence of symptoms such as severe chest pain, dyspnea, dizziness or fatigue (Banerjee, 2012; Mayo Foundation, 2011). Patients begin exercise with incremental changes in speed and incline every 3 minutes according to the commonly-employed "Bruce protocol" while continuously monitored with a 12-lead EKG (Banerjee, 2012). As patients advance through 7 levels of exercise, the goal is to reach 85% of their age-adjusted maximum heart rate (Banerjee, 2012). The ETT lasts approximately 15 minutes or until a patient becomes uncomfortable during testing (Mayo Foundation, 2011). Potential adverse events include low blood pressure, abnormal heart rhythms and rarely, MI (Mayo Foundation, 2011). Contraindications to an ETT include uncontrolled heart failure, severe aortic stenosis and acute myocarditis (Banerjee, 2012). Bicycle testing may be performed in frail or elderly patients with postural instability (Banerjee, 2012).

Stress Echocardiography

An echocardiogram (ECHO) may also be performed for patients undergoing a stress test, at baseline, during peak activity, and/or immediately following exertion (Banerjee, 2012). Utilizing sound waves, ECHO analyzes wall motion in the heart and the left ventricular ejection fraction, providing a dynamic evaluation of cardiac function (Banerjee, 2012; Mayo Foundation, 2011). As with an ETT, patients will exercise on a treadmill or a bicycle,

or may receive a pharmacologic stressor agent, predominantly dobutamine (Schiller, 2013). Physical exercise is preferred over pharmacologic stress as achievement of adequate myocardial exertion limits the recording of false-negative studies (Schiller, 2013). Patients will lie on an examination table for the initial baseline echocardiogram, and then begin exercising as described above for the ETT (Cleveland Clinic, 2011). Once peak exercise is achieved or the patient is incapable of exercising further, another echocardiogram is undertaken (Schiller, 2013). While the exercise time is approximately 15 minutes, the entire testing procedure may take up to 1 hour (Schiller, 2013; Cleveland Clinic, 2011). Adverse events including arrhythmias, chest pain and fatigue are similar to those described for ETT (Mayo Foundation, 2011).

To improve the sensitivity of the ECHO, image contrast may be provided by "microbubble" agents such as perflutren (Weissman(b), 2012). These agents assist by delineating anatomical borders more clearly and enhancing transmission of the sound waves. The FDA issued a "black box warning" for these agents in 2007 based on reports of serious complications including cardiopulmonary reactions and death within 12 hours of injection (FDAnews, 2007). The warning included a ban on perflutren use in acutely ill patients and a 30-minute monitoring requirement for all patients. However, after findings from a meta-analysis of ECHO contrast agents in over 200,000 patients showed no statistical differences in the rate of adverse cardiopulmonary events and death between patients who did and did not receive contrast (Khawaja, 2010), the FDA revised the warning to remove monitoring requirements and preclude use only in patients with certain cardiac shunts and those with known hypersensitivity to perflutren (FDA, 2012).

Coronary Computed Tomography Angiography (CCTA)

CCTA is a technique in which a CT scanner is used to acquire multiple simultaneous tomographic sections ("slices") of the coronary arteries. At the time of this outpatient procedure, an IV is placed into a peripheral vein and a contrast dye is administered for the purposes of visually defining the arteries for the scan. Beta blockers may be given to the patient to slow the heart rate in order to prevent artifacts of heart motion that may affect image quality. The patient is positioned on the CT scanner and a large number of x-ray images are taken from multiple angles and reconstructed using computer software. Multi-detector row CT scanners contain rotating gantries that capture multiple images, or "slices".

Emerging Technologies

CT Perfusion

Combined in a single modality, CT perfusion provides functional and anatomical imaging (Becker, 2013). The procedure involves the use of rest CCTA followed by stress imaging to obtain perfusion data. Stressor agents employed have included adenosine and

regadenoson (Becker, 2013). As with other forms of hybrid imaging, however, CT perfusion is a technically demanding procedure, and is currently performed by only a few research centers (Becker, 2013).

Cardiac Magnetic Resonance Imaging (CMR)

Utilizing magnetic fields and radiofrequency, CMR provides cardiovascular images in 3D (Fuisz, 2013). Techniques commonly used include EKG-gating for improved image quality and late gadolinium enhancement to evaluate areas of fibrosis and damaged tissue. Patients must hold their breath during image acquisition. The procedure may be quite lengthy (at least 30 minutes); contraindications include metal implants in the body (Gerber, 2013). CMR has been described as a potential option for cardiac evaluation in women, as other forms of noninvasive testing may produce suboptimal imagery due to breast tissue interference (Coelho-Filho, 2013).

3. Clinical Guidelines & Accreditation Standards

Major guideline statements as well as competency and/or accreditation standards regarding cardiac nuclear imaging can be found in the sections that follow below. Statements from the "Choosing Wisely" campaign are also provided where relevant. Documents are organized by patient population where feasible.

Asymptomatic, High Risk

<u>ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM Cardiac Radionuclide Imaging Appropriate</u> <u>Use Criteria (2009)</u> <u>http://content.onlinejacc.org/article.aspx?articleid=1139755</u>

• Cardiac radionuclide imaging is considered appropriate for use in detection of CAD or risk assessment in asymptomatic patients at high risk (based on ATP III criteria).

Symptomatic Low-Intermediate Risk

<u>ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of</u> <u>Patients with Stable Ischemic Heart Disease (2012)</u> <u>http://circ.ahajournals.org/content/126/25/e354.full.pdf+html</u>

- Exercise stress nuclear perfusion imaging is not indicated as an initial test in low risk patients who have an interpretable EKG.
- Exercise stress nuclear perfusion imaging is recommended for diagnosis of patients with intermediate pre-test probability of ischemic heart disease, uninterpretable

EKG, moderate physical functioning or no disabling co-morbidity. It is reasonable in patients with interpretable EKG.

• Pharmacologic stress nuclear perfusion imaging is not recommended for diagnosis and risk stratification in patients with interpretable EKG, at least moderate physical functioning, or no disabling co-morbidity.

<u>NICE Guidelines for Chest Pain of Recent Onset-2010</u> <u>http://www.nice.org.uk/nicemedia/live/12947/47931/47931.pdf</u>

• When the estimated likelihood of CAD is 30-60 % and stable angina cannot be diagnosed, non-invasive functional tests such as SPECT are recommended.

<u>ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM Cardiac Radionuclide Imaging Appropriate</u> <u>Use Criteria (2009)</u> <u>http://content.onlinejacc.org/article.aspx?articleid=1139755</u>

- Cardiac radionuclide imaging is inappropriate in patients with a low pretest probability of CAD, an interpretable EKG, and the ability to exercise.
- Cardiac radionuclide imaging is considered appropriate for all other combinations of pretest probability, EKG interpretability, and ability to exercise.

<u>Guidelines on the Management of Stable Angina Pectoris: The Task Force on the Management of</u> <u>Stable Angina Pectoris of The European Society Of Cardiology (2006)</u> <u>http://www.escardio.org/guidelines-surveys/esc-guidelines/guidelinesdocuments/guidelines-angina-ft.pdf</u>

• There is reasonable evidence suggesting stress SPECT can be used as an alternative to exercise EKG in patients with low probability of CAD, such as women with atypical chest pain.

Symptomatic, High-Risk

<u>ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of</u> <u>Patients with Stable Ischemic Heart Disease (2012)</u> <u>http://circ.ahajournals.org/content/126/25/e354.full.pdf+html</u>

• Exercise stress nuclear perfusion imaging is recommended for diagnosis of patients with an intermediate-to-high pre-test probability of ischemic heart disease, uninterpretable EKG, at least moderate physical functioning, or no disabling comorbidity. Nuclear perfusion imaging is also considered a reasonable option in patients meeting the above criteria who have an interpretable EKG.

• Pharmacological stress nuclear perfusion imaging is recommended in patients with an intermediate-to-high pre-test probability of ischemic heart disease and are incapable of at least moderate physical functioning, or have a disabling comorbidity.

<u>ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM Cardiac Radionuclide Imaging Appropriate</u> <u>Use Criteria (2009)</u> <u>http://content.onlinejacc.org/article.aspx?articleid=1139755</u>

• Cardiac radionuclide imaging is considered appropriate in patients with an intermediate or high pretest probability of CAD, regardless of whether EKG is interpretable or the patient is able to exercise.

Guidelines on the Management of Stable Angina Pectoris: The Task Force on the Management of Stable Angina Pectoris of The European Society Of Cardiology (2006) http://www.escardio.org/guidelines-surveys/esc-guidelines/guidelinesdocuments/guidelines-anginaft.pdf

- SPECT is recommended for diagnostic assessment in patients with inconclusive EKG, whose diagnosis is still not determined.
- SPECT is recommended for risk stratification in patients with intermediate to high probability of CAD.

Known CAD

<u>ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of</u> <u>Patients with Stable Ischemic Heart Disease (2012)</u> <u>http://circ.ahajournals.org/content/126/25/e354.full.pdf+html</u>

• Stress nuclear perfusion imaging is recommended for risk assessment in patients who are candidates for revascularization of known coronary stenosis of unclear physiological significance.

<u>ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM Cardiac Radionuclide Imaging Appropriate</u> <u>Use Criteria (2009)</u> <u>http://content.onlinejacc.org/article.aspx?articleid=1139755</u>

- Cardiac radionuclide imaging is inappropriate or of uncertain appropriateness in any individual with known CAD who is asymptomatic or has stable symptoms and has not had a prior revascularization procedure.
- In patients with new or worsening symptoms, cardiac radionuclide imaging is considered appropriate in patients with an abnormal angiography or prior stress imaging study.

- Cardiac radionuclide imaging is appropriate within 3 months of an acute coronary syndrome in patients who are hemodynamically stable, have no recurrent chest pain symptoms or signs of heart failure, and have not had prior angiography.
- Such imaging is considered inappropriate in patients who:
 - Have had prior percutaneous intervention with complete revascularization;
 - Are hemodynamically unstable, have signs of cardiogenic shock or mechanical complications;
 - Are candidates for evaluation post-PTCA or CABG prior to discharge; OR
 - Are entering cardiac rehabilitation (as a stand-alone indication).
- Cardiac radionuclide imaging is appropriate following PTCA or CABG in patients who have new symptoms, or in asymptomatic patients with evidence of incomplete revascularization or who are at least 5 years post-CABG.
- Cardiac radionuclide imaging is considered inappropriate or of uncertain appropriateness in patients who:
 - Are less than 5 years post-CABG;
 - Are post-PTCA, regardless of duration; OR
 - Are entering cardiac rehabilitation (as a stand-alone indication).

Guidelines on the Management of Stable Angina Pectoris: The Task Force on the Management of Stable Angina Pectoris of The European Society Of Cardiology (2006) http://www.escardio.org/guidelines-surveys/esc-guidelines/guidelinesdocuments/guidelines-anginaft.pdf

- It is reasonable to perform SPECT for localization of ischemia in patients with prior revascularization.
- There is evidence suggesting stress SPECT is reasonable for risk stratification in patients with deteriorating symptoms post-revascularization.

Choosing Wisely

American Society of Nuclear Cardiology

http://www.choosingwisely.org/doctor-patient-lists/american-society-of-nuclear-cardiology/

- "Don't perform stress cardiac imaging or coronary angiography in patients without cardiac symptoms unless high-risk markers are present."
- "Don't perform cardiac imaging for patients who are at low risk."
- "Don't perform radionuclide imaging as part of routine follow-up in asymptomatic patients."

• "Use methods to reduce radiation exposure in cardiac imaging, whenever possible, including not performing such tests when limited benefits are likely."

Society of Nuclear Medicine and Molecular Imaging

http://www.choosingwisely.org/doctor-patient-lists/society-of-nuclear-medicine-and-molecularimaging/

• "Don't perform routine annual stress testing after coronary artery revascularization."

American College of Cardiology

http://www.choosingwisely.org/doctor-patient-lists/american-college-of-cardiology/

- "Don't perform stress cardiac imaging or advanced non-invasive imaging in the initial evaluation of patients without cardiac symptoms unless high-risk markers are present. Stress cardiac imaging should only be conducted in patients who have diabetes and are >40 years, if patients have peripheral artery disease, or if yearly risk of cardiovascular events is >2%."
- "Don't perform annual stress cardiac imaging or advanced non-invasive imaging as part of routine follow-up in asymptomatic patients."

Accreditation Standards

Intersocietal Accreditation Commission for Nuclear/PET Accreditation http://www.intersocietal.org/nuclear/standards/IACNuclearPETStandards2012.pdf

Requirements for Medical Staff

The interpreting medical staff members should be board certified (or board eligible within two years of finishing training) in one of the following specialties:

- a) Nuclear Cardiology with a 4 month formal training in nuclear cardiology OR
- b) Nuclear medicine OR
- c) Cardiology with at least one year full time experience with independent interpretation of at least 800 nuclear cardiology studies
- d) Radiology with at least 4 months of nuclear cardiology training /1 year of nuclear cardiology practice with independent interpretation of at least 800 nuclear cardiology studies OR
- e) Any other medical specialty recognized by American Board of Medical Specialties, American Osteopathic Association, Royal College of Physicians and Surgeons of Canada or Le College des Medicins du Quebec with one year full time experience in

nuclear cardiology/nuclear medicine/PET practice with independent interpretation of at least 800 nuclear cardiology studies.

f) Continuing Medical Education (CME): All interpreting physicians must obtain at least 15 hours of AMA category 1 CME relevant to nuclear medicine, every 3 years.

Requirements for Nuclear Medicine Technologists

- a) All nuclear medicine technologists must have an appropriate credential in nuclear medicine technology and a current BLS (Basic life support certification).
- b) Continuing Education (CE): At least 15 hours of accredited CE relevant to nuclear medicine every 3 years.
- c) American College of Radiology: Nuclear Medicine/PET accreditation Program Requirements
- d) <u>http://www.acr.org/~/media/ACR/Documents/Accreditation/Nuclear%20M</u> <u>edicine%20PET/Requirements.pdf</u>

Requirements for Physicians interpreting or supervising nuclear medicine examinations:

- a) Nuclear medicine physicians should be board certified in radiology/diagnostic radiology/nuclear radiology/ nuclear medicine by American Board of Radiology/ American Board of Nuclear Medicine/ American Osteopathic Board of Radiology / American Osteopathic Board of Nuclear Medicine/ Royal College of Physicians and Surgeons of Canada/ Le College des Medicins du Quebec.
- b) Physicians trained prior to 1975 are accepted if they have interpreted an average of 50 scintigrams per month in last 10 years.
- c) Non-nuclear medicine physician or radiologist interpreting nuclear images should be board certified in cardiology by American Board of Internal Medicine/American Osteopathic Board of Internal Medicine/ Royal College of Physicians and Surgeons of Canada/ Le College des Medicins du Quebec. OR
- d) Complete a general nuclear medicine program (includes 200 hours in radiation physics, 500 hours preparation in instrumentation, radiochemistry, radiopharmacology, radiation dosimetry, radiation safety, protection and quality control)and 1000 hours training in general nuclear medicine approved by Accreditation Council of Graduate Medical Education.
- e) Continuing experience: Upon renewal, Read a minimum of 200 studies every 3 years OR meet Maintenance of Certification (MOC) in Radiology or Nuclear.
- f) Continuing Education: Upon renewal, meet MOC requirements by American Board of Radiology or American Board of Nuclear Medicine OR complete 150 hours in 36 prior months OR complete 15 hours CME in prior 36 months specific to imaging modality or organ system.

Requirements for Nuclear Medicine Technologists

- a) Qualification: American Registry of Radiologic Technologists or registered equivalent state license for nuclear medicine technology or complete a training program in nuclear medicine.
- b) Continuing Education: Registered Technologists must be compliant with the CE requirements of their certifying organization. State-licensed technologists must complete 24 hours of CE every 2 years.

4. Medicare and Representative Private Insurer Policies

Centers for Medicare and Medicaid Services (CMS)

SPECT National Coverage Determination Local Coverage Determination

In 2002, Medicare established a National Coverage Determination (NCD) for SPECT allowing for contractor discretion with respect to clinical indications and limitations of coverage. The only restriction placed was that SPECT may not follow an inconclusive PET scan for myocardial viability. The policy is currently under review. A Local Coverage Determination (LCD) focused on Washington State provides the following indications of coverage for SPECT perfusion imaging:

- Abnormal EKG, stress test or inability to complete a standard stress test; OR
- Patients who are symptomatic following cardiovascular reperfusion; OR
- Intermediate-risk patients undergoing high-risk surgery; OR
- Patients with known CAD with new or significant symptoms; OR
- Evaluation post-cardiac transplant

SPECT is considered medically *unnecessary* when no changes in medical management are anticipated, in absence of a changing clinical presentation, or in asymptomatic patients of low-intermediate risk with first-degree atrioventricular block. SPECT is also not covered for screening of coronary disease or as a routine follow-up test following revascularization without clinical indications.

PET National Coverage Determination

An original NCD provided coverage of PET imaging for perfusion assessment in patients with known or suspected CAD. An NCD specific to myocardial perfusion PET was made in 2005, providing coverage for testing meeting the following requirements:

- PET imaging is done with rubidium-82 or ammonia N-13 radiotracers; AND
 - Rest or rest/stress imaging is not conducted in addition to SPECT; OR
 - PET scan follows an inconclusive SPECT image

As with the NCD on SPECT, this policy is also under review. There are no available LCDs issued for the use of PET myocardial perfusion imaging.

Representative Private Insurer Policies

Aetna

SPECT http://www.aetna.com/cpb/medical/data/300_399/0376.html

Aetna provides coverage of SPECT for the diagnosis of CAD in patients with an uninterpretable EKG who are incapable of exercise. SPECT may also be used prior to revascularization procedures. Other situations where SPECT is a covered procedure include:

- At least 2 years following revascularization in asymptomatic patients
 - At least 2 years following negative nuclear imaging in asymptomatic, high-risk patients without known CAD
 - At least 1 year following a prior abnormal cardiac study in asymptomatic patients with known CAD, or with stable symptoms

SPECT is *not* covered for:

- Screening of asymptomatic, low-risk patients
 - Patients undergoing low-risk non-cardiac surgery, as well as those undergoing intermediate-risk non-cardiac surgery without contraindications to stress testing
 - Asymptomatic patients undergoing high-risk surgery with prior normal cardiac intervention or nuclear test within 1 year

• Patients with acute chest pain and with a high likelihood of an acute coronary event, or with hemodynamic instability

PET http://www.aetna.com/cpb/medical/data/1_99/0071.html

Aetna policy allows coverage of PET perfusion scans in patients with known or suspected CAD who are at risk for attenuation artifacts on SPECT (e.g. BMI>40, large breasts or implants, patients with pleural effusion), or in patients with inconclusive or uninterpretable SPECT imaging.

Hybrid Imaging

SPECT or PET combined with CT imaging is considered experimental and investigational.

CIGNA

SPECT

https://cignaforhcp.cigna.com/public/content/pdf/coveragePolicies/medical/mm_0169_ coveragepositioncriteria_nuclear_imaging.pdf

CIGNA covers SPECT in patients with known or suspected CAD and new or worsening symptoms as well as in those with a history of false positive ETT. SPECT is also covered for:

- Repeat imaging:
 - at least 2 years following identified silent ischemia during a stress test; OR
 - at least 2 years following percutaneous intervention and previous stress test or angiography; OR
 - at least 5 years following CABG
- Evaluation of inducible ischemia within 3 months of an acute coronary event
- Pre-operative evaluation in patients with fluctuating heart conditions such as angina, heart failure, valvular disease, or malignant arrhythmias
- Pre-operative evaluation in patients undergoing high- or intermediate-risk surgery with clinical risk factors or without ETT data

PET

https://cignaforhcp.cigna.com/public/content/pdf/coveragePolicies/medical/mm_0091_ coveragepositioncriteria_positron_emission_tomography.pdf

Cigna provides coverage of PET imaging for patients incapable of exercise stress testing or with equivocal results from a stress EKG who have at least one of the following indications: 1)BMI >35; 2) women with large breasts or implants; or 3) inconclusive SPECT findings.

Hybrid Imaging

SPECT or PET combined with CT imaging is considered investigational.

UniCare

http://www.unicare.com/shared/noapplication/f0/s0/t0/pw_a109814.pdf?refer=chpfoot er

SPECT

SPECT is covered for symptomatic patients with known CAD. SPECT is also covered in patients with abnormal findings on EKG, ETT, CCTA or cardiac catheterization, or with equivocal findings on stress ECHO within the previous 60 days. Symptomatic patients with suspected CAD, with or without concurrent conditions such as diabetes, and who do not have a cardiac evaluation in the prior 60 days may undergo a SPECT scan. Other settings where SPECT is covered include the following:

- Symptomatic patients with previous revascularization
- Patients with a myocardial infarction or unstable angina within 90 days
- Repeat imaging at least 5 years since CABG and 2 years without cardiac evaluation
- Repeat imaging at least 3 years since percutaneous intervention and subsequent cardiac evaluation
- Patients with known CAD who are asymptomatic or with stable symptoms, without cardiac evaluation within 3 years Asymptomatic patients with moderate-to-high risk of CAD without cardiac evaluation within 3 years Patients with known or suspected CAD, who are asymptomatic or symptomatic, with new onset arrhythmias or heart failure Prior to intermediate-to-high risk surgery without a normal cardiac evaluation in previous year, and an underlying condition (e.g., known CAD, diabetes).

PET

http://www.unicare.com/medicalpolicies/policies/mp_pw_a050587.htm

Coverage is provided for patients with inconclusive SPECT or stress ECHO images, in patients with risk of attenuation artifacts (e.g., BMI \geq 40, large breasts or implants, pericardial effusion), and in patients with the high likelihood of morbidity during angiography (e.g., allergy to contrast medium).

Hybrid Imaging

Imaging using SPECT or PET technology with CT is considered investigational. PET/MRI is also not covered as an experimental procedure.

5. Previous Systematic Reviews/Technology Assessments

Recent technology assessments focusing on the use of SPECT in the diagnosis and management of CAD were identified from international organizations as described below. No recent reviews focusing on PET perfusion imaging were identified.

Agency for Healthcare Research & Quality (AHRQ, 2012) http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-andreports/?pageaction=displayproduct&productID=1019

In an evidence review focused on the diagnostic performance of non-invasive tests in women, the diagnostic accuracy of SPECT was found to be better than ECHO, CMR, and ETT, but not better than CCTA in women without known CAD. Data were insufficient to evaluate the prognostic benefit of SPECT compared to angiography. Data were insufficient to provide a comparative analysis of SPECT, CCTA, ECHO, CMR and EKG with respect to clinical decision-making and associated patient outcomes.

National Institute for Health and Care Excellence (NICE, 2003)

http://publications.nice.org.uk/myocardial-perfusion-scintigraphy-for-the-diagnosis-and-management-of-angina-and-myocardial-ta73

While SPECT has overall increased sensitivity over ETT, uncertainty remains regarding its true sensitivity and specificity relative to all alternatives. Evidence suggests that SPECT provides independent and incremental data that may help risk-stratify patients and impact clinical management. Among comparative diagnostic pathways, SPECT-angiography is more cost-effective in patients with a lower likelihood of CAD, while in patients with a higher likelihood of CAD who are potential candidates for revascularization, direct angiography and ETT-angiography are more cost-effective.

Partial updates provided in 2 recently issued documents:

Chest Pain of Recent Onset (NICE, 2010)

http://guidance.nice.org.uk/CG95/Guidance/pdf/English;

In patients with intermediate pre-test likelihood of CAD (20-50%), SPECT is less costly than angiography. For patients with a likelihood of CAD of <20%, CCTA is more accurate and less costly than SPECT.

Management of Stable Angina (NICE, 2011)

<u>http://publications.nice.org.uk/management-of-stable-angina-cg126</u> SPECT provides incremental value in the prediction of cardiovascular outcomes including death, myocardial infarction and revascularization.

Health Quality Ontario (2010)

http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/ontariohealth-technology-assessment-series/single-photon-emission-computed-tomography-forthe-diagnosis-of-coronary-artery-disease

Compared with contrast echo or CCTA in patients with stable chest pain, SPECT was not a cost-effective intervention. At a higher willingness-to-pay threshold, with other technologies unavailable and with CAD prevalence >55%, SPECT becomes cost-effective. Technological considerations including attenuation correction and EKG-gating improve the specificity of SPECT imaging.

National Institute for Health Research (NIHR, 2004)

http://www.hta.ac.uk/project/1345.asp

Available evidence suggests that SPECT has superior sensitivity and similar specificity in comparison to ETT. Data from prognostic studies indicate that normal SPECT findings are associated with a benign prognosis and the option of medical rather than invasive management, and that a selective angiography referral strategy involving SPECT may identify lower-risk patients for whom angiography may be avoided.

At a low prevalence of CAD (~10%), the diagnostic pathway of SPECT-angiography is costeffective relative to ETT-SPECT-angiography and ETT-angiography. As prevalence increases above 50%, however, SPECT-angiography is associated with higher cost and reduced quality-adjusted survival relative to these strategies.

6. Ongoing Clinical Studies

Information on ongoing clinical studies that have been submitted to the U.S. National Institutes of Health's registry of publicly- and privately-supported studies (<u>www.clinicaltrials.gov</u>) is presented in the table below and on the following page.

Title/ Trial Sponsor	Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Effectiveness study of single photon emission computed tomography (SPECT) versus positron emission tomography (PET) myocardial perfusion imaging (Aspire Foundation) NCT00976053	RCT	SPECT PET	 n=330 30 - 90 years History of coronary artery disease New or worsening symptoms Outpatients and in- hospital patients 	Diagnostic failure at 60 days	June 2014
PROspective Multicenter Imaging Study for Evaluation of chest pain (PROMISE) (Duke University) NCT01174550	RCT	Functional stress test (including echo, nuclear and exercise EKG) CCTA	 n=10,000 ≥ 45 years New or worsening chest pain Planned non-invasive testing Patients with increased probability of CAD based on age and risk factors 	Time to MACE events (death, MI, major complications, unstable angina hospitalization)	August 2014
Randomized evaluation of patients with stable angina comparing diagnostic examinations (RESCUE) (ACRIN) NCT01262625	RCT	SPECT/ angiography CCTA	 n=4,300 ≥ 40 years Patients with or without known CAD with symptoms of stable angina (Class I to III) or angina equivalent 	MACE (MI, cardiac- related death, crossover to revascularization) up to 24 months	August 2014
ProspEctive First Evaluation in Chest Pain Trial (PERFECT) (St. Luke's-Roosevelt Hospital Center) NCT01604655	RCT	SPECT or ECHO	 n=500 ≥ 45 years Patients with chest pain or SOB admitted for rule out ACS EKG non-diagnostic for ACS At least 1 set of negative troponin I 	Change in medication regime Change in CAD risk profile Evaluated up to 24 months	September 2015

Title/ Trial Sponsor	Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Integrated Dual Exercise and Lexiscan Positron Emission Tomography (IDEALPET) (Brigham & Women's Hospital) NCT01109992	RCT	Lexiscan/PET Exercise + Lexiscan/PET	 n=50 18 - 90 years Clinically-indicated PET study Known CAD or intermediate-high pretest likelihood of CAD Able to exercise 	Safety and tolerability of combined exercise and Lexiscan stress within 1 hour of testing	July 2013
A study to assess regadenoson administration following an inadequate exercise stress test as compared to regadenoson alone for myocardial perfusion imaging using single photon emission computed tomography (EXERRT) (Astellas Pharma) NCT01618669	RCT	Exercise + regadeonoson/S PECT Regadenoson/S PECT	 n=1,130 ≥ 18 years Patients referred for exercise or pharmacologic stress SPECT test 	Median count of number of segments with reversible defects up to 15 days	May 2014
Stress ECHO ultrasound Contrast in an Urban safety net hospital to Refine ischemia Evaluation (SECURE) (Denver Health and Hospital Authority) NCT01572220	RCT	SPECT Stress echo	 n=200 ≥ 18 years Symptoms of chest discomfort or ischemic equivalent Clinical indication for stress imaging 	Rate of non- diagnostic tests between comparators within 5 days of testing	May 2014

Source: <u>www.clinicaltrials.gov</u>

CAD: coronary artery disease; CCTA: cardiac computed tomography angiography; CV: cardiovascular; EKG: electrocardiogram; MACE: major cardiac adverse events; N: number; PET: positron emission tomography; RCT: randomized controlled trial; SPECT: single photon emission computed tomography

7. The Evidence

Objectives

The primary objectives of the systematic review were to:

Evaluate and compare the published evidence on the impact of cardiac nuclear imaging tests on clinical decision-making, downstream testing and other resource utilization, and patient outcomes in multiple tested populations;

Evaluate and compare the risks of these tests, including exercise, pharmacologic stressor and radiotracer reactions, and radiation exposure;

Examine the differential effectiveness and safety of cardiac nuclear imaging tests according to patient subgroups of interest, including patient characteristics, clinical setting, ordering specialty, and testing protocol (e.g., quantitative vs. qualitative assessment, stressor/radiotracer employed); and

Assess the costs and cost-effectiveness of cardiac nuclear imaging tests in multiple patient populations relative to alternative approaches.

The target populations for this appraisal included patients for whom functionallysignificant CAD is suspected as an underlying cause of symptoms, those who are asymptomatic but nonetheless at higher risk of CAD (e.g., patients with diabetes), and patients with known CAD who receive nuclear imaging tests for prognostic purposes such as risk stratification, treatment selection, and/or follow-up monitoring. As described in further detail in Section 7.6, we focused attention on evidence for cardiac nuclear imaging tests and the common testing options to which they have been compared in randomized controlled trials (RCTs) or cohort studies; the latter design was accepted if multiple testing options were compared in separate groups of patients or performed in the same patient population. Case series of a single nuclear imaging test were not abstracted for effectiveness data but were accessed for information on potential risks, extracardiac findings, and appropriateness of testing.

Information on test accuracy (e.g., sensitivity/specificity, positive/negative predictive values) was not a primary focus of this evaluation, as the "reference standard" for CAD diagnosis has historically been anatomic evidence of significant artery stenosis (typically ≥70%) on invasive coronary angiography. The use of angiography as the gold standard for *functional* tests such as those under consideration here has been called into question, however, as the mere presence of stenosis has been found to correlate poorly with that of "functionally significant" lesions, especially at moderate levels (e.g., 50-70%) (Tonino, 2010). For example, a quantitative assessment of patients undergoing coronary computed tomographic angiography (CCTA) and PET perfusion imaging for known or suspected CAD found that only certain anatomic parameters on CCTA were statistically-significantly associated with reduced myocardial perfusion, and that the correlation even in these parameters was "clinically modest" (Naya, 2011). Multiple other studies have shown that

myocardial perfusion is affected primarily by the level of diffusion in the stenosis as well as the extent to which "arterial remodeling" (i.e., change in vessel size in reaction to stenosis) has occurred rather than the percentage of stenotic occlusion itself (Gould, 2009; Ward, 2000). This dissociation has been manifested in multiple studies of invasive treatment of CAD showing little impact of anatomically-guided percutaneous or bypass procedures on long-term prognosis (Boden, 2007; Henderson, 2003; Stone, 2011). In contrast, findings from a recent randomized controlled trial indicate that treatment guided by angiography that included measurement of the "fractional flow reserve" (FFR), a measure of myocardial ischemia, resulted in significantly fewer major cardiovascular events at 1 year than treatment guided by angiography without FFR measurement (13.2% vs. 18.3% respectively, p=0.02) (Tonino, 2009). Based on data such as these, the Blue Cross Blue Shield Technology Assessment Center (TEC) recently determined that FFR measurement meets all criteria for coverage in guiding decisions on revascularization (BCBS TEC, 2011).

Where available, however, we summarized any diagnostic accuracy data involving the use of an independent *functional* reference standard such as FFR. Because such data was expected to be limited for the tests of interest, historical accuracy data using anatomic reference standards was also summarized for background purposes and used as a means to estimate progression through testing pathways in the decision-analytic model (see Section 8).

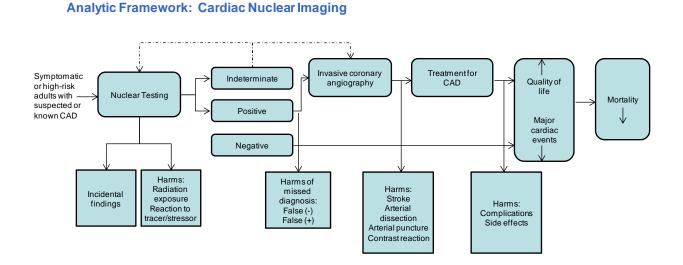
Tests of interest and relevant comparators are described in detail in Sections 7.2 and 7.3. Of note, the focus was on noninvasive tests that provide information on inducible myocardial ischemia – i.e., perfusion defects on SPECT and PET imaging, wall motion abnormalities on ECHO, and abnormal electrical activity on EKG. Tests that provide information on cardiac *anatomy*, such as CCTA, were not considered unless part of a hybrid testing modality with a functional test. In addition, emerging non-nuclear tests such as cardiac magnetic resonance (CMR) imaging were not included because their use is not yet widespread in Washington.

While all potential risks of testing were recorded, the primary focus of attention was on adverse effects requiring medical attention (where such designations were available). As noted above, while not technically a risk, all cardiac imaging tests have the potential for "extracardiac" findings – that is, issues of potential concern outside the heart, which may in turn result in follow-up testing and invasive treatment that may be unnecessary in some cases.

Finally, published studies of the economic impact of cardiac nuclear imaging are summarized in Section 8 to provide additional context for the ICER decision analytic model.

Analytic Framework

The analytic framework for this review is shown in the Figure below. Note that the figure is intended to convey the conceptual links involved in evaluating outcomes of cardiac nuclear imaging tests and their alternatives, and is not intended to depict a clinical pathway through which all patients would flow. This framework also does not represent the clinical pathways as they were constructed for the decision analytic model (see Section 8).



The available literature varies with respect to how directly the impact of nuclear imaging is measured. Some studies are randomized or observational comparisons focused directly on rates of mortality and major cardiovascular events, while in other studies a series of conceptual links must be made between clinical decisions and/or further testing and clinical outcome, or in some cases, test accuracy, downstream utilization, and clinical outcome.

The evidence hierarchy for diagnostic imaging differs from that for treatment, as RCTs are often not feasible and key patient outcomes of interest may lie many years in the future following the use of a test. In the early 1990s, Fryback and Thornbury developed an influential hierarchy of evidence specifically for imaging tests (Fryback, 1991). The hierarchy is presented in Table 1 on the following page. Each level of evidence is shown with corresponding examples of the relevant outcome measures for studies at that level.

Diagnostic Imaging Evidence Hierarchy Level	Example of Outcome Measures
1. Technical Efficacy	Interpretable scan resolution, inter-reader and inter-laboratory reliability of test results
2. Diagnostic Accuracy	Sensitivity/specificity vs. gold standard test or vs. some other standard
3. Diagnostic Impression	Change in presumptive diagnosis following introduction of new test results
4. Diagnostic Action	Initiation or cessation of treatment; impact on use of additional diagnostic studies
5. Patient Outcomes	Mortality, rates of major cardiovascular events, side effects of treatment driven by test results
6. Societal Outcomes	Cost-effectiveness of testing

Table 1. Evidence hierarchy for diagnostic imaging.

Source: Fryback and Thornbury, Medical Decision Making, 1991

Patient Populations

The focus of this appraisal was on adults who are candidates for cardiac nuclear imaging tests. As noted previously, populations of interest for this evaluation included (1) patients with symptoms suggestive of myocardial ischemia who are at low, intermediate, or high risk of CAD; (2) those without symptoms but who are considered at higher risk of CAD due to one or more risk factors (e.g., diabetes); and (3) patients with known CAD who are candidates for prognostic testing to guide treatment selection and/or conduct post-procedure or post-event monitoring. All relevant settings for testing were considered (e.g., emergency department vs. outpatient, primary care vs. specialty).

As noted in the Project Scope (see page 54), we defined low, intermediate, and high CAD risk based on the Diamond-Forrester model of pretest probability (Diamond, 1979), based on age, gender, and type of chest pain; these equate to probability ranges of <10%, 10-90%, and >90% respectively. Other pretest probability and risk classification systems are in use, however; we abstracted information on the system utilized where this was reported.

Other potential uses of nuclear imaging, such as pre-operative assessment of cardiovascular risk in patients undergoing noncardiac surgery and assessment of congenital defects or valvular disorders were not considered, as these uses represent a small percentage of nuclear imaging test volume at HCA agencies and/or are not considered to be major areas of controversy regarding appropriate use. In addition, while studies exist of the prognostic capabilities of nuclear imaging tests in apparently healthy individuals, such studies were

used for background purposes only, as major clinical societies do not recommend the use of nuclear imaging tests for general population screening (Hendel, 2009).

Certain patient subpopulations were also identified as of interest in evaluating whether testing effects and/or risks differed in these groups. These included subpopulations defined by demographic characteristics (e.g., age, sex, race/ethnicity), clinical setting (e.g., emergency department vs. outpatient, primary care vs. specialty), radioisotope employed, stressor employed, qualitative vs. quantitative assessment, as well as other subgroups as defined in available studies.

Interventions

The imaging tests of primary interest for this evaluation involve visualization of myocardial perfusion: single photon emission computed tomography (SPECT) and positron emission tomography (PET). Hybrid tests also were considered if at least one component focused on myocardial perfusion, including PET/MRI, PET/CT, and SPECT/CT. All of these tests are performed in conjunction with exercise- or pharmacologically-induced stress. Attention was focused on tests and imaging protocols that represent the current "state of the art"; for example, use of attenuation correction and EKG gating for reduction of image or motion artifacts.

No limitations were placed on studies with respect to testing and interpretation protocol, manufacturer, scanning software, method of attenuation correction, or other such factors.

Comparators

The comparator tests of interest included ETT and stress-ECHO as the other non-invasive tests commonly employed to provide information on inducible myocardial ischemia. As described previously, non-invasive tests that visualize coronary anatomy <u>only</u> (e.g., electron beam computed tomography, coronary computed tomography angiography) were not considered in this evaluation.

Outcomes

A variety of patient clinical outcomes were assessed as measures of effectiveness for this evaluation, as listed below:

- Cardiovascular and/or all-cause mortality
- Incidence of major cardiovascular events (myocardial infarction, stroke, requirement for revascularization, cardiovascular and/or all-cause hospitalization)
- Health-related quality of life (HrQoL)

- Referral for subsequent testing and treatment
- Clinician impression and/or decision-making

Additional test outcomes of interest included the rate of indeterminate and/or equivocal findings as well as the incidence of extracardiac findings requiring follow-up. Test and diagnostic strategy costs were also abstracted where available.

As mentioned previously, the studies of interest in this evaluation focused on the diagnostic and/or prognostic ability of nuclear imaging tests in comparison to an alternative method (e.g., test A vs. test B, testing pathways with vs. without test A). Studies that provided only data correlating results of a single testing strategy with downstream outcomes were not considered, as such studies provide no comparative information on the predictive capabilities of the test of interest relative to an alternative.

Risks of Testing

While the focus of attention was on adverse effects requiring medical attention, all available data on testing risks were abstracted where available. These included adverse effects attributed to the test, stressor, and/or radioisotope. Examples of adverse effects are listed below:

- Cardiac irregularities (e.g., premature ventricular complexes, arrhythmias)
- Chest pain
- Dyspnea
- Blood pressure changes
- Nausea/vomiting
- Flushing/chills
- Headache/dizziness

We also collected information on radiation exposure during nuclear imaging tests where reported. The primary downstream risk associated with exposure to ionizing radiation is cancer. According to the FDA, estimates based on the experience of atomic bomb survivors suggests that a dose of 10 millisieverts (mSv) may be associated with an increase in the possibility of fatal cancer of approximately 1 chance in 2000 (FDA, 2012). This risk level is relatively small in comparison to the approximately 400 out of 2,000 individuals expected to develop cancer from all other causes combined.

There is considerable controversy on extrapolating cancer death risks from those experienced by adults with high radiation exposure at Hiroshima and Nagasaki to the potential risks at much lower radiation doses. However, linear extrapolation has been the approach generally used, although the uncertainties inherent in this approach become progressively greater at lower doses. Also controversial is whether a natural threshold of radiation exposure exists before excess risk from specific exposures can be realized. The current guidance from a variety of regulatory authorities is that no threshold exists, but this has also been intensely debated. On the other hand, exposure to ionizing radiation has increased; a recent estimate indicates that the average per capita annual exposure in the U.S. has risen from approximately 3.6 mSv in the early 1980s to 6.25 mSv in 2006, and increase that has been attributed almost entirely to medical imaging (National Council on Radiation Protection and Measurements, 2009).

Because there is no consensus regarding the long-term effects of radiation received during cardiac nuclear imaging, we opted to abstract effective radiation dose where reported, and to model simply whether or not a patient was exposed to radiation in a given diagnostic pathway in our economic evaluation (see Section 8).

Timeframe

Data on all relevant measures were abstracted at all relevant timepoints regardless of study duration.

Study Designs

Data from both RCTs and selected types of observational studies were considered for measures of effectiveness. Observational studies of interest included those comparing multiple distinct testing strategies (e.g., test A vs. test B, strategies with test A vs. without test A) in multiple populations as well as those comparing the effects of multiple testing strategies in the same population. Case series of a single testing strategy were not considered for any measure of effectiveness except for diagnostic accuracy. Separate criteria were applied to diagnostic accuracy evaluations as shown below:

- Comparison of one or more tests of interest to a functional reference standard (e.g., FFR, CMR)
- Results reported on per-patient basis (or ability to construct per-patient findings)
- Receipt of reference standard by entire study population or random sample
- Time between index test and reference standard did not exceed 3 months
- Blinded review of both index and reference test

Studies with less than 30 participants were excluded from consideration, regardless of study design.

Information on risks of testing, indeterminate and/or extracardiac findings, and strategy costs were obtained from all potential study designs, including case series.

Literature Search and Retrieval

The general timeframe for literature search and retrieval for other study designs was January 1996 – February 2013. We focused on English-language reports with 30 or more participants only. As noted previously, RCTs and comparative cohort studies were limited to those comparing alternative testing strategies, either analysis of a single group receiving multiple tests or separate comparator groups receiving different tests. The one exception was diagnostic accuracy studies, whose inclusion was guided by separate entry criteria as described in Section 7.6 above.

The electronic databases we searched as part of the systematic review included MEDLINE, EMBASE, and *The Cochrane Library* (including the Database of Abstracts of Reviews of Effects [DARE]) for health technology assessments (HTAs), systematic reviews, and primary studies. Reference lists of all eligible studies were also searched. The strategies used for MEDLINE, EMBASE, and *The Cochrane Library* are shown in Appendix B.

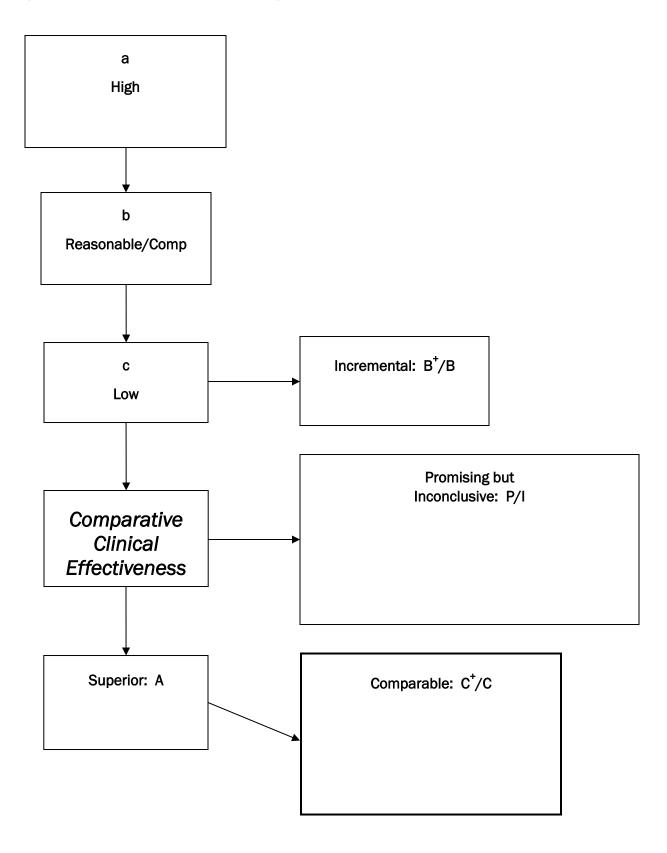
Studies were not further restricted by instrumentation, manufacturer, or testing protocol. Figure 1 on the following page shows a flow chart of the results of all searches for RCTs (n=6), cohort studies (n=27), diagnostic accuracy studies (n=8), and case series focusing on risks of testing, indeterminate/equivocal and/or extracardiac findings, and strategy costs (n=35).

Study Quality

We used criteria published by the U.S. Preventive Services Task Force to assess the quality of RCTs and comparative cohort studies, using the categories "good", "fair", or "poor". Guidance for quality rating using these criteria is presented below (AHRQ, 2008).

- **Good:** Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.
- **Fair:** Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done for RCTs.
- **Poor:** Studies will be graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

Figure 1. PRISMA flow chart showing results of literature search.



Quality of diagnostic accuracy studies was assessed using the revised Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2), which assesses risk of bias and level of study applicability in 4 distinct domains: patient selection, index test, reference standard, and flow and timing (Whiting, 2011). The QUADAS-2 does not produce a single summary score, but rather ratings for each domain that describe whether the level of concern regarding bias and applicability is low, high, or unclear.

Data from all retrieved studies were included in evidence tables regardless of study quality. However, the focus of attention in presentation of results was primarily on good- or fairquality studies.

Study quality was not assessed for case series or single-arm cohorts, as the focus of quality ratings was on the level of bias in assessing the *comparative* impact of cardiac nuclear imaging versus alternatives on measures of effectiveness and harm.

Data Synthesis

If data were sufficient, estimates of treatment effect were synthesized using meta-analysis. Random-effects models were generated based on head-to-head data from available RCTs. Data were deemed to be sufficient if (a) the number of eligible higher-quality RCTs was 2 or more; (b) the measure of interest was reported using uniform methods; and (c) judgment of the clinical heterogeneity of the patient populations in candidate studies was judged to be low enough to attempt meta-analysis. For continuous variables such as quality of life, the measure of choice for generating pooled estimates of effect was the standardized mean difference (SMD) at the latest reported timepoint. For dichotomous variables (e.g., mortality, referral to angiography), the rate ratio (RR) was used. Primary meta-analyses focused on comparisons of cardiac nuclear imaging tests to a uniform comparator (e.g., ECHO); data permitting, sensitivity analyses also were conducted comparing nuclear imaging to any available control population. Finally, while cohort studies were not candidates for meta-analyses of treatment effect, qualitative findings from these studies are described for each measure of interest. Detailed evidence tables are presented in Appendix C for all key outcomes and study designs evaluated in this review.

Results

Overview of Evidence and Quality Assessment

Limited RCT evidence was available comparing nuclear imaging tests to alternative strategies. Five RCTs were identified that met study entry criteria, all of which measured the impact of testing on patient outcomes (i.e., level "5" on the Fryback and Thornbury hierarchy). These included a multicenter outpatient trial comparing SPECT screening vs. no screening in 1,123 asymptomatic patients with diabetes (Young, 2009); a study comparing SPECT with ETT in 772 women across 43 cardiology practices with suspected CAD who had low-to-intermediate pretest probability of disease (Shaw, 2011); a comparison of SPECT with ETT in 457 patients seen at a hospital chest pain clinic, most of whom had intermediate-to-high pretest likelihood of CAD (Sabharwal, 2007); a study of 898

primarily high-risk patients referred for angiography at a tertiary cardiothoracic center who were randomized to receive SPECT, ECHO, CMR, or direct referral to angiography (Sharples, 2007); and a randomized comparison of the interaction of imaging modality (SPECT vs. PET) and patient gender on outcomes (Mullani, 2000). This latter study was rated poor quality due to treatment group imbalances and lack of standardized outcome measurement. The remainder of the RCTs were rated good- or fair-quality.

The evidence base for comparative cohort studies varied by patient population and is summarized by study quality in Table 2 on the following page. No such studies were identified in purely asymptomatic populations. In fact, of the 21 cohort studies identified, 8 (38%) were in "mixed" populations comprised of asymptomatic and symptomatic patients, those with suspected and known CAD, and/or a relatively even distribution of low, intermediate, and high CAD risk. Among symptomatic populations, a greater number of studies were performed in higher-risk individuals (5 vs. 4 for low-to-intermediate risk), while 4 studies were available in patients with known CAD. Sixteen cohort studies assessed the impact of testing on patient outcomes (level 5), 9 measured the effects of imaging on downstream testing and treatment (level 4), and one assessed the impact of testing on glient outcomes (level 5).

The majority of comparative studies were comparisons of SPECT-based strategies to alternative testing approaches. Only 3 studies involved the use of PET, and 2 assessed the impact of hybrid testing. Twelve cohort studies involved the use of multiple tests in a single population, while 9 compared the results of imaging strategies in multiple comparator groups.

Population		Study Design							
	RCT	Obs (2+ Groups)*	Obs (2+ Tests)†	Other	Good	Fair	Poor		
Asymptomatic, high-risk	1 SPECT/No test				1				
Symptomatic, low-to- intermediate risk	1 SPECT/ETT	2 SPECT/angiography Rest/Stress	2 SPECT/ECHO SPECT-CCTA hybrid/SPECT/angiography			2	1		
Symptomatic, high-risk	1 SPECT/ETT	2 SPECT/PET/CCTA SPECT Tracers	3 SPECT/ECHO SPECT/CCTA (2)		1	2			
Known CAD		3 Routine/Selective Testing SPECT before/after angiography SPECT Tracers	1 Before PET / After PET			3			
Mixed‡	2 SPECT/MRI/ECHO SPECT/PET	2 SPECT/PET Rest/Stress	6 ECHO/SPECT(3) SPECT-CCTA/SPECT/CCTA ETT/SPECT/angiography ETT/SPECT		1	1	2		
Diagnostic Accuracy			,	8 ⁰ SPECT: 5 PET/PET-CT: 3		N/A			
TOTAL	5	9	12	8	3	8	3		

Table 2. Evidence base for cardiac nuclear imaging, by population, study design, and study quality.

*Observational study comparing 2 or more distinct groups of patients.

†Observational study comparing results of 2 or more tests in a single group of patients (quality not rated for these studies).

‡Mix of pretest probability and/or known vs. suspected CAD.

⁰Per study entry criteria, represents studies of nuclear imaging tests that used a functional reference standard.

CCTA: coronary computed tomography angiography; ECHO: echocardiography; ETT: exercise treadmill test; PET: positron emission tomography; SPECT: single photon emission computed tomography

We rated study quality as "good" or "fair" for 7 of the 9 comparative cohort studies. Two studies were rated good quality — a prospective study examining downstream testing and treatment changes in patients receiving SPECT, PET, or CCTA (Hachamovitch, 2012), and a matched comparison of the impact of PET vs. SPECT on downstream testing, revascularization, and costs (Merhige, 2007). Both studies are discussed in further detail in the "Key Studies" section.

We identified 8 studies that evaluated the diagnostic accuracy of cardiac nuclear imaging tests (4 each of PET or PET-CT and SPECT respectively) in relation to a functional reference standard. Of the 8 studies, 7 used an FFR threshold (either 0.75 or 0.80) on angiography as the reference standard, either alone or in combination with anatomic stenosis measurements; one study compared SPECT to a reference standard of myocardial contrast echocardiography (MCE) (Oraby, 2002).

QUADAS-2 ratings of the study quality are presented in Table 3 below. There were few applicability concerns in any of the studies. Risk of bias, however, was deemed to be unclear or high in multiple domains on several studies, including 2 evaluations of a 2-day stress/rest SPECT protocol vs. FFR (De Bruyne, 2001; Melikian, 2010), the aforementioned comparison of SPECT to MCE (Oraby, 2002), and 2 separate evaluations of stress SPECT to FFR (Yanagisawa, 2002 and 2004).

Study		Risk	of bias		Applicability concerns				
	Patient Selection	Index test	Reference Standard	Flow and Timing	Patient Selection	Index test	Reference Standard		
Danad I. et al. (2013)	Low	Low	Low	High	Low	Low	High		
De Bruyne B. et al. (2001)	High	Unclear	Unclear	Low	Low	Low	Low		
Kajander S. et al. (2010)	Low	Low	Low	High	Low	Low	Unclear		
Kajander S. et al. (2011)	Low	Low	Low	High	Low	Low	Unclear		
Melikian N et al. (2010)	High	Low	Unclear	Low	Low	Low	Low		
Oraby M.A et al. (2002)	High	Low	Unclear	High	Low	Low	Low		
Yanagisawa H. et al. (2002)	High	Unclear	Unclear	Unclear	Low	Low	Low		
Yanagisawa H. et al. (2004)	High	Unclear	Unclear	Low	Low	Low	Low		

Table 3. QUADAS-2 ratings of risk of bias and applicability concerns, by study domain.

Given the small number of comparative studies within each patient population, we did not attempt to quantitatively synthesize data for any outcome measure of interest.

Key Studies

A number of key studies were identified to provide context for the overall results, based on considerations of study quality, sample size, innovative design, and/or applicability to clinical practice. Brief summaries of each study are provided below.

Asymptomatic, high-risk individuals

Young (2009); the "DIAD Study": An RCT of SPECT vs. no screening test measuring impact on clinical outcomes.

The Detection of Ischemia in Asymptomatic Diabetics (DIAD) study, the only available RCT in an asymptomatic population, included 1,123 patients across multiple clinics and practices with Type 2 diabetes and no symptoms of CAD who were randomized to be screened with a single adenosine-stress SPECT perfusion imaging test (Tc-99m sestamibi) or to receive no screening. Patients were followed for a mean (SD) of 4.8 (0.9) years to assess rates of cardiovascular events and mortality as well as revascularization. Patients were age 61 years on average; 54% were male. No statistically-significant differences in clinical outcomes, including nonfatal MI, cardiovascular or all-cause mortality, unstable angina, heart failure, or stroke. The overall rates of percutaneous coronary angioplasty (PTCA) and coronary artery bypass graft (CABG) surgery also did not differ between groups; however, the rate of any revascularization within 120 days after randomization was significantly higher in the screened group (1.6% vs. 0.4% for no screening, p=.03). Referral to angiography was significantly higher in the screened group (4.4% vs. 0.5% for no screening, p<.001), while the use of subsequent stress testing for clinical indications was higher in the no screening group (30% vs. 21% for SPECT, p<.001). The positive predictive value of moderate-to-large SPECT perfusion defects for cardiovascular events was 12%.

Symptomatic, low-to-intermediate risk

Shaw (2011); the "WOMEN Study": An RCT of ETT vs. SPECT measuring impact on clinical outcomes.

The <u>W</u>hat Is the <u>Optimal Method</u> for Ischemia <u>Evaluation in WomeN</u> (WOMEN) trial enrolled 772 women from 43 cardiology practices with chest pain or ischemic-equivalent symptoms who were at intermediate likelihood of CAD. Patients (median age: 63) were randomized to an initial diagnostic test of ETT vs. rest/exercise stress SPECT (Tc99m tetrofosmin or dual-isotope Tc-99m and ²⁰¹Thallium) and followed for 2 years. The 2-year Kaplan-Meier probability of survival free of major cardiovascular events (i.e., cardiac death, nonfatal MI, or hospital admission for acute coronary syndrome or heart failure) was 98% in both groups (p=.59). The rate of hospitalization for chest pain also did not differ statistically. Eighteen percent of women randomized to ETT received downstream SPECT testing by 2 years, while 9% of SPECT patients required repeat SPECT. This study also estimated index and follow-up testing costs, which were statistically-significantly higher in the SPECT group (median \$493 vs. \$174 for ETT, p<.001).

Symptomatic, intermediate-to-high-risk patients

Sabharwal (2007): An RCT of ETT vs. SPECT measuring referral for angiography and overall costs.

This was a single-center RCT in the UK comparing an ETT-based diagnostic strategy with stress SPECT (Tc-99m sestamibi) in 457 patients with suspected CAD (mean age, 59 years; 56% male) who were primarily at intermediate-to-high risk of CAD and followed for 2 years. The rate of referral for angiography was statistically-significantly higher in the ETT group (47% vs. 16% for SPECT, p<.0001), as was the rate of referral for any further imaging study (71% vs. 16%, p<.0001). A separate analysis of the cost from initiation of testing to diagnosis found that costs did not statistically differ between ETT and SPECT in patients with an intermediate or high pretest likelihood of CAD due to the higher referral rate for subsequent imaging in the ETT group; costs were significantly lower among those at low CAD risk (mean £106 vs. £439, p<.001).

Hachamovitch (2012); the "SPARC Study": A comparative cohort study of SPECT, PET, and CCTA measuring referral for angiography and medication changes.

The <u>S</u>tudy of Myocardial <u>P</u>erfusion and Coronary <u>A</u>natomy Imaging <u>R</u>oles in <u>C</u>oronary Artery Disease (SPARC) study was a prospective multicenter registry evaluating referral to angiography and medication management after non-invasive cardiac imaging by SPECT, PET, or CCTA. Patients (mean age 62 years; 48% male) were symptomatic, clinically-stable, and at intermediate-to-high risk of CAD, and were followed for 90 days after the index test. Testing protocols were institution-specific. On an overall basis, imaging results led to neither referral for angiography nor changes in aspirin, beta-blocker, or lipid-lowering agent usage in 60% of patients. In multivariable analyses, both the clinical modality employed (CCTA and PET vs. SPECT) and degree of abnormality on imaging was associated with a greater likelihood of angiography or medication changes, but the clinical effects were modest. For example, fewer than 50% of patients with a moderately-toseverely abnormal PET or SPECT results were referred for angiography within 90 days, and significant proportions (23-43%) did not receive cardioprotective medication.

Patients with known CAD

Siegrist (2008): Cohort study of PET, measuring impact on pre-post test clinical management plans.

This study was a prospective cohort evaluation of 100 patients (mean age 60.9 years; 72% male), 80% of whom had known CAD, who received rest-adenosine stress PET perfusion testing (¹³N-ammonia) with CT attenuation correction. Planned patient management, including angiography alone, angiography with PTCA, CABG, transplantation, or medical management was recorded both before and after PET results were available. Before PET, angiography was recommended in 62%, medical management in 28%, and PTCA or CABG in 9%. Recommendations changed for 78% of patients after PET testing, including PTCA or CABG in 23%, and medical management in 76%. Cost differences between recommendation sets were also assessed; savings from reduced use of angiography were found to offset the increased costs of PTCA and of PET itself, yielding estimated cost savings of €206 per patient tested.

Mixed patient populations

Merhige (2007): A comparative cohort study of PET and SPECT measuring clinical outcomes, downstream testing, and costs among a mixed population of patients with suspected or known CAD.

This study prospectively evaluated cardiac event rates, downstream testing, and costs in 2,159 patients receiving pharmacologic stress PET (⁸²Rubidium) with suspected or known CAD who were followed for 1 year in comparison to both internal (n=102) and external (n=5,826) control groups receiving SPECT. PET and SPECT patients were matched on software-based pretest probability of CAD (mean: 47%). Patients were a median age of 64, and 54% were male in all groups. Rates of acute MI and cardiovascular mortality did not differ between groups. Referral to angiography was 34% and 31% in the SPECT groups vs. 13% for PET (p<.0001). Revascularization rates were also statistically-significantly higher in the SPECT groups (11% and 13% vs. 6%, p<.01). While diagnostic costs did not differ between groups, total costs (including costs of revascularization) were lower in the PET group (\$4,110 vs. \$5,937 for SPECT), although this difference was not statistically tested.

Impact of Cardiac Nuclear Imaging Tests on Clinical Outcomes, Downstream Testing, and Clinical Decision-Making (KQ 1)

Findings are organized by patient population, type of outcome, and comparators in the sections that follow. An exception to this is diagnostic accuracy, which is summarized as a distinct subsection. Detailed evidence tables are provided in Appendix C, Tables C1-C2 for each study. A summary table is also provided beginning on page 99 for all populations, outcomes, and comparisons in this section to provide an overall assessment of the strength of evidence for each.

Asymptomatic Patients at High Risk of CAD

The one available study assessing the impact of cardiac nuclear imaging in asymptomatic, high-risk patients found no difference between SPECT screening and no screening in mortality or cardiovascular events, although many patients in both groups received subsequent stress testing for clinical reasons over approximately 5 years of follow-up. SPECT screening did increase the short-term rates of referral for angiography and revascularization versus no screening.

As shown previously in Table 2, and described in the Key Studies section of this report, a single, good-quality RCT was available assessing the impact of cardiac nuclear imaging on clinical outcomes, downstream testing, and clinical decision-making in asymptomatic, high-risk patients. This study, the DIAD study (Young, 2009), compared outcomes between SPECT screening and no screening among 1,123 patients with Type 2 diabetes.

<u>Correlation of Imaging Study Findings with Mortality and Cardiovascular Events</u> At 5 years of follow-up in the DIAD study, there were no statistically-significant differences between the group receiving SPECT screening and the no-screening group in cardiac, noncardiac, or all-cause mortality, MI, unstable angina, heart failure, stroke, or the rates of either PTCA or CABG. However, the revascularization rate within 120 days after randomization was statistically-significantly higher in the screened group (1.6% vs. 0.4% for no screening, p=.03), principally as a result of greater use of angiography in the screened population (see below).

Downstream Testing and Clinical Decision-Making

Referral to angiography within 120 days after randomization occurred in 4.4% of the screened population in the DIAD study vs. 0.5% of the no-screening group (p<.001). In contrast, the use of additional stress testing at any point during follow-up was higher in the no-screening population (30% vs. 21% for SPECT screening, p<.001). Receipt of antidiabetic and cardioprotective medications generally increased in both groups during follow-up, and did not statistically differ between them.

Health-related Quality of Life

The DIAD study did not evaluate the impact of screening on any measure of HrQoL.

Table 4. Summary evidence table: Impact of SPECT, PET, and hybrid imaging modalities on patient management and outcomes.

Study Information	Comparators	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Direction of Effect	Comments	
MORTALITY AND RISE	COF CARDIOVAS	SCULAR EV	TENTS						
Asymptomatic, high-risk individuals									
SPECT (N=1,123) RCT=1 Mean follow-up: 4.8 yrs		Low	N/A	Direct	N/A	++ Low	No differences	>short-term revasc for SPECT	
PET	0		,		No Studies				
Hybrid					No Studies				
Symptomatic patients at	low-to-intermediat	te CAD risk							
SPECT (N=24,458) RCT=1; CC=3 Mean follow-up: 2.2 yrs	ECHO (1), stress	Medium	Inconsistent	Direct	Imprecise	+++ Moderate	No differences vs. ECHO; mixed evidence vs. ETT		
PET					No Studies				
Hybrid					No Studies				
Symptomatic patients at	high CAD risk								
SPECT (N=4,279) RCT=1; CC=4 Mean follow-up: 2.3 yrs	CCTA (1), ECHO	Medium	Inconsistent	Direct	Imprecise	+++ Moderate	Superior to ETT; no difference vs. ECHO; mixed evidence vs. PET/CCTA		
PET (N=1,703) CC=1 Follow up: 3 mo	SPECT or CCTA (1)	Medium	N/A	Direct	N/A	+ Insufficient		Mixed evidence on revasc	
	Matched vs. unmatched images (1)	High	N/A	Indirect	N/A	+ Insufficient		Matched images superior to unmatched for revasc	

Study Information	Comparators	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Direction of Effect	Comments
Known CAD								
SPECT (N=5,098) CC=2 Mean follow-up: 4 yr	sequence (1), by	High	Inconsistent	Indirect	Imprecise	+ Insufficient		SPECT reduced revasc when after angiography
PET					No Studies		I	
Hybrid					No Studies			
Mixed Populations								
SPECT (N=5,439) RCT=2; CC=2; SA=4 Mean follow-up: 2.5 yr	(2), PET (2), CMR	Medium	Inconsistent	Direct	Imprecise	+++ Moderate	Mixed evidence vs. ECHO; superior to ETT; mixed evidence vs. PET	
PET (N=2,471) RCT=1; CC=1 Mean follow-up: 11 mo		Medium	Inconsistent	Direct	Imprecise	++ Low	PET superior to SPECT for revasc; no other differences	
	unmatched images (1)	High	N/A	Indirect	N/A	+ Insufficient		Matched images superior to unmatched for revasc
DOWNSTREAM TESTIN	NG AND CLINICA	L DECISIO	N-MAKING			•		•
Asymptomatic, high-risk	individuals							
SPECT (N=1,123) RCT=1 Mean follow-up: 4.8 yr	Ũ	Low	N/A	Direct	N/A	++ Low	Mixed evidence	SPECT > for angiography referral; no screening > for add'1 stress tests
PET					No Studies			
Hybrid					No Studies			

Study Information	Comparators	Risk of Bias	Consistency	Directross	Precision	Strength of Evidence	Direction of Effect	Comments		
Study InformationComparatorsBiasConsistencyDirectnessPrecisionEvidenceDirection of EffectCommentsSymptomatic patients at low-to-intermediate CAD risk										
SPECT (N=772) RCT=1 Follow-up: 2 yr	ETT	Low	N/A	Direct	N/A	++ Low	Mixed evidence	>repeat testing for SPECT; > crossover for ETT		
PET		1			No Studies					
Hybrid					No Studies					
Symptomatic patients at	high CAD risk			-						
SPECT (N=2,160) RCT=1; CC=1 Mean follow-up: 1.1 yr	CCTA (1)	Low	Inconsistent	Direct	Imprecise	++ Low	Superior to ETT; mixed evidence vs. PET and CCTA			
PET (N=1,703) CC=1 Follow up: 3 mo	SPECT or CCTA (1)	Medium	N/A	Direct	N/A	+ Insufficient		PET >SPECT for angiography referral; no differences in medication use		
	unmatched images (1)	High	N/A	Indirect	N/A	+ Insufficient		Matched >unmatched for angiography referral		
Known CAD					-	•	•	-		
SPECT					No Studies					
PET (N=100) SA=1 Mean follow-up: 9 mo	before/after PET	High	N/A	Direct	N/A	+ Insufficient		>use of med mgmt after PET		
Hybrid					No Studies					

		Risk of				Strength of			
Study Information	Comparators	Bias	Consistency	Directness	Precision	Evidence	Direction of Effect	Comments	
Mixed Populations									
SPECT (N=1,037) RCT=1; SA=1 Mean follow-up: 1.5 yr	(1), angiography	Medium	Inconsistent	Direct	Imprecise	++ Low	No difference vs. ECHO, CMR, or angiography; superior w/ and w/o ETT vs. ETT alone	ETT comparison based on hypothetical referral rate	
PET (n=2,261) CC=1 Mean follow-up: 1 yr	SPECT (1)	Medium	N/A	Direct	N/A	+ Insufficient		PET superior for angiography referral	
Hybrid					No Studies	·	·		
HEALTH-RELATED QU	ALITY OF LIFE								
Asymptomatic, high-risk	individuals					No studi	es		
Symptomatic patients at	low-to-intermedia	te CAD risk							
SPECT (N=772) RCT=1 Follow-up: 2 yr	ETT	Low	N/A	Direct	N/A	++ Low	No differences	General QoL and SAQ	
PET		•			No Studies				
Hybrid					No Studies				
Symptomatic patients at i	high CAD risk					No Studies			
Known CAD			No Studies						
Mixed populations									
SPECT (N=898) RCT=1 Follow-up: 1.5 yr	ECHO (1), CMR (1), angiography (1)	Low	N/A	Direct	N/A	++ Low	No differences	SAQ, SF-36, EQ-5D	
PET		No Studies							
Hybrid		No Studies							

CAD: coronary artery disease; CC: comparative cohort; CCTA: coronary computed tomography angiography; CMR: cardiac magnetic resonance; EQ-5D: EuroQoL; ETT: exercise treadmill testing; N: Number; N/A: Not applicable; QoL: quality of life; PET: positron emission tomography; RCT: randomized controlled trial; SA: single-arm cohort; SAQ: Seattle Angina Questionnaire; SPECT: single photon emission tomography

Symptomatic Patients at Low-to-Intermediate Risk of CAD

There is a single randomized study evaluating the impact of cardiac nuclear imaging versus other testing on patient mortality or major cardiac event outcomes in symptomatic patients at low-to-intermediate CAD risk. Limited available evidence suggests that cardiac imaging may provide incremental diagnostic and prognostic value and reduce unnecessary referral to angiography over treadmill testing and clinical parameters alone, but these effects are less apparent at the lower end of the risk spectrum. Nuclear imaging and ECHO appear to perform comparably in this population.

The evidence base for populations of patients with chest pain or other symptoms of ischemia which are at low-to-intermediate risk of CAD included 3 good- or fair-quality comparative studies. These were the previously-described good-quality WOMEN Study RCT comparing SPECT and ETT diagnostic strategies, (Shaw, 2011), a fair-quality comparative cohort study evaluating stress-only vs. stress/rest SPECT protocols (Chang, 2010), and an evaluation of the independent benefits of exercise ECHO, exercise SPECT, ETT, and clinical parameters in a single cohort (Olmos, 1998). A fourth study, comparing rates of revascularization and downstream testing between patients tested with SPECT vs. those referred directly to angiography, was rated poor quality due to failure to control for significant between-group differences. All studies are summarized in Tables C1-C2 in Appendix C.

<u>Correlation of Imaging Study Findings with Mortality and Cardiovascular Events</u> Rates of mortality and MACE events did not generally differ between imaging modalities in available studies. Patients in the WOMEN study were at very low CAD risk. Adverse cardiovascular events were relatively infrequent (17 events in 772 women over 2 years of follow-up); among these, only one death was reported. The rates of all major adverse cardiovascular events at 2 years were 1.7% and 2.3% for ETT and rest/stress SPECT respectively, but this difference was not significant (Hazard Ratio [HR]: 1.3; 95% CI: 0.5, 3.5; p=.59). The rate of revascularization also did not statistically differ between groups.

The long-term prognostic value of exercise SPECT (²⁰¹Thallium), exercise ECHO, ETT, and clinical parameters was measured in a single cohort of 248 patients (mean age, 56 years; 76% male) who were followed for a mean of 3.7 years (Olmos, 1998). A total of 64 MACE events occurred during follow-up. In multivariate analyses examining the incremental impact of (1) clinical + ETT data; (2) data in (1) + rest ECHO data; (3) data in (1) + exercise ECHO data; and (4) data in (1) + exercise SPECT data on predicting MACE events, the area under the curve did not statistically differ between the SPECT and ECHO models (0.78 and 0.77 respectively), but was significantly (p<.05) higher than the base model (0.68) or the rest ECHO model (0.72).

Chang and colleagues evaluated the impact on all-cause mortality of normal findings on stress-only vs. stress/rest SPECT (Tc-99m sestamibi or tetrofosmin) protocols in nearly 17,000 low-to-intermediate risk patients (mean age, 59 years; 44% male) followed for a median of 4.5 years (Chang, 2010). Annualized unadjusted mortality rates were

statistically-significantly greater in the stress/rest group (2.92% vs. 2.57% for stress-only, p=.02); however, this difference was no longer apparent after multivariate adjustment for differences in baseline characteristics. The authors conclude that a stress/rest protocol may be unnecessary in lower-risk individuals. It should be noted that these protocols employed CT-based attenuation correction, however, which is not yet in wide use with SPECT. Potential cost savings from performing stress-only protocols would need to be weighed against additional costs for equipment and investigation of extracardiac findings in such a setting.

Downstream Testing and Clinical Decision-Making

The impact of testing on downstream resource utilization and clinical decisions was evaluated only in the WOMEN study, an RCT of ETT vs. SPECT in symptomatic, low-to-intermediate risk patients (Shaw, 2011). Over 2 years of follow-up, repeat testing with the same modality was more frequent in the SPECT group vs. ETT (9% vs. 3%), although this difference was not statistically tested. However, 18% of women randomized to ETT crossed over to SPECT during follow-up. The overall rate of referral to angiography was higher in the ETT group (9.0% vs. 5.5% for SPECT, p<.0001);. Changes in the use of nitrates, beta-blockers, and antidepressant therapies during follow-up did not differ between the two arms in the study.

Health-related Quality of Life

The impact of testing on HrQOL also was examined only in the WOMEN study (Shaw, 2011). General QoL and life satisfaction were assessed using categorical rating scales, while functional status was assessed using the Seattle Angina Questionnaire (SAQ), a 19-item instrument assessing physical limitations, treatment satisfaction, disease perception, and anginal symptoms (Spertus, 1995). Similar proportions of women in each treatment group reported "excellent" or "very good" QoL as well as "best" or "average" life satisfaction, with no statistical differences between groups. There were also no statistically-significant differences between ETT and SPECT groups in relation to changes in any of the SAQ subscales.

Symptomatic Patients at High Risk of CAD

Limited randomized evidence is available evaluating the impact of cardiac nuclear imaging versus other testing on patient mortality or major cardiac event outcomes in symptomatic patients at high CAD risk. The evidence suggests that cardiac nuclear imaging may be associated with lower rates of revascularization vs. ETT, but that overall cardiac event rates are similar by imaging modality, including SPECT, ECHO, and with limited evidence, PET. ETT is associated with a higher angiography referral rate (and more false-positives) than SPECT in this population.

Two good- or fair-quality comparative studies were available with information on the clinical impact of cardiac nuclear imaging in symptomatic, high-risk populations, including the previously-mentioned fair-quality single-center RCT comparing ETT and SPECT

(Sabharwal, 2007) and multicenter prospective registry of SPECT, PET, and CCTA (Hachamovitch, 2012). An additional 2 single cohort studies compared the prognostic ability of stress SPECT vs. stress ECHO (Schinkel, 2004) and the effects of unmatched vs. matched fused images on hybrid SPECT/CCTA (Pazhenkottil, 2011). Detailed study descriptions are available in Tables C1-C2 in Appendix C.

<u>Correlation of Imaging Study Findings with Mortality and Cardiovascular Events</u> In high risk populations, some differences in event rates by modality were apparent. The Sabharwal RCT focused primarily on the period between testing and diagnosis, but did report on the rate of revascularization, which occurred more frequently in the ETT group (18% vs. 11% for SPECT, not statistically tested) (Sabharwal, 2007). In the Hachamovitch study, revascularization rates at 90 days did not materially differ between PET and SPECT, regardless of whether findings were mildly or moderately-severely abnormal (Hachamovitch, 2012).

Schinkel and colleagues assessed the prognostic value of both dobutamine ECHO and dobutamine SPECT (Tc99m-sestamibi) in 301 patients (mean age unreported; 56% male) who were unable to exercise and were at intermediate-to-high risk of CAD; patients were followed for a mean of 7.3 years (Schinkel, 2004). Event-free survival was significantly better for patients with normal versus abnormal findings on both tests, and did not differ statistically between tests. In multivariate models based on clinical data, stress testing, and imaging results, abnormal findings on either SPECT or ECHO were the strongest predictors of both cardiac death (HR [95% CI]: 4.4 [1.2, 21.0] and 3.4 [1.2, 12.0] for SPECT and ECHO respectively) and cardiac events (3.1 [1.1, 8.9] and 2.6 [1.1-6.2] respectively).

Finally, information from an evaluation of fused stress-rest Tc-99m tetrofosmin SPECT with CCTA in 335 patients (mean age, 61 years; 67% male) who were at primarily intermediateto-high risk of CAD was used to correlate matched and unmatched test results with MACE events (Pazhenkottil, 2011). Patients were followed for a median of 2.8 years. A total of 69 MACE events occurred in 47 patients; annual rates were 21.0%, 7.8%, and 2.2% for patients with matched (abnormal) findings, unmatched findings, and normal findings on both tests respectively (p<.005). In multivariate analyses controlling for patient characteristics and CAD risk factors, matched findings were the strongest predictor of unfavorable outcome (HR: 3.80; 95% CI: 1.76, 8.21; p=.002).

Downstream Testing and Clinical Decision-Making

Two studies reported on the effects of testing on downstream resource use and/or clinical decisions. Of the 207 patients randomized to ETT in the Sabharwal RCT, a total of 146 (71%) were referred for further testing (47% to angiography and 23% to stress ECHO) (Sabharwal, 2007). In contrast, further testing was requested in only 16% of patients randomized to SPECT, all of which were angiography procedures (p<.0001 for the comparison). ETT also appeared to generate more false-positives for significant CAD. Only 38% of ETT patients referred to angiography were revascularized, vs. 66% of SPECT patients so referred (p<.05).

In the SPARC registry, referral for angiography occurred in a greater percentage of PET patients (11.1% vs. 4.3% for SPECT; p<.001). In multivariate analyses controlling for patient characteristics, comorbidities, and testing location, imaging modality was significantly and positively correlated with referral to angiography for PET (OR: 5.0; 95% CI: 1.0, 24.4) in comparison to SPECT. Neither PET nor SPECT were associated with significant medication changes.

Health-Related Quality of Life

There were no studies in symptomatic, high-risk individuals that reported on the impact of cardiac nuclear imaging tests on HrQoL.

Known CAD

There are no randomized studies evaluating the impact of cardiac nuclear imaging on patient mortality or major cardiac event outcomes. Data are also lacking on the impact of cardiac nuclear imaging on clinical decisions and patient outcomes in populations comprised mostly or entirely of patients with known CAD. Findings from a single study suggest that PET perfusion testing data would change planned clinical management in approximately 75% of patients. There were no comparative studies evaluating the impact of serial nuclear imaging in asymptomatic patients with known CAD.

One fair-quality study was available with comparative information in populations consisting entirely or primarily of patients with known CAD, an evaluation of revascularization in patients receiving nuclear stress testing before angiography, after angiography, or no nuclear testing (Bourque, 2004). A second study evaluated changes in treatment strategies after PET imaging (Siegrist, 2008). Details of these studies are available in Appendix C, Tables C1-C2. Note that, because these studies did not clearly differentiate between patients with known CAD who did and did not exhibit symptoms, the population is described as a single entity. *We did not identify any comparative studies evaluating the impact of serial nuclear imaging in asymptomatic patients with known CAD*.

<u>Correlation of Imaging Study Results with Mortality and Cardiovascular Events</u> Bourque and colleagues conducted a comparative cohort study comparing the rate of revascularization in 2,951 patients (median age 65 years, 73% male) with known CAD and left ventricular dysfunction and (1) who had been tested with SPECT before referral for angiography; (2) were tested with SPECT only after a positive angiography; or (3) had no SPECT before or after angiography (Bourque, 2004). The rate of revascularization differed significantly (p=.001) among groups, with the lowest rate of 35.8% seen in postangiography SPECT patients, 45.6% in patients who had SPECT neither before nor afterward.

Downstream Testing and Clinical Decision-Making

In the study by Siegrist and colleagues, 100 consecutive patients (mean age, 60.9 years; 72% male), 79% of whom had known CAD, underwent adenosine rest-stress PET (¹³N-ammonia) perfusion testing (Siegrist, 2008). Physicians were first queried on proposed patient management strategies without PET perfusion data; actual patient management was measured 4 weeks after PET. Proposed patient management was altered in 78% of patients. Most prominently, conservative medical management was initially proposed in 28% of patients; after PET testing, 76% were managed this way in actuality. In addition, use of angiography to guide treatment via PTCA was proposed in 6%, but was performed in 20% after PET testing.

Health-Related Quality of Life

There were no studies in patients with known CAD that reported on the impact of cardiac nuclear imaging tests on HrQoL.

Mixed Populations

Limited evidence from randomized trials demonstrates no difference among cardiac imaging modalities on patient mortality or major cardiac event outcomes. Most of the studies evaluating the impact of cardiac nuclear imaging have been conducted in heterogeneous populations at varying levels of CAD risk, symptoms, and proportions of patients with known versus suspected disease. As with the other populations, available data suggest that cardiac imaging may provide incremental diagnostic and prognostic value over ETT, but that the performance is similar across imaging modalities. A single study suggests that PET's and SPECT's impact on MI and cardiovascular mortality is similar, but that PET is associated with lower rates of referral to angiography.

The largest number of studies was available for populations that did not fit neatly into the categories described above. They represented a true "mix" of patients based on relatively uniform distributions by risk or pretest probability, presence or absence of symptoms, and/or inclusion of patients with known vs. suspected CAD. A total of 10 studies were identified, including a fair-quality RCT comparing SPECT to ECHO, CMR, and direct referral to angiography (Sharples, 2007), the aforementioned good-quality prospective cohort study comparing PET to both matched internal and external SPECT control groups (Merhige, 2007), and an RCT comparing the interaction of imaging modality (PET vs. SPECT) and patient gender on outcomes (Mullani, 2000). This latter study was rated poor quality, however, because of imbalance in treatment groups and lack of standardization in outcome measurement, and so is not reported in detail here. Another poor-quality study evaluated outcomes in patients undergoing rest-only vs. rest-stress SPECT (Abdoul-Enein, 2003).

Six additional studies examined the effects of multiple imaging tests performed in a single patient population. These included 3 studies comparing SPECT and ECHO (Basic, 2006; De Lima, 2003; Hoque, 2002), and one each comparing SPECT with ETT (Muzzarelli, 2010),

SPECT with ETT and angiography (Pattilo, 1996), and findings from hybrid SPECT and CCTA (Fiechter, 2012).

Given the heterogeneity of patient populations and comparisons for this category, study descriptors and findings with respect to mortality and cardiovascular events are summarized in Table 5 on the following page. Detailed study results are also discussed in the sections that follow and are available in Appendix C, Tables C1-C2.

<u>Correlation of Imaging Study Results with Mortality and Cardiovascular Events</u> Data on mortality and cardiovascular events were available in 8 studies. The <u>C</u>ost-<u>E</u>ffectiveness of Functional <u>Ca</u>rdiac <u>T</u>esting (CeCAT) Trial was an RCT comparing multiple diagnostic strategies – rest-adenosine stress SPECT (Tc-99m sestamibi), ECHO (dobutamine stress), adenosine stress CMR, and direct referral to angiography – among 898 primarily high-risk patients (mean age, 62 years; 70% male) with known or suspected CAD and stable symptoms of ischemia who were referred to a tertiary center in the UK for angiography and were followed for 18 months (Sharples, 2007). In this study, the number of total, cardiac, and noncardiac deaths did not statistically differ by imaging modality. When compared with the referent angiography group, the number of nonfatal adverse cardiac events did not differ for SPECT or CMR, but was statistically-significantly higher for ECHO (relative risk [RR]: 1.95; 95% CI: 1.23, 3.08; p=.012). When the number of *patients* reporting adverse cardiac events was compared, however, no significant differences were observed.

Findings from the Merhige study comparing PET and SPECT were somewhat mixed. No differences in cardiovascular mortality or the rate of MI were observed between groups. (Merhige, 2007). However, the rates of CABG (3.4% vs. 7.8%, p<.01) and any revascularization (6.0% vs. 11.4%, p<.01) were statistically-significantly lower for PET vs. the internal SPECT control group. The rate of any revascularization was also significantly lower in comparison to the external SPECT control group (6.0% vs. 13.0%, p<.0001).

The 3 single cohorts comparing the prognostic ability of SPECT and ECHO generally showed comparable results for both tests. No statistical differences between imaging modalities in event rates or event-free survival were observed in 2 studies (Basic, 2006; De Lima, 2003). In the third, an evaluation of exercise stress ECHO vs. exercise stress SPECT (²⁰¹Thallium) in 206 symptomatic veterans who received both tests (Hoque, 2002) and were followed for up to 10 years, moderate-to-large ischemia on ECHO was the strongest independent predictor of overall mortality (RR: 6.2; p<.0001), cardiovascular death (RR: 17.6; p=.01), congestive heart failure (RR: 17.4; p=.0005), or sudden death (RR: 26.8; p=.003). The presence of moderate-to-large fixed defects on SPECT was the strongest independent predictor of nonfatal MI (RR: 8.1; p=.0002) and unstable angina (RR: 3.0; p=.005).

Pattilo and colleagues assessed the predictive capability of functional data from ETT, exercise stress SPECT (²⁰¹Thallium), and the "Gensini score" from angiography evaluation in 732 patients (mean age, 59 years; 71% male) who were followed for a mean of 3.5 years (Pattilo, 1996). Abnormal results on SPECT and the Gensini score were significantly ($p\leq.01$)

associated with poorer event-free survival, while ETT data were not. Analyses of the receiver operator curve (ROC) for events indicated that SPECT was the strongest independent predictor of events (0.67 vs. 0.61 and 0.46 for Gensini score and ETT, p<.05).

Table 5. Correlation of cardiac nuclear imaging with mortality and cardiovascular events in mixed populations (good- and fair-quality studies only).

Study	Design	CAD Risk	% w/ Symptoms	% Known CAD	Comparison	Main Findings
Sharples 2007 (n=898)	RCT	High: 69%	NR	NR	SPECT vs. ECHO/MRI/ angiography	SPECT ↑ vs. ECHO for readmission
Merhige 2007 (n=2,261)	Comparativ e Cohort	NR	NR	49	SPECT vs. PET	PET ↑ for CABG/total revasc
Basic 2006 (n=51)	Single Cohort	NR	100	NR	SPECT vs. ECHO	No differences
De Lima 2003 (n=126)	Single Cohort	Intermediate to High	NR	58	SPECT vs. ECHO	No differences
Hoque 2002 (n=206)	Single Cohort	NR	100	NR	SPECT vs. ECHO	SPECT↑ for MI/angina, ECHO↑for mortality/CHF
Fiechter 2012 (n=62)	Single Cohort	NR	50	NR	SPECT/CCT A	Matched results ↑for revasc
Pattilo 1996 (n=732)	Single Cohort	NR	100	NR	SPECT vs. ETT vs. angiography	SPECT ↑ETT and angiography

NOTE: \uparrow indicates (a) reduced rates of mortality or adverse CV events; or (b) better ability to predict mortality or adverse CV events

Downstream Testing and Clinical Decision-Making

A total of 3 good- or fair-quality studies examined the impact of cardiac nuclear imaging on further testing and clinical decision-making. In the CeCAT trial, the proportions of patients in the SPECT, ECHO, and CMR groups who were referred to angiography ranged between 75-80% and did not statistically differ between groups (Sharples, 2007); in addition, decisions on further invasive or medical management were also similar.

The rate of referral to angiography in the Merhige comparison of PET and SPECT was statistically-significantly lower for PET (13%) in comparison to both the internal and external SPECT groups (31% and 34% respectively, p<.0001). The rate of angiography-negative results was also significantly lower for PET vs. internal SPECT controls (5.2% vs. 15.6%, p<.0001).

Finally, a hypothetical referral rate to angiography was assessed in 955 patients (mean age 61 years; 70% male) undergoing ETT and rest-exercise stress SPECT (²⁰¹Thallium/Tc-99m sestamibi) (Muzzarelli, 2010). Algorithms using ETT data alone, SPECT data alone, and a combination of the 2 tests were applied. An estimated 27% of patients would have been referred to angiography based on ETT results alone, vs. 13% for SPECT data alone and 12% using both ETT and SPECT data (p<.01 for both comparisons to ETT alone). Findings were similar when compared among patients without known CAD.

Health-Related Quality of Life

HrQoL was assessed in the CeCAT trial using the Seattle Angina Questionnaire, the SF-36, and the EuroQol EQ-5D instruments (Sharples, 2007). While some statistically-significant differences were noted in certain subscales at particular timepoints, improvements in HrQoL were clinically comparable across testing groups for all measures.

Diagnostic Accuracy

Limited information was available on the diagnostic accuracy of cardiac nuclear imaging tests in comparison to a <u>functional</u> reference standard, most commonly fractional flow reserve (FFR). No direct comparisons of PET and SPECT were available. SPECT sensitivity and specificity ranged from 58-90% and 50-100% respectively in populations that varied according to age, presence of comorbidities, and CAD risk. Estimates for PET ranged from 74-95% and 63-100% for sensitivity and specificity. Data from recent systematic reviews using <u>anatomic</u> reference standards suggest that SPECT and ECHO have similar accuracy, while limited information on PET suggests greater sensitivity and/or specificity.

A total of 8 studies were available that examined the accuracy of cardiac nuclear imaging tests in relation to a functional reference standard. As described previously, this is currently believed to be a more accurate method to determine whether a defect noted on non-invasive imaging relates to CAD that is functionally-significant – that is, likely to be the cause of an adverse cardiovascular event if not treated. Details on these studies are provided in Table 6 on the following page. Meta-analysis of these data was not attempted for the evidence review due to heterogeneity in patient populations and the threshold for positivity, but was conducted to inform sensitivity analyses in the economic model.

Study	Test	CAD Risk	Stressor	Reference Standard	Sensitivity	Specificity
DeBruyne 2001 (n=107)	SPECT	100% Prior MI	Adenosine	FFR <0.75	82%	87%
Melikian 2010 (n=67)	SPECT	100% Known CAD	Adenosine	FFR <0.80	66%	50%
Oraby 2002 (n=38)	SPECT	NR	Dipyridamole	ECHO	58%	100%
Yanagisawa 2002 (n=165)	SPECT	70% Prior MI	Dipyridamole	FFR <0.75	90% (DM+) 71% (DM-)	70% (DM+) 74% (DM-)
Yanagisawa 2004 (n=245)	SPECT	100% Known CAD	Adenosine	FFR <0.75	83% (DM+) 79% (DM-)	75% (DM+) 83% (DM-)
Danand 2013 (n=120)	PET PET/CCTA	High	Adenosine	FFR ≤0.80 or Stenosis ≥50%	76% 76% (H)	83% 92% (H)
Kajander* 2010 (n=107)	PET PET/CCTA	30-70%	Adenosine	FFR ≤0.80 or Stenosis ≥50%	95% 95% (H)	91% 100% (H)

Table 6. Diagnostic accuracy in PET and SPECT studies using a functional referencestandard.

DM: diabetes mellitus; FFR: fractional flow reserve; H: hybrid PET/CCTA test

*A second publication using the same population showed sensitivity of 74% and specificity of 73% when analyzed using relative uptake vs. absolute blood flow

SPECT Studies

A total of 5 SPECT studies were found that analyzed the diagnostic accuracy of SPECT in relation to a functional reference standard – FFR in 4 studies, and contrast perfusion ECHO in 1 (Oraby, 2002). Of note, the perfusion ECHO technique utilized in this latter study has not yet been integrated into widespread clinical practice, and is performed by only a few centers worldwide.

All studies were performed under pharmacologic stress, and most were conducted in populations known to have CAD. Sensitivity ranged widely between 58-90% in these studies, while specificity ranged between 50-100%. Melikian and colleagues reported poor concordance between SPECT perfusion data and FFR (sensitivity and specificity of 66% and

50% respectively) (Melikian, 2010). The population tested had multivessel CAD; the authors note that perfusion imaging techniques preferentially identify defects in the most ischemic territories, thereby underestimating the presence of significant disease (Oraby, 2002). A study by Yanagisawa documented better performance of SPECT in patients with diabetes (Yanagisawa, 2002); a later study that included a heterogeneous group of patients with varying levels of glycemic control did not find such an effect, however (Yanagisawa, 2004).

PET Studies

Three studies of the diagnostic accuracy of PET were available, all of which also evaluated the accuracy of hybrid PET/CCTA (Danand, 2013; Kajander, 2010 and 2011). Sensitivity and specificity also ranged widely in PET studies, from 74-95% and 63-100% respectively. All studies showed better specificity for the hybrid technique vs. PET alone; this was statistically-significant in the Kajander 2010 comparison (100% vs. 95%, p=.014).

In the Danand study, both PET and PET/CCTA were found to have greater specificity than CCTA alone (92% and 83% vs. 34%, difference not tested) (Danand, 2013). Available studies also documented the influence of different measurement parameters for FFR. Imaging tests had greater accuracy when applied to hyperemic myocardial blood flow (MBF) as a perfusion parameter vs. coronary flow reserve (CFR) in Danand, and CFR outperformed a categorical analysis of "relative uptake" in Kajander 2010. It should be noted that, in the Danand and Kajander studies, the reference standard included either a functional *or* anatomic measure, and so their applicability to a construct of accuracy to detect important ischemia is limited.

Historical Evidence Using Anatomic Reference Standards

As described previously, recent research has raised questions about the use of anatomic data on angiography to confirm findings of functional tests such as ECHO, SPECT, and PET. There is nevertheless a large body of evidence evaluating the accuracy of non-invasive functional tests using visualization of coronary arteries as the reference standard. One of the most widely-cited meta-analyses compared the diagnostic accuracy of exercise ECHO and exercise SPECT based on 44 studies (Fleischmann, 1998). Pooled sensitivity of the 2 tests was similar (85% and 87% for ECHO and SPECT respectively), but pooled specificity was rated higher for ECHO (77% vs. 64% for SPECT, p<.05). However, substantial heterogeneity in study populations, imaging protocols, and SPECT radiotracers was noted for this sample; subsequent reanalysis with controls for heterogeneity found no statistical differences between the tests (Kymes, 2000).

Methods to assess diagnostic accuracy have also evolved, and feature newer techniques designed to capture the natural correlation between sensitivity and specificity (Reitsma, 2005). A recent meta-analysis using newer bivariate methods found that ECHO was slightly more sensitive than SPECT (87% vs. 83% respectively), while SPECT was somewhat more specific (77% vs. 72% for ECHO) (de Jong, 2012). An additional bivariate meta-analysis using a much larger set of 113 SPECT studies found greater sensitivity (88%) and

similar specificity (76%) (Parker, 2012), although other commentators have noted that the older SPECT studies included in this review were subject to "verification bias" (i.e., use of the reference standard only in test-positive or other selected individuals) (de Jong, 2012), which tends to inflate sensitivity and may also reduce specificity (Knottnerus, 1987). The Parker meta-analysis also included estimates of diagnostic accuracy from 9 PET studies (pooled estimates of 93% and 81% for sensitivity and specificity respectively) (Parker, 2012). Finally, a third recent meta-analysis estimated diagnostic performance from 114 SPECT and 15 PET studies (Jaarsma, 2012). SPECT sensitivity was similar to that reported elsewhere (88%), but specificity was somewhat lower (61%). Sensitivity and specificity for PET was estimated to be 84% and 81% respectively. It should be noted, however, that the Jaarsma analysis did not use modern meta-analytic techniques, instead meta-analyzing sensitivity and specificity as separate variables.

Other Outcomes

Extracardiac Findings

With the enhanced imagery available for many noninvasive tests, incidental findings outside of the area of interest can be problematic given the additional resources required for investigation (Stone, 2006). The reported rate of incidental extracardiac findings is very low with nuclear imaging tests given the limited field of detection, however; most available studies are limited to case reports of mediastinal masses (Kim, 2002; Hawkins, 2007; Paull, 2000). One recent study compared the rate of such findings between CCTA and SPECT in 479 patients; extracardiac findings requiring further investigation were detected in 7% of CCTA patients but in no SPECT patients (p=.0001) (Cheezum, 2011). Another analysis examined images of 2,155 patients undergoing SPECT studies, 6 (0.3%) of whom had extracardiac findings requiring follow-up. Four of the 6 patients had malignancies requiring further treatment (Gratz, 2008). We identified no PET studies reporting extracardiac findings.

While SPECT itself is associated with a low rate of extracardiac findings, the increasing use of CT for attenuation correction may result in increased detection of these findings. In a cohort study assessing prevalence of extracardiac findings from 582 SPECT/CT studies, a total of 400 (68.7%) included noncardiac findings, 196 (33.7%) of which were felt to be potentially relevant (Husmann, 2009).

Equivocal/Indeterminate Results

While equivocal or indeterminate findings are possible with any diagnostic test, these results are rarely published. A recent systematic review of nearly 1,200 diagnostic accuracy studies found that only 35% reported the presence of inconclusive results (Shinkins, 2013). Inconclusive results were reported in only one of the available studies in our sample. In the CeCAT trial comparing SPECT with ECHO, CMR, and angiography, rates of equivocal findings were 4.0%, 6.6%, 6.6% and 2.0% respectively (Sharples, 2007).

Risks of Testing (KQ 2)

SPECT and PET appear to be very safe tests, although data are lacking comparing adverse effects across testing modalities. Adverse events occurring before or immediately after these tests are typically transient and insignificant. When such events occur, they are most often attributable to the effects of exercise or pharmacologic stress, although adverse effect profiles for pharmacologic stressors appear to be similar. Effective radiation dose ranges widely for SPECT from 7-30 MSv depending on testing protocol and tracer; the reported range is lower for PET (2-14 MSv) due to shorter tracer half-life. Correlation of radiation dose with long-term health effects remains controversial due to lack of epidemiologic data and other sources of radiation exposure.

Patients appear to be at minimal immediate risk from cardiac nuclear imaging tests in and of themselves, although harms data are reported in only a small number of comparative studies. The risks that are reported are related primarily to the stressor employed (i.e., exercise or pharmacologic stress). Data on harms are presented in detailed evidence tables in Appendix C, Table C6.

Comparative Data on Testing Risks

Only 2 studies in our sample compared adverse effects of multiple testing modalities. In the WOMEN study that randomized patients to ETT or exercise SPECT, no statisticallysignificant differences between groups were noted in rates of chest pain, dyspnea, or fatigue after testing (Shaw, 2011). In the CeCAT trial comparing SPECT, ECHO, CMR, and angiography specific reasons for failed tests were recorded (Sharples, 2007). Failure to complete the test due to adverse effects occurred in 4 ECHO patients (1.8%), due to vasovagal reactions, blood pressure changes and dyspnea; no patient failed to complete SPECT due to adverse effects. Findings from comparative studies are summarized on the following page.

Adverse Effects by Stressor

Information on adverse effects attributed to specific stressors was obtained from 15 studies. Of these, 4 were RCTs involving SPECT, comparing binodenoson vs. adenosine stressors (Udelson, 2004), an accelerated vs. conventional protocol for dobutamine (Leão Lima, 2008), adenosine, dobutamine, and arbutamine stress (Wright, 2001), and 2 different infusion durations for adenosine (Treuth, 2001). Another 5 studies were comparative cohort studies, 2 of which featured comparisons of exercise vs. pharmacologic stress (Kabasakal, 1996; Chaptini, 2010). Regardless of the comparisons made, events were typically described as nonserious and resolved once the stressor infusion ended.

Reported ranges of adverse effects by category and type of stressor are summarized in Table 8 on page 116 as well as in a separate summary table in Appendix C. Rates were similar across pharmacologic agents. Limited data suggest lower rates of adverse effects for exercise vs. pharmacologic stress in the 2 studies making this comparison, although statistical comparisons were not available for all event types.

Table 7. Summary evidence table: Risks of SPECT, PET, and hybrid imaging.	
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Study Information	Comparators	Adverse Effect	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Direction of Effect	Comments
SPECT vs. Com	parator								
N=772 RCT=1	ETT vs. SPECT w/ no stressor (1)	Chest pain	Low	N/A	Direct	N/A	++ Low	No difference	
		Dyspnea	Low	N/A	Direct	N/A	++ Low	No difference	
N=898 RCT=1	Echo/MRI/ angiography vs. SPECT w/adenosine (1)	Chest pain	Low	N/A	Direct	N/A	++ Low	No difference	

ETT: exercise treadmill test; N: number; N/A: not applicable; RCT: randomized controlled trial; SPECT: single photon emission computed tomography

	_						
Range (# studies reporting)	Exercise	Adenosine	Arbutamine [†]	Binodenoson†	Dobutamine	Dipyridamole	Regadenoson
Arrhythmias	NR	0-5% (4)	NR	3-4% (1)	1-39% (3)	NR*	NR
Chest Pain	3% (1)	0-46% (6)	77% (1)	21-47% (1)	12-62% (4)	NR*	13% (1)
Dyspnea	16% (1)	3-59% (6)	NR	16-58% (1)	6-12% (2)	NR*	12% (1)
Flushing/ Chills	0% (1)	3-68% (6)	35% (1)	17-40% (1)	0-54% (4)	NR*	NR
GI Effects	0-6% (2)	6-7% (2)	NR	NR	0-8% (3)	11% (1)	2% (1)
Headache/ Dizziness	NR	18-23% (2)	NR	NR	5-14% (3)	NR*	7% (1)
Hyper-/ Hypotension	NR	NR	NR	0% (1)	1-3% (2)	NR*	NR

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NOTE: Binodenoson rates ranged by dose in 1 study.

*Side effects requiring medical intervention occurred in 24-53% of patients receiving dipyridamole in 2 comparative studies vs. adenosine (p<.001 for greater side-effect rate vs. adenosine) *Not commercially available in U.S.

Radiation Exposure

Potential adverse health effects associated with radiation exposure are important factors to consider in the evaluation of cardiac nuclear imaging tests, particularly because patients may already be exposed to radiation at other points along the diagnostic pathway (e.g., CCTA, angiography), cumulative radiation dose may be substantial in patients receiving serial imaging studies, and imaging alternatives such as ECHO and CMR exist that do not involve radiation. Radiation dose is a measure of ionizing energy absorbed per unit of mass, expressed as units of Gy (Gray) or mGy; it often is quoted as an equivalent "effective" dose to major organs in the scanned area, in units of Sv (Sievert) or mSv. For x-rays, the radiation type produced by CT scanners, 1 mSv = 1 mGy. To place the effective radiation dose received from SPECT and PET in context, the effective doses based on varying test protocols and radiotracers are listed in Table 9 on the following page, based on data

presented in guidelines from the American Society of Nuclear Cardiology and other sources (Di Carli, 2011).

Protocol	MPI: Average Effective Dose (mSv)*	CT w/Attenuation Correction: Average Effective Dose (mSv)†	Average Total Effective Dose (mSv)
1-Day 99m-Tc SPECT	9.9 - 11.4	0.5	10.9 - 12.4
2-Day 99mTc SPECT	12.8 - 15.7	0.5	13.8 - 16.7
²⁰¹ Thallium/99mTc SPECT	29.3	0.5	30.3
Stress-only 99mTc SPECT	7.1 – 8.0	0.5	8.1 - 9.0
¹³ N-ammonia PET	2.2	0.5	2.7
⁸² Rubidium PET	3.7	0.5	4.2

Table 9. Myocardial perfusion with SPECT and PET: Average effective radiation doses

Adapted from DiCarli, 2011.

* Estimated per American Society of Nuclear Cardiology Guidelines; Senthamizhchelvan, 2010 & 2011.

† CT attenuation based on typical protocol. Attenuation correlation for SPECT based on separate rest and stress scans.

CT: computed tomography; MPI: myocardial perfusion imaging; mSv: millisievert; PET: positron emission tomography; SPECT: single photon emission computed tomography

As shown in the table, doses for SPECT vary widely by testing protocol and radiotracer employed, with the lowest doses seen with stress-only Tc99m sestamibi, and the highest for dual-isotope testing with ²⁰¹Thallium. Doses for PET testing are much lower, which has been attributed to the shorter half-life of the radiotracers employed (DiCarli, 2011). In either case, dosing is increased when CT is used as the method for attenuation correction. Radiation doses for SPECT were reported in 5 studies in our sample. Average doses ranged from 7 mSv for a 2-day stress-rest protocol (Schaap, 2013) to 24 mSv for dual-isotope SPECT (Shaw, 2011).

These lower dose estimates for PET have been provided largely by manufacturers, however; findings from an earlier analysis based on data obtained from the International Commission on Radiological Protection suggest that the effective dose of ⁸²Rubidium PET, for example, ranges from 13-14 mSv (Einstein, 2007). A single study of PET/CCTA in our sample reported radiation dose, which averaged 21.8 mSv in patients receiving spiral CT and 9.3 mSv in protocols employing prospective EKG gating (Kajander, 2010). Dose ranges for SPECT and PET have also been placed alongside typical doses from other tests and exposures to radiation in the graphic on the following page. Note that the doses received from angiography are similar to those at the lower end of the reported range for

SPECT, while the upper end of the reported range approaches the current annual exposure limit for radiation workers. The range of PET doses overlaps with that of CCTA for both the lower and upper end of the reported range.

Radiation Exposure Scenario	Approximate Effective Dose (mSv)
Chest x-ray	0.02
Round-trip flight, New York-Seattle	0.06
Low-dose CT colonography	0.5-2.5
Lumbar spine x-ray	1.3
Head CT	2.0
Single-screening mammogram (breast dose)	3.0
Annual background dose caused by natural radiation	3.0/yr
ССТА	2.0-14.0
Cardiac PET Imaging	2.0-14.0
Invasive coronary angiography	5.0-7.0
Adult abdominal CT scan	10.0
Cardiac SPECT Imaging	7.0-30.0
Typical dose to A-bomb survivor at 2.3 km distance from ground zero Hiroshima	13.0
Annual radiation worker annual exposure limit	50.0/yr
Annual exposure on international space station	170.0/yr

Sources: Brenner, 2005; FDA [www.fda.gov/ForConsumers/ConsumerUpdates/ucm115329.htm]; ICER CCTA systematic review; Van Gelder 2004, Mettler 2008, Shuman 2008; Earls 2008; Husmann 2008 [2].

While exposure to ionizing radiation at these levels is associated with potential increase in cancer risk, the latency period for the development of such cancers may range from 10 to 40 years for solid tumors depending on the age and sex of the patient being tested (Gerber, 2009). The intended use of cardiac imaging tests then becomes a critical consideration. For example, the clinical tradeoff may be clearly in favor of imaging in the case of a symptomatic patient with known 3-vessel CAD or at very high CAD risk, with survival on medical therapy expected to be 50% or less within 5 years (Gerber, 2010); in other populations, such as stable patients undergoing serial imaging or in asymptomatic individuals, the tradeoff may be less certain.

Differential Effectiveness & Safety of Cardiac Nuclear Imaging in Key Patient Subgroups (KQ 3)

Data are extremely limited on the <u>comparative</u> effects of cardiac nuclear imaging tests versus alternative testing modalities in important patient subgroups. The literature in our set was limited to studies assessing the effectiveness of SPECT with different radiotracers or using alternative testing protocols. No clear differences within any specific subgroup were identifiable in these data. While no data were available on test effectiveness or risk based on ordering specialty, several papers have been published examining test ordering in relation to appropriateness criteria, indicating the inappropriate use of nuclear imaging tests may be more frequent in certain demographic subgroups (women, younger patients, asymptomatic individuals) and when ordered by noncardiologists.

Several subgroups were deemed to be of interest in this evaluation, as noted below:

- A. Patient age, sex, race or ethnicity, and comorbidities (e.g., obesity)
- B. Clinical setting (e.g., emergency department vs. outpatient)
- C. Selection of test by primary care vs. specialty physician
- D. Scan vendor, type of assessment (i.e., quantitative vs. qualitative), type of radioisotope, and type of stressor (e.g., adenosine, exercise)

We sought information on the *comparative* impact of cardiac nuclear imaging tests vs. alternative testing strategies in these subgroups. Results are summarized by subgroup category in the sections that follow, as well as in the summary evidence table (Table 10).

Patient Age, Sex, Race or Ethnicity, and Comorbidities

A single comparative cohort study was available that assessed all-cause mortality for stressonly versus stress-rest SPECT (n=16,854) in specific subgroups over a mean of 4.5 years of follow-up (Chang, 2010). On a univariate basis, stress-rest protocols were associated with a statistically-significantly higher mortality rate in older (age >65) individuals, men, patients with a BMI <30 kg/m², and patients with diabetes. However, after multivariate adjustment for baseline characteristics, no statistically-significant differences remained.

While not part of our sample of studies comparing diagnostic modalities, several large cohort studies and meta-analyses have assessed the performance of SPECT in certain patient subgroups. For example, several studies have found that SPECT's diagnostic and prognostic performance is similar for women and men (Berman, 2003; Iskandar, 2013). Comparable results have also been found in several large ECHO studies (Wake, 2007; Arruda-Olson, 2002). A meta-analysis of risk-stratification studies in over 13,000 patients age >65 years found that both stress SPECT and stress ECHO accurately risk-stratified patients vs. ETT (Rai, 2012). A multicenter cohort study of approximately 1,100 patients found that SPECT results were predictive of cardiac events in both Caucasian and African-American patients (Alkeylani, 1998).

Table 10. Summary evidence table: Differential effectiveness and/or safety of cardiac nuclear imaging in key subgroups.

Study Information	Comparator Sub-groups	Risk of Bias	Consistenc y	Directne ss	Precision	Strength of Evidence	Direction of Effect	Comments
Mortality and Cardiovas	scular Events							
Patient Demographics: S	Sex							
SPECT (N=16,854) CC=1 Mean follow-up: 4.5 yrs	Stress vs. stress rest (1) Subgroups: Men vs. women	Medium	N/A	Direct	N/A	+ Insufficient		No differences after multivariate adjustment
Patient Demographics: A	Age							
SPECT (N=16,854) CC=1 Mean follow-up: 4.5 years	Stress vs. stress rest (1) Age(<65 vs. >65)	Medium	N/A	Direct	N/A	+ Insufficient		No differences after multivariate adjustment
Patient Demographics:	Comorbidities							
SPECT (N=16,854) CC=1 Mean follow-up:4.5 years	Stress vs. stress rest (1) Subgroups: Obesity (<30 kg/m ² vs. >30 kg/m ²), Diabetes	Medium	N/A	Direct	N/A	+ Insufficient		No differences after multivariate adjustment
Clinical Setting								
SPECT (N=16,854) CC=1 Mean follow-up:4.5 years	Stress vs. stress rest (1) Subgroups: Inpatient vs. outpatient	Medium	N/A	Direct	N/A	+ Insufficient		No differences after multivariate adjustment
Scan Vendor, Tracer Ty	pe, Stressor Type							

Study Information	Comparator Sub-groups	Risk of Bias	Consistenc y	Directne ss	Precision	Strength of Evidence	Direction of Effect	Comments
SPECT (N=20,819)	Tetrofosmin vs.	Medium	Consistent	Direct	Precise	+++	No	
CC=3	sestamibi (2)					Moderate	difference	
Mean follow-up:1.5-4.5							s	
years	Subgroups:							
	Tetrofosmin vs.							
	sestamibi							
	Stress vs. stress and rest (1) Subgroups: Exercise vs. pharmacologic stress	High	N/A	Direct	N/A	+ Insufficient		No differences after multivariate adjustment
Diagnostic Accuracy			_		_			_
SPECT	Diabetes,	High	Inconsisten	Direct	Imprecise	++	Mixed	Better accuracy
Cohort=2	Hypertension		t			Low	evidence	among pts
N=410								w/diabetes in 1 of
Mean follow up: NR								2 studies; no
								differences for
								hypertension

CC: comparative cohort; N: Number; N/A: Not applicable; NR: Not reported; SPECT: single photon emission computed tomography

Analyses comparing patients with and without diabetes suggest that, while diabetes is a predictor of mortality for any nuclear imaging result, SPECT testing provides incremental prognostic information in patients with and without diabetes alike (Berman, 2003; Kang, 1999). Multiple studies have found that SPECT is feasible and has comparable diagnostic and prognostic performance in normal-weight, overweight, and obese patients (Gimelli, 2012; Berman, 2006; Kang, 2006). Finally, a meta-analysis SPECT and ECHO studies in hypertensive patients showed diagnostic accuracy similar to that observed in all patients with suspicion of CAD (Gargiulo, 2011).

Clinical Setting

In the previously-described comparison of stress-only vs. stress-rest SPECT (Chang, 2010), mortality was initially statistically-significantly higher in stress-rest patients in an inpatient setting. After multivariate adjustment, however, no significant differences remained.

Limited additional data are available explicitly comparing the performance of SPECT by setting. One study evaluating the potential benefit of an emergency department chest pain clinic estimated that unnecessary hospitalizations would be reduced in 30% of patients and inappropriate discharges avoided in 6% through the use of a selective SPECT protocol (Abbott, 2001).

Selection of Test by Primary Care vs. Specialty Physician

No study in our sample assessed the impact of ordering specialty on patient outcomes, clinical decision-making, or costs. There are, however, several studies that have assessed the impact of specialty on whether ordered cardiac SPECT studies meet published appropriate use criteria (AUC). In a multicenter assessment of an online SPECT appropriateness classification system, Hendel and colleagues found that the rate of inappropriate studies was statistically-significantly higher among noncardiologists (19.5% vs. 13.2% for cardiologists, p<.0001). Similar findings have been observed in several single-center studies (Gupta, 2011; Druz, 2011; Mehta, 2008). Of note, most inappropriate ordering of SPECT perfusion studies appears to have occurred in women, younger patients, and/or those without symptoms.

Scan Vendor, Type of Assessment, Type of Radioisotope, and Type of Stressor No study in our sample assessed the impact of scan vendor or qualitative vs. quantitative assessment on patient outcomes, clinical decision-making, or costs.

Most of the studies evaluating differences according to stressor type focused on rates of adverse effects of pharmacologic testing (see "Risks of Testing" on page 107). Chang's evaluation of stress-only vs. stress-rest SPECT found no statistically-significant effects on mortality with subgroups defined by exercise vs. pharmacologic stress on either a univariate or multivariate-adjusted basis (Chang, 2010).

Two studies examined the impact of different SPECT radiotracers on outcomes. In one, a total of 1,818 patients (median age, 63 years; 66% male) underwent exercise or

pharmacologic stress SPECT with Tc-99m sestamibi or Tc-99m tetrofosmin at Duke University Medical Center (Borges-Neto, 2004). Patients were followed for a mean of 1.5 years, during which no statistically-significant differences were observed between groups in the rates of overall mortality, cardiovascular mortality, or the composite endpoint of cardiovascular mortality or nonfatal MI.

Adams et al. compared mortality outcomes among 2,147 patients with known CAD (median age, 67 years; 55% male) undergoing pharmacologic stress SPECT with either Tc-99m sestamibi or Tc99m tetrofosmin who were followed for a median of 4 years (Adams, 2007). During follow-up, a total of 704 all-cause deaths (493 cardiovascular-related) were reported. There was no significant difference in either overall or cardiovascular mortality between radiotracer groups on both an unadjusted and multivariate-adjusted basis.

Economic Impact of Cardiac Nuclear Imaging (KQ 4)

Assessment of Published Studies

A total of 16 study reports were identified that included assessment of the costs of cardiac nuclear imaging strategies. Findings of major studies are reported by population in the sections that follow below.

Asymptomatic Patients at High Risk of CAD

Findings were available from a single decision analysis assessing the cost-effectiveness of one-time screening with SPECT, ECHO, and ETT compared to no screening in a hypothetical cohort of 60 year-old men with Type 2 diabetes and no symptoms of CAD (Hayashino, 2006). On a lifetime basis, the difference between the most and least effective testing strategies was 10 quality-adjusted days of survival; SPECT and ECHO had essentially identical effectiveness. The SPECT screening strategy was most costly, followed by ECHO and ETT. Cost-effectiveness was similar (<\$40,000 per QALY gained) for all tests compared to no screening; the cost-effectiveness of SPECT vs. ECHO was estimated to be \$326,000 per QALY gained. When repeat testing was assumed over intervals of 3, 5, and 10 years, cost-effectiveness of any test exceeded \$1 million per QALY gained.

Symptomatic Patients at Low-to-Intermediate Risk of CAD

Available evidence in patients at low-to-intermediate CAD risk included data from 2 RCTs. In the WOMEN study, an RCT of 772 women with suspected CAD randomized to ETT or SPECT-based testing (Shaw, 2011), estimated costs of initial and subsequent testing were compared based on published Medicare payments. Costs of initial SPECT testing were threefold higher than ETT (\$495 vs. \$154, p<.001), while subsequent testing costs were

higher in the ETT arm (\$180 vs. \$145 for SPECT, p<.001). Total testing costs remained higher in the SPECT arm, however (\$643 vs. \$338 for ETT, p<.001).

The second RCT involved 457 primarily intermediate-risk patients seen at a chest pain clinic in the UK who were also randomized to ETT or SPECT-based strategies (Sabharwal, 2007). Costs were estimated from both the hospital and payer perspective from randomization to the time of diagnosis. Overall, the cost of the ETT strategy was significantly higher (\$1,244 vs. \$743 for SPECT), as the rate of downstream testing was substantially greater among ETT patients due to greater numbers of equivocal and false-positive results.

Costs to diagnose CAD were also estimated in a cohort analysis of 955 patients receiving both ETT and SPECT (Muzzarelli, 2010). A hypothetical angiography referral rate was assumed based on data from (a) ETT alone; (b) SPECT alone; or (c) both tests. Costs included those of initial testing and angiography. Expected referral rates were higher in the ETT-only scenario (27%) vs. SPECT-only (13%) and combined ETT-SPECT (12%) strategies. However, costs were comparable for the ETT-alone and combined algorithms (\$798 and \$776 respectively), but were substantially higher for the SPECT-alone strategy (\$1,686) due to receipt of SPECT in all patients and similar procedure costs for SPECT and angiography in this setting (Switzerland).

Lifetime direct and indirect costs of 6 non-invasive strategies were examined in a decision analysis of 1,000 patients with acute chest pain at low-to-intermediate CAD risk: troponin, ETT, exercise ECHO, pharmacologic stress ECHO, exercise SPECT, or direct angiography referral. On a per-patient basis, the cost per "correctly identified patient" (i.e., true positive or true negative on angiography) for SPECT was lower than for the direct angiography, ETT, and troponin strategies, but higher than the ECHO strategy (\$1,634 vs. \$803).

Symptomatic Patients at High Risk of CAD

There were no economic evaluations meeting study entry criteria that focused primarily on symptomatic patients at high risk of CAD.

Known CAD

Results of a study comparing planned management before PET perfusion testing in 100 patients to actual management after PET results were made available included estimated costs of both planned and actual management (Siegrist, 2008). PET results reduced the number of angiographies required, resulting in costs savings of \$240 per patient.

Mixed Populations

The economic impact of non-invasive testing with SPECT, CMR, ECHO, or direct referral to angiography was assessed in an RCT of 898 primarily high-risk patients who were asymptomatic or symptomatic and had suspected or known CAD (Sharples, 2007). Compared to angiography alone, mean incremental costs from randomization to the end of 18 months of follow-up were higher for ECHO (\$1,246) than for SPECT (\$630) or CMR (\$647), due primarily to a greater number of hospital readmissions for chest pain in the ECHO arm. The authors also note that SPECT is a much more established testing modality than ECHO in this setting (the UK). Differences in quality-adjusted survival were minimal between groups.

Costs of diagnosis and treatment were also assessed in a comparative cohort analysis of PET and SPECT in patients with known or suspected CAD with a mix of underlying risk and symptoms (Merhige, 2007). Mean costs of diagnostic testing were approximately \$2,500 for both groups, reflecting a relative balance between higher initial test costs for PET and increased referral to angiography for SPECT. When costs of downstream events and revascularization were included, however, total costs were 30% lower in the PET group (\$4,110 vs. \$5,937; statistical significance not reported).

Decision-Analytic Model

Objective

The primary objective of this decision analytic model was to evaluate the short-term effectiveness and economic outcomes of cardiac nuclear imaging tests and comparator strategies for diagnosing CAD.

Methods

Target Population and Subgroups

The target population of the decision model involved men and women with suspected or known CAD who had stable symptoms of myocardial ischemia (i.e., atypical or typical chest pain or other symptoms such as dyspnea). As previously described, models of CAD pretest probability often overestimate actual CAD prevalence seen in clinical practice. As CAD prevalence was required for our model to estimate the results of diagnostic testing (e.g., identifying true negatives vs. false positives), we chose levels of prevalence that would approximate constructs of low, intermediate, or high "risk". These levels of prevalence were 10%, 30%, and 50-70% respectively.

As noted previously, evidence of test accuracy to detect *functionally-significant* ischemia is quite limited and not available for all testing strategies of interest. We were therefore required to use anatomic reference standard data to depict test results.

Setting and Location

An outpatient setting was assumed for the initiation of noninvasive testing.

Study Perspective

We adopted a public payer perspective for the reference case (i.e., primary analysis). In other words, costs were assumed to be those borne by the payer for services rendered. Indirect costs (e.g., lost work time) were not considered.

Comparators

The imaging tests of primary interest for this evaluation were those that involved nuclear imaging for visualization of myocardial perfusion: single photon emission computed tomography (SPECT), and positron emission tomography (PET). The comparator tests of interest included the exercise treadmill test (ETT) and echocardiogram (ECHO) as the other non-invasive tests commonly employed to provide information on inducible myocardial ischemia. Exercise was assumed to be the stressor employed for SPECT, ETT, and ECHO, while pharmacologic stress with regadenoson (the most frequent pharmacologic stressor employed based on HCA data) was assumed for PET. Radiotracers employed for nuclear imaging were Tc99m-tetrofosmin for SPECT and ¹³N-ammonia for PET, again based on reported frequency in HCA data.

Based on expert clinical input, we developed 7 different strategies, alone and in combination, to capture a wide range of management approaches for evaluating patients with stable symptoms of ischemia and a low, intermediate or high risk of CAD:

- 1. ECHO, followed by invasive coronary angiography if ECHO is positive or inconclusive
- 2. ETT, followed by angiography if ETT is positive or inconclusive
- 3. SPECT, followed by angiography if ETT is positive or inconclusive
- 4. PET, followed by angiography if ETT is positive or inconclusive
- 5. ETT, followed by ECHO if ETT is positive or inconclusive, followed by angiography if the ECHO is positive or inconclusive
- 6. ETT, followed by SPECT if ETT is positive or inconclusive, followed by angiography if the SPECT is positive or inconclusive
- 7. ETT, followed by PET if ETT is positive or inconclusive, followed by angiography if the PET is positive or inconclusive

<u>Time Horizon</u>

The model was designed to evaluate the short-term clinical and economic outcomes of noninvasive testing for CAD. As such, the analysis adopts a time horizon that was limited to that of the diagnostic phase itself and the 90 days following, as we believe there is little utility in extrapolating the results of "point-in-time" testing over long-term or lifetime time horizons. For example, some patients with false-negative test results will suffer a major

clinical event or die because of the missed diagnosis, while others will have their symptoms recur, will present again for testing, and will be correctly diagnosed. Any attempt to estimate the distribution of future behavior for such patients would be highly speculative.

Discount Rate

The model employed a time horizon of only 90 days. As such, neither outcomes nor costs were discounted.

Choice of Outcomes

In the interest of transparency, a cost-consequence analysis was conducted in which diagnostic and economic outcomes are presented in disaggregated form. Key outcomes obtained from the decision model included:

- 1) numbers of true positive non-invasive test results per 1,000 population tested;
- 2) numbers of false positive non-invasive test results per 1,000 population tested;
- 3) numbers of true negative non-invasive test results per 1,000 population tested;
- 4) numbers of false negative non-invasive test results per 1,000 population tested;
- 5) numbers of patients referred for angiography per 1,000 population tested;
- 6) numbers of angiography-negative results per 1,000 population tested (i.e., truenegative and false-positive results from non-invasive testing);
- 7) numbers of angiography-related deaths per 1,000 population tested;
- 8) numbers exposed to radiation per 1,000 population tested;
- 9) numbers of incidental extracardiac findings requiring follow-up per 1,000 population tested; and
- 10) total (90-day) costs per patient

As discussed above, we did not extrapolate the results of "point-in-time" testing over longterm or lifetime time horizons to forecast downstream clinical events or QALYs gained for each diagnostic strategy.

Measurement of Diagnostic Accuracy and Transition Probabilities

As shown in Table 11 on the following page, we derived model estimates of diagnostic accuracy to detect CAD largely from 2 recently published systematic reviews that employed modern bivariate meta-analytic techniques and used angiography as the reference standard. The bivariate meta-analysis by de Jong and colleagues provided the sensitivity and specificity values for ECHO and SPECT (de Jong, 2012). We derived the sensitivity and specificity of PET from a second bivariate meta-analysis (Parker, 2012). Diagnostic accuracy values for ETT were derived from the CE-MARC study (Greenwood, 2013). Data on inconclusive results are rarely reported in diagnostic accuracy studies; we opted instead to obtain these data from available RCTs in our study sample (Table 11). The probability of mortality with angiography was derived from a Report from the CathPCI

Registry of the National Cardiovascular Data Registry in the United States, 2010 through June 2011 (Dehmer, 2012), and was calculated as a cumulative risk for all angiographies performed within a given strategy.

	Base	Probability	
Parameters	Estimate	Distribution	Reference
Sensitivity and Specificity Va	alues		
ЕСНО			
Sensitivity	0.87	Beta(150,22)	de Jong 2012
Specificity	0.72	Beta(30,12)	de Jong 2012
ETT			
Sensitivity	0.68	Beta(155,72)	Greenwood 2013
Specificity	0.73	Beta(256,97)	Greenwood 2013
SPECT			
Sensitivity	0.83	Beta(69,14)	de Jong 2012
Specificity	0.77	Beta(43,13)	de Jong 2012
PET			
Sensitivity	0.93	Beta(144,11)	Parker et al 2012
Specificity	0.81	Beta(35,8)	Parker et al 2012
Probability Inconclusive			
ЕСНО	0.07	Beta(15,211)	Sharples et al 2007
ETT	0.16	Beta(62,326)	Shaw et al 2011
SPECT	0.04	Beta(9,224)	Sharples et al 2007
РЕТ	0.04	Beta(9,224)	Assumed equivalent to Sharples et al 2007– based on Parker et al 2012
Angiography Mortality			

Table 11. Diagnostic accuracy inputs for the decision model.
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Parameters	Base Estimate	Probability Distribution	Reference
Angiography Mortality	0.0060	Beta(6549,1085008)	Dehmer et al 2012

ECHO, echocardiogram, ETT, Exercise treadmill testing; PET= Positron Emission Tomography; SPECT= Single Photon Emission Computed Tomography

Note that accuracy estimates in Table 11, even those from bivariate analyses, are based on use of anatomic data from angiography as the reference standard. As noted in our systematic review, only a small number of studies have assessed the accuracy of the tests of interest in comparison to a functional reference standard, which precluded our use of such data in primary analyses. We nevertheless included pooled estimates of accuracy for PET and SPECT using FFR-based reference standards in sensitivity analyses.

Estimating Resources and Costs

Direct costs were considered from the payer perspective; reimbursement rates from the Washington Health Care Authority were used (see Table 12 below). Estimates of direct costs included professional and technical fees as well as facility charges for the initial noninvasive diagnostic test and those for any subsequent noninvasive diagnostic test and/or invasive coronary angiography costs. While we displayed the number of patients for whom extracardiac findings requiring follow-up would be observed, we did not model the costs, benefits, or risks of identifying such findings, as available data are extremely sparse with respect to the costs and consequences of such findings.

Procedure, CPT C	Code (Description)	Total Costs	Source
ЕСНО	93351 (stress echo continuous monitoring)	\$696	Washington HCA
ETT	93000 (Electrocardiogram, Complete) 93015 (cardiovascular stress test)	\$166	Washington HCA
SPECT	A9502 (Technetium Tc99M Tetrofosmin) 93015 (cardiovascular stress test) 78452 (Heart Image SPECT, Multiple)	\$1,311	Washington HCA
PET	PET 78492 (Heart Image PET, Multiple) J2785 (Regadenoson Injection) A9526 (Ammonia N-13, Per Dose)		Washington HCA
Angiography	93454 (Coronary Artery Angiography S&I)	\$3,054	Washington HCA

Table 12. Cost informatio	n for treatments considered.
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ECHO, echocardiogram, ETT, Exercise treadmill testing; PET= Positron Emission Tomography; SPECT= Single Photon Emission Computed Tomography

As noted above, we assumed that SPECT, ETT, and ECHO would be done with exercise stress, while PET would be conducted under pharmacologic stress. The costs of stress modalities are included in the estimated costs for each test, as are radiotracer costs for PET and SPECT.

Currency, Price Date, and Conversion

All costs are provided in 2012 U.S. dollars, consistent with the latest available payment data from the HCA.

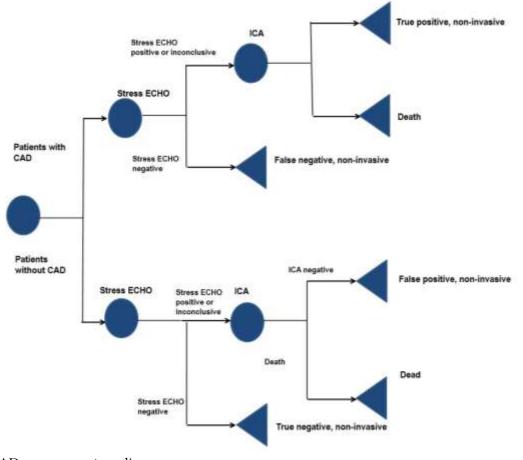
Model Choice

To enhance transparency, a parsimonious decision-analytic model was developed to evaluate the short-term diagnostic accuracy and economic outcomes of cardiac nuclear imaging and comparator tests to detect CAD.

The decision analytic model begins in an outpatient setting with evaluation of patients with stable symptoms of ischemia. Patients enter the model either with or without CAD. The probability of underlying CAD varies depending on the analysis – low (10%), intermediate (30%), or high risk (50% or 70%) of CAD. The probability of transitioning through the model is affected by the sensitivity and specificity of each diagnostic strategy as well as the probability of an inconclusive result. The sensitivity and specificity values applied for each diagnostic strategy in the reference case analysis have been presented in Table 11.

As an example, the structure for the decision model using Strategy 1 is presented in Figure 2 on the following page. A similar model structure is employed for other 1-test strategies (see Comparators), but the model structure differs slightly between 1 and 2-test strategies. In the 1-test strategy (Figure 2), a single test is performed and patients with a positive test or whose test results are inconclusive are sent for angiography. Depending on the angiography findings, patients can either be labeled as having true positive non-invasive test results or true negative non-invasive test results. Patients whose diagnostic test indicates no evidence of CAD receive no additional therapies beyond baseline care. Depending on their true disease status, they can either be labeled as having true negative non-invasive test results. The 2-test strategy (Appendix D) differs from the 1-test strategy in that patients whose initial test is inconclusive or positive will not be sent immediately for angiography, but will receive a second noninvasive test. Similar to the 1-test strategy, the second test is performed and patients with a positive test or whose test results are inconclusive are sent for angiography.

Figure 2. Decision model for short-term diagnostic and economic outcomes of noninvasive testing for coronary artery disease (structure of decision tree using Strategy 1 as an example).



CAD: coronary artery disease

All analyses were conducted using Microsoft Excel 2010 (Microsoft Corporation, Seattle, Washington).

Assumptions

Listed in Table 13 on the following page are assumptions made in designing the model for this evaluation in order to preserve model transparency and simplicity. Our model was based to some degree on past decision models evaluating short-term diagnostic and economic outcomes of myocardial perfusion testing for CAD (Walker, 2013; Institute for Clinical and Economic Review, 2009; Kim, 1999).

Table 13. Key model assumptions.

It is assumed that all patients are fit enough to undergo exercise stress (use of pharmacologic stress for PET is a function of the device)

All patients are able to complete each test (exercise patients achieve target heart rate, stressor infusion is successful, there are no technical failures)

Angiography is assumed to have sensitivity and specificity of 100% for detection of CAD (i.e., the "gold" standard)

The studies included in the underlying meta-analyses are similar enough in terms of study and patient characteristics to compare across diagnostic strategies

Analytical Methods

Several univariate sensitivity and variability analyses were also conducted to explore the impact of varying parameter values and assumptions within the model. These included the following factors of interest: baseline CAD prevalence (as described above); variation in sensitivity and specificity values; variation in probability of inconclusive results; and incorporation of CAD severity in the model. Probabilistic sensitivity analyses were also performed using Monte Carlo simulation and adopted standard methods for defining uncertainty around parameters. Transition probabilities were characterized by beta distributions. The costs of the different treatment strategies and cost-consequences associated with clinical outcomes were assigned gamma distributions. Costs and outcomes were calculated for each diagnostic strategy, as derived from 1,000 Monte Carlo iterations.

Results

Table 14 on the following page depicts the results for 1,000 adults with an underlying prevalence of CAD of 50%. Each column represents the results if all patients had undergone the specific screening strategy.

From the data in Table 14, it can be seen that there are important trade-offs to consider when comparing these strategies. For example, PET alone has the highest number of true positives at 464 and the lowest number of false negatives at 34 among all strategies. ETT \rightarrow PET has the highest number of true positives and lowest number of false positives among all 2-test strategies. However, PET (and SPECT) also carry radiation exposure risks for all patients. PET also had the highest cost per patient, with a cost of \$5,074.

		ETT	SPECT	PET	ETT → ECHO	ETT → SPECT	ETT → PET
True Positive, non-invasive	437	365	416	464	320	305	340
False Positive, non-invasive	163	194	130	111	64	51	43
True Negative, non-invasive	336	305	370	389	436	449	457
False Negative, non-invasive	61	133	82	34	178	193	158
Referred for angiography	603	562	549	578	386	358	386
Angiography negative results	163	194	130	111	64	51	43
Angiography related deaths	4	3	3	3	2	2	2
Exposed to radiation	603	562	1000	1000	386	562	562
Incidental findings requiring f/u	57	0	8	8	32	5	5
Total costs/patient [excluding all f/u costs, \$)	2538	1883	2987	5074	1737	1996	3204

Table 14.	Results from	patients with	high risk	(50%) of CAD.

ECHO: echocardiogram; ETT: exercise treadmill testing; PET: positron emission tomography; SPECT: single photon emission computed tomography

In comparing ECHO and SPECT, SPECT as a single-test strategy produces 21 more false negative results but 33 fewer false positive results. SPECT results in radiation for all patients, compared to 60% of patients who begin evaluation with ECHO. ECHO requires follow-up for incidental extracardiac findings in 57 patients, however, vs. 8 for SPECT. ECHO is also less expensive overall by approximately \$450 per patient tested. When combined with ETT in a 2-test strategy, SPECT still produces more false negatives and fewer false positives, but the differences with ECHO are much less, on the order of 13-15 patients per 1,000 evaluated.

Value judgments are required to evaluate the trade-offs in the outcomes of these different testing approaches. Some of these judgments include: whether false positives are more important than false negatives; the relative importance of differences in diagnostic accuracy and the costs of competing testing strategies; and the importance of radiation exposure.

Because the underlying CAD prevalence varies in different patient populations, we present Tables 15, 16 and 17 on the following pages depicting the result of the identical testing strategies for a population with 10%, 30% and 70% CAD prevalence.

Comparing these results to Table 14 demonstrates the importance of the underlying prevalence on the relative balance of false negatives, false positives, rates of referral to angiography, and costs. For example, among a patient population with a CAD prevalence of 10%, the difference in false negatives between SPECT and ECHO almost vanishes (4 per 1,000). In contrast, the difference in false positives between SPECT and ECHO in a population with 50% CAD prevalence was 33 per 1,000 but is increased to 60 per 1,000 when the underlying prevalence of CAD is only 10%. The relative differences in angiography referral, patients exposed to radiation, and costs also shift, emphasizing again the importance of value judgments to comparisons of the clinical and economic outcomes of these different testing strategies as simulated in this model.

	ECHO	ETT	SPECT	PET	ETT → ECHO	ETT → SPECT	$\begin{array}{c} \text{ETT} \rightarrow \\ \text{PET} \end{array}$
True Positive	87	73	83	93	64	61	68
False Positive	293	350	233	199	115	91	78
True Negative	605	548	665	700	785	808	822
False Negative	12	27	16	7	36	39	32
Referred for angiography	383	425	319	294	180	153	147
Angiography negative results	293	350	233	199	115	92	78
Angiography related deaths	2	3	2	2	1	1	1
Exposed to radiation	383	425	1000	1000	180	425	425
Incidental findings requiring f/u	57	0	8	8	24	4	4
Total costs/patient [excluding all f/u costs, \$)	1865	1464	2284	4206	1011	1191	2021

Table 15.	Results from	patients with	low risk	(10%) of CAD.
		r · · · · ·		(

ECHO: echocardiogram; ETT: exercise treadmill testing; PET: positron emission tomography; SPECT: single photon emission computed tomography

	ЕСНО	ETT	SPECT	PET	ETT → ECHO	ETT → SPECT	ETT → PET
True Positive	262	219	250	278	192	183	204
False Positive	228	272	182	155	89	71	61
True Negative	471	426	517	544	610	629	639
False Negative	36	80	49	20	107	116	95
Referred for angiography	493	494	434	436	283	256	266
Angiography negative results	228	272	182	155	90	71	61
Angiography related deaths	3	3	3	3	2	2	2
Exposed to radiation	493	494	1000	1000	283	494	494
Incidental findings requiring f/u	57	0	8	8	28	4	4
Total costs/patient [excluding all f/u costs, \$)	2201	1674	2636	4640	1374	1594	2613

Table 16.	Results from	patients with	intermediate risk	(30%) of CAD.
		P		(

ECHO, echocardiogram, ETT, Exercise treadmill testing; PET= Positron Emission Tomography; SPECT= Single Photon Emission Computed Tomography

	ECHO	ETT	SPECT	PET	ETT→ ECHO	ETT → SPECT	ETT → PET
	LCIIO		SILCI	111		JILCI	ILI
True Positive	611	510	582	649	449	427	476
False Positive	98	117	78	66	38	30	26
True Negative	202	183	222	233	262	269	274
False Negative	85	186	114	47	249	270	221
Referred for angiography	713	631	664	720	490	460	505
Angiography negative results	98	117	78	66	38	31	26
Angiography related deaths	4	4	4	4	3	3	3
Exposed to radiation	713	631	1000	1000	490	631	631
Incidental findings	. 10	001	2000	1000			
requiring f/u	57	0	8	8	36	5	5
Total costs/patient							
[excluding all f/u							
costs, \$)	2874	2092	3339	5507	2100	2399	3796

Table 17.	Results from	patients with	high risk ((70%) of CAD.
14010 177	Iteo alto II o III			

ECHO, echocardiogram, ETT, Exercise treadmill testing; PET= Positron Emission Tomography; SPECT= Single Photon Emission Computed Tomography

Sensitivity Analyses

We also conducted a number of sensitivity analyses in which we varied the diagnostic accuracy estimates for the different tests. For example, we ran one analysis using sensitivity and specificity values for ECHO and SPECT from an older but still influential meta-analysis reporting higher sensitivity for SPECT (87% vs. 85% for ECHO) and higher specificity for ECHO (77% vs. 64% for SPECT) (Fleischmann, 1998). The primary result of using these alternative estimates for sensitivity and specificity is to put ECHO and SPECT "on par" in the number of false negative results while creating a relative advantage of ECHO in the number of false positive test results. Total costs per patient were ~\$800 lower for ECHO vs. SPECT under these assumptions. Accordingly, ECHO emerges looking "better" in its comparative diagnostic relationship with SPECT (see Table E1 in Appendix E).

As described previously, we used diagnostic accuracy estimates for ECHO and SPECT from the de Jong meta-analysis (de Jong, 2012), which focused on recent diagnostic accuracy studies not subject to verification bias (i.e., the reference standard test was not performed in all patients). We used another meta-analysis to obtain available estimates for PET (Parker, 2012). While this analysis also included SPECT studies, verification bias could not be ruled out for all, and the timeframe for this meta-analysis (beginning in 1980) included many studies in which state-of-the-art imaging techniques were not employed. Nevertheless, pooled estimates for SPECT (88% and 76% for sensitivity and specificity respectively) were included in sensitivity analyses presented in Table E2 in Appendix E. The effect of these estimates is to produce small advantages for SPECT over ECHO in the number of false positives (a difference of 29 patients), and similar numbers of false negatives (61 vs. 56 for ECHO vs. SPECT respectively). Total costs were \$542 lower per patient for ECHO vs. SPECT.

Table E3 in Appendix E presents another sensitivity analysis we conducted using a "very low" CAD prevalence of 2% in the tested population, the low boundary of several other studies evaluating the potential effectiveness of nuclear imaging strategies (Priest, 2011). At a 2% prevalence, 2-test strategies starting with ETT gain significant advantages in reducing false positive test rates without a commensurate increase in false negative test results. The costs for 2-test strategies also are estimated to be two- to threefold less expensive than single test strategies given the much larger number of patients who receive an initial negative test result with the less expensive ETT and do not require further testing.

Results based on an ICER meta-analysis of SPECT and PET accuracy using a functional reference standard such as FFR can be found in Table E4 in Appendix E. Sensitivity and specificity estimates from this analysis were 74% and 79% respectively for SPECT and 84% and 87% respectively for PET. The difference in specificity between SPECT and PET is greater than in the basecase; as a result, SPECT produces 37 more false-positives in this analysis (vs. 19 in the basecase). Similar numbers of patients were referred for angiography, however; as a result, the reduction in cost for SPECT was only slightly less than in the basecase analysis (\$2,035 vs. \$2,087 for basecase).

Findings from probabilistic sensitivity analyses are presented in Table E5 in Appendix E. While estimates changed slightly for each testing strategy, the direction and magnitude of differences between strategies was very similar to the primary analysis.

Strengths and Limitations

There are a number of strengths of this study. First, clinical inputs were derived from systematic reviews that were based largely on recently-published underlying studies (2000 and onward if possible) and used statistical approaches that incorporated the correlation between sensitivity and specificity (i.e., bivariate models). Other decision models and economic evaluations in this area were based on accuracy estimates from meta-analyses that did evaluated sensitivity and specificity as distinct variables and/or included older studies of technically obsolete forms of nuclear imaging tests (Hayashino, 2004; Kim, 1999). Second, our analysis followed a transparent and accepted methodology and largely adheres to the International Society of Pharmacoeconomics and Outcomes Research Consolidated

Health Economic Evaluation Reporting Standards (CHEERS) Statement (Husereau, 2013). Third, wherever possible, the model used costing data reflective of the Washington Health Care Authority experience. Finally, detailed sensitivity analyses were performed to examine the robustness of results to variation in model parameters and assumptions.

Despite its strengths, this analysis has certain limitations that warrant discussion. First, and perhaps most importantly, available data were insufficient to design a model based on detection of functionally-important ischemia. As with previous decision models, we were required to rely on estimating test accuracy based on anatomic angiography findings. As described previously, the correlation between anatomic evidence of stenosis and presence of functionally-important ischemia is quite weak. However, it is also the case that use of anatomic data from angiography still informs a substantial percentage of treatment decisions, even in the presence of functional data from non-invasive tests (Chan, 2011).

Even with a focus on anatomic reference standards, we were unable to identify a single systematic review and meta-analysis which considered all of our treatment strategies simultaneously, used recently published data, and was based on a bivariate statistical model. Therefore, we were forced to use different sources for different treatments. We did conduct detailed sensitivity analyses to adjust for potential heterogeneity across data sources, as well as to use alternative estimates of test accuracy, however.

Second, the results of studies on diagnostic test accuracy for CAD are often reported as a 2×2 classification matrix (Shinkins, 2013). This is problematic because restricting test results to be either positive or negative fails to represent the complete reality of how they are used in clinical practice, where there is a probability that the test is inconclusive and different clinical decisions may in fact be made on the basis of whether results are "mildly, moderately, or severely" abnormal (Shinkins, 2013). To account for this issue, we were forced to derive estimates for the probability of inconclusive tests from alternative sources.

Third, to enhance transparency we adopted a simplistic decision model which does not account for the severity of CAD. We opted for this simplistic approach because we had limited data to populate sensitivity, specificity, and the probability of inconclusive results for all of the strategies when the decision model was stratified by severity of CAD. Nevertheless, the model is adaptable and does allow one to consider disease severity if robust data become available to populate these parameters (see Figure D2 in Appendix D). This simplistic approach also precluded us from incorporating all of the permutations of testing that may occur in clinical practice, such as use of pharmacologic stress in patients unable to exercise and/or in those who do not achieve target heart rate, and restarting the test (or referral to another test) due to technical failure or problematic image acquisition. Even if data on these concerns were available for all of the testing strategies of interest, however, it is likely that their inclusion would have affected the magnitude of our findings rather than their direction.

RECOMMENDATIONS FOR FUTURE RESEARCH

As documented in this appraisal report, published literature suggests that cardiac nuclear imaging tests are accurate and safe non-invasive tests that provide important diagnostic and prognostic information for certain patient populations. However, the available evidence on SPECT and PET is limited with respect to measurement of the direct impact of these tests on clinical decision-making and patient outcomes in comparison to other common non-invasive alternatives such as ETT and ECHO. Evidence gaps are particularly pronounced in certain populations, such as asymptomatic individuals with high levels of CAD risk and populations with known CAD, whether asymptomatic or under evaluation for changes in symptoms. There is also little to no evidence available on patterns of test utilization after an initial "point-in-time" examination – for example, what proportion of patients with a false-negative nuclear imaging test have a subsequent major cardiovascular event as opposed to having their symptoms lead to later testing and successful clinical management?

Informed by the evidence gaps highlighted by our systematic review, we present below recommendations for research on cardiac nuclear imaging for coronary artery disease diagnosis and prognosis.

- 1. New RCTs should compare multiple diagnostic strategies in broadly representative populations across a variety of clinical settings with relatively few exclusions. For example, all patients with symptoms consistent with ischemia who are being considered for non-invasive testing, regardless of pretest probability and type of symptoms, could be included in a pragmatic trial design intended to reflect use of these tests in clinical practice. The few RCTs that have been conducted to date include either very specific populations or heterogeneous groups not sufficiently sized to perform appropriate subgroup analysis. Future RCTs will necessarily have to be large, however, in order to capture differences in major cardiovascular events and other important patient outcomes as well as to inform subgroups defined by CAD risk, symptoms, comorbidities, and other key factors.
- 2. Other prospective study designs should provide a complement to RCT data by focusing on the impact of cardiac nuclear imaging tests on treatment decisions. These studies would be useful given that the conduct of large multicenter RCTs is an expensive and time-consuming undertaking. While studies such as the SPARC registry provide some information on treatment changes after non-invasive testing (Hachamovitch, 2012), this information does not involve any comparison to decision-making without the test information. Examples of such studies from our review include an evaluation of potential angiography referral based on algorithms derived from ETT data alone, SPECT data alone, or both tests (Muzzarelli, 2010) as well as a comparison of planned vs. actual patient management before and after PET perfusion testing (Siegrist, 2008). Expansion of such study designs to multiple centers and patient populations would yield potentially useful information.

- 3. Long-term cohort studies should be designed to provide information on both resource utilization and radiation exposure in patients receiving cardiac nuclear imaging tests. There are a variety of poorly-understood outcomes from available studies of cardiac nuclear imaging, including long-term rates of re-testing and the cumulative effects of radiation exposure on rates of secondary malignancy. For the former, an assessment of imaging frequency and its association with cardiac event rates could inform future comparative studies to identify the best intervals for serial imaging strategies. For the latter, comparisons of malignancy rates between clinically and demographically similar populations with greater or lesser exposure to imaging radiation would provide more granular information than the speculative approaches currently taken. There will be a strong need to control for other malignancy risks and radiation exposures in such designs, however.
- 4. Future diagnostic accuracy studies on cardiac imaging should report test failures using a "3x2" classification table rather than the classic 2x2 design (Shinkins, 2013). As with many other diagnostic tests, studies assessing the diagnostic and prognostic performance of cardiac nuclear imaging tests do not routinely report the number of "test failures" due to mechanical concerns, patient refusal, and equivocal and/or other non-diagnostic results. This is far from ideal, as such failures require re-testing or referral for other testing in actual clinical practice. Such data could be used to inform alternative estimates of diagnostic accuracy (i.e., with vs. without test failures reported) to provide full information on the possible range of performance.
- 5. Collection of data on downstream resource utilization and costs should be included in the design of broad-based multicenter RCTs such as those described in point #1. Relatively few studies have directly compared the economic impact of different cardiac non-invasive testing strategies. Data gathered as part of RCTs would be preferable, but even nonrandomized studies, such as those employing large administrative or clinical databases, could prove useful in this regard as long as steps were taken to ensure that strategies evaluated involved populations that were clinically comparable at baseline (or if not, differences could be controlled for statistically).

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