Washington State Health Care Authority

Health Technology Assessment

Cardiac Nuclear Imaging

Draft Key Questions – Public Comments

April 29, 2013

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Cardiac Nuclear Imaging

Draft Key Questions
Public Comment and Response

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Response to Public Comments

The Institute for Clinical and Economic Review (ICER) is an independent vendor contracted to produce evidence assessment reports for the Washington HTA program. For transparency, all comments received during the public comment period are included in this response document. Comments related to program decisions, process, or other matters not pertaining specifically to the draft key questions, project scope, or evidence assessment are acknowledged through inclusion only.

This document responds to comments from the following parties:

Draft Key Questions

- Neal S. Perlmutter, MD, FACC, Nuclear Cardiology Director, Overlake Medical Clinics and Chair, Advocacy Committee, Washington Chapter, American College of Cardiology; Kathleen B. Flood, Chief Executive Officer, American Society of Nuclear Cardiology; M. Eugene Sherman, MD, FACC, Chair, Advocacy Steering Committee, American College of Cardiology; and Frederic H. Fahey, DSc, President, Society of Nuclear Medicine and Molecular Imaging

- Neal S. Perlmutter, MD, FACC, Nuclear Cardiology Director, Overlake Medical Clinics and Chair, Advocacy Committee, Washington Chapter, American College of Cardiology

- James H. Caldwell, MD, FACC, FAHA, Director of Nuclear Cardiology, UW Medicine; Marko Yakovlevitch, MD, FACP, FACC, Clinical Assistant Professor of Medicine, UW Medicine; William P. Shuman, MD, FACR, Vice Chairman and Professor, Department of Radiology, University of Washington School of Medicine; and Hubert Vesselle, MD, PhD, Director of Nuclear Medicine, UW Medicine

	Comment	Response
Neal S. Perlmutter, MD, FACC, Nuclear Cardiology Director, Overlake Medical Clinics and Chair, Advocacy Committee, Washington Chapter, American College of Cardiology; Kathleen B. Flood, Chief Executive Officer, American Society of Nuclear Cardiology; M. Eugene Sherman, MD, FACC, Chair, Advocacy Steering Committee, American College of Cardiology; and Frederic H. Fahey, DSc, President, Society of Nuclear Medicine and Molecular Imaging		
1	We would like to highlight the paper Appropriate Use Criteria for Cardiac Radionuclide Imaging, published in JACC Vol. 53, No 23, 2009 (June 9, 2009, pages 2201-29), which is enclosed. This paper primarily covers SPECT MPI and Cardiac PET and reviews appropriate imaging use, defined by clinical indication (Tables 1-8. Pages 2207-2210). The paper also classifies the indication based upon appropriate use (Tables 9-11, pages 2211-2214), with all Appropriate indications listed first, Uncertain indications listed second, and Inappropriate indications listed last. This paper should answer the majority of the commission's concerns and questions about imaging selection in patients.	*Thank you for your comments. No changes to key questions. Relevant guideline and appropriate use statements such as the paper cited will be summarized as part of the evidence synthesis.*
2	It should be noted that, under provisions of the Affordable Care Act, all laboratories which perform MPI now must be accredited by the Intersocietal Accreditation Commission (IAC), the American College of Radiology (ACR), or the Joint Commission. These accreditation processes include mandatory assessment of inter and intra-observer variability, as well as assessment of the noninvasive imaging compared to coronary angiography, in patients who have undergone both procedures. There are also standardized requirements for imaging report content and display, with emphasis on reducing the number of equivocal interpretations. Similar requirements are in place for echocardiography laboratories.	*Thank you for this reference. In addition to guideline and appropriate use statements, we will also plan to cite all available publications on training, competency, and accreditation standards.*
3	Sensitivity and Specificity-- There are a large number of papers which look at this issue, and the "gold standard" for comparison is generally invasive coronary angiography. Head to head comparisons of MPI vs. stress echo in the literature tend to include only patients who have a clinical indication to undergo invasive coronary angiography. In these studies, invasive angiography determines which of the noninvasive tests is "correct." This approach has several limitations. First, patients already selected for invasive angiography on clinical grounds have a much higher likelihood of obstructive coronary disease than those undergoing testing in an office setting. Patients with a negative study most often are reassured in practice, and seldom then also undergo angiography. A proper outcome for patients with a negative test might be "percent	*We have reworded key question 1 to focus on issues of patient management and clinical outcome, due in part to the limitations stated here. Comparative evidence on diagnostic accuracy will be considered only when the reference standard provides functional information (such as FFR). Historical data using anatomic reference standards will be included for background purposes only.*

	Comment	Response
	event free at 3 years," though this is an exceedingly difficult assessment to make in patients who will not be having regular cardiac follow up. Second, invasive angiography is an anatomic test, whereas MPI and stress echo are physiologic tests. Angiography will often identify a stenosis in the range of 50-70%, which is considered equivocal on anatomic grounds. Multiple studies have shown that MPI is more likely to demonstrate ischemia in such territories, as compared to stress echo. Though fractional flow reserve (FFR) assessment can be done at the time of angiography, and this does provide a functional assessment of whether such lesions are flow limiting, currently we are not aware of any literature comparisons which have utilized this technology to compare the results to those of stress echo or MPI.	
4	Incidence of indeterminate or equivocal test findings—The true incidence is unknown, but has improved with both stress echo and MPI in recent years. Under both current laboratory accreditation standards, reporting of indeterminate or equivocal studies is strongly discouraged. Echo studies are more often of less than ideal quality than are MPI studies, though literature numbers are lacking.	*As with all other outcomes of interest, we will record data on indeterminate and/or equivocal findings where reported.*
5	Frequency of incidental findings (outside the heart)—This is not known precisely, but is uncommon with both technologies. MPI will occasionally pick up abnormalities in the thyroid and the lungs, which most often represent real pathology, modifying treatment when further studied. Echo imaging will occasionally identify liver or renal cysts, which are usually benign and do not require further study. Pleural effusions are often seen by echo. Echo does, of course, find other cardiac abnormalities unrelated to coronary disease, such as chamber enlargement, ventricular hypertrophy, pericardial effusion, or valvular heart disease. Echo would be the preferred imaging modality in evaluation of ischemia, if any of these other abnormalities are also suspected or also require evaluation.	*As above, we will record data on incidental findings where reported.*
6	Use of downstream and follow up testing, incidence of major cardiovascular events, as well as cardiovascular related and all cause mortality, and test as well as total diagnostic strategy utilization and costs.-- Both stress echo and MPI testing have relatively good downstream and follow up testing records. Both generally will answer the questions of whether the presenting symptoms are related to coronary disease, whether coronary angiography is required, and if so, whether medical, interventional, or surgical therapy is appropriate long term. Differences may be imputed based upon the above head	*Thank you for this information. We will seek to identify studies that have examined the impact of the testing strategies of interest on all of these outcomes, with particular attention to recording the settings of interest that have been noted.*

	Comment	Response
	to head comparisons (favoring MPI), though direct comparisons on future utilization are lacking in the literature. When a patient fails to achieve target heart rate during stress echo testing, the test is considered non-diagnostic, and the patient is usually referred for pharmacologic stress imaging, usually with MPI. When a similar circumstance arises during exercise MPI, the radionuclide is not injected at peak exercise, the patient is converted to pharmacologic stress imaging in the same immediate setting, and there is no increase in radiation exposure or any substantial increase in testing time. Thus stress echo does have downstream utilization in this limited setting, where MPI does not.	
7	Expecting one DIAGNOSTIC test to have a superior effect on improving major cardiovascular events, or CV or all-cause mortality, is extremely unrealistic, is not a standard utilized for assessing a DIAGNOSTIC test in any other field, and to our knowledge, no investigator has attempted to perform such an appropriately powered assessment in the literature. There are simply too many other variables involved affecting these outcomes (which cannot be controlled), beyond the initial imaging test which starts the process. The same is true of total diagnostic strategy utilization and costs.	*This is an important issue. Our review will not be based on an expectation that there will be evidence demonstrating the impact of diagnostic or prognostic tests on clinical management or patient outcome; our task is to seek out what evidence does exist and present it to the decision-making body. There are, however, good examples of published studies demonstrating the impact of diagnostic imaging on clinical management and patient outcomes, such as studies on the impact of CCTA on ED decision-making and clinical outcomes for patients with acute chest pain. The level of evidence judged necessary to demonstrate the clinical benefits of nuclear cardiac imaging will be determined ultimately by the Clinical Committee. General methodological guidance on this issue, however, suggests that randomized controlled trials focusing on patient outcomes are desirable whenever tests may differ in the spectrum of patients identified as "diseased" (e.g., MPI vs. ECHO for vessels with 50-70% stenosis), or when tests vary widely in other aspects of accuracy (Lord, 2009).* *The need for evidence on improved patient outcomes from diagnostic tests has also been highlighted in a recent paper conducted on behalf of the new Patient-Centered Outcomes Research Institute (Gatsonis, 2012). Finally, we note that RCTs do exist that compare strategies for*

	Comment	Response
		diagnosing CAD and are powered based on clinical outcomes; for example, a recent RCT compared treadmill testing to MPI in women with suspected CAD with a primary endpoint of MACE-free survival at 2 years (Shaw, 2011).
8	DRAFT KEY QUESTIONS 1) What is the diagnostic accuracy as well as the impact on patient outcomes and clinical decision making of PET, SPECT MPI, and relevant combination modalities relative to stress echo when used for myocardial perfusion testing to detect clinically significant CAD?	
9	Most of these are addressed in the above discussion. Combination modalities such as PET/CT MPI have been shown to be superior to non-attenuation corrected SPECT MPI, but are rarely used in Washington, and so are not addressed here. Again, in the detection of CAD or myocardial ischemia, comparisons of the sensitivity and specificity of stress echo and MPI tend to favor MPI, as described above.	*Thank you for your comments. We will evaluate the evidence on all tests determined to be in our review scope, including combination modalities, as limited as such evidence may currently be.*
10	It is important to note the terminology used in this question is not correct. Exercise radionuclide imaging is a form of myocardial perfusion imaging, as is PET and cardiac MR perfusion imaging. Stress echo testing attempts to produce exercise induced wall motion abnormalities in patients with obstructive coronary disease, but does not directly assess myocardial perfusion. All of these tests are noninvasive tests designed to detect myocardial ischemia, however.	*We have modified the description of each test of interest to accurately reflect its use and diagnostic approach.*
11	2) What are the documented and potential harms associated with these tests, including contrast and radiotracer reactions, patient anxiety, radiation exposure, renal damage, and incidental findings? Neither stress echo testing nor MPI utilize iodinated or other contrast material routinely. Stress echo occasionally uses albumin based contrast in patients with poor image quality. This contrast material is generally safe (though prior versions did have safety concerns), but not inexpensive. The need to place an iv for echo contrast (normally not required for a stress echo test) limits its utilization. Radionuclide tracer reactions are rare—indeed we do not believe we have ever seen one in practice. Patient anxiety is minimal with both technologies, particularly given the advances in MPI camera and improved gantry and upright imaging with some of the newer scanner designs in recent years. Claustrophobia is not common, as is often seen in MRI. Neither carries risks of renal damage.	*Thank you for your comments. The harms listed in the key question are examples. We will identify all reported harms from available studies.*

	Comment	Response
	imaging is associated with radiation exposure (generally about 10-12 mSv), whereas stress echo is not. As the application of new technology within the imaging equipment improves, MPI radiation exposure may potentially be reduced to 6-8 mSv in the next few years. Overall, MPI radiation exposure is generally greater than that associated with invasive coronary angiography, and comparable to that seen for advanced cancer imaging studies. Clinicians should make efforts to avoid repeating studies to limit radiation exposure. Literature studies imply a longer "event free warranty period" after MPI (usually about 1 year in patients with prior CAD and as much as a median of 5 years for patients without prior CAD (Carryer et al Circulation: Cardiovascular Imaging. 2010; 3: 520-526)) than after stress echo testing. Current MPI imaging generally uses technetium based agents, which provide lower radiation exposure than is seen with older thallium agents, which are generally not recommended.	
12	A responsible and appropriate means of patient education should place radiation in its proper context. Radiation is an unavoidable part of daily life due to varying levels of background exposure from natural sources including radionuclides in our bodies, cosmic rays, ground sources, and radon. While unnecessary radiation exposure is clearly unwelcome, we note the appropriate use of low levels of radiation in medical procedures is integral to the current state of cardiovascular care. When nuclear cardiology tests are appropriate, the benefits of accurate diagnosis and management are greater than the potential risk from radiation exposure. Effective diagnosis and treatment of cardiovascular disease often requires some exposure to radiation. Therefore, the goal should be ensuring appropriate use rather than the outright elimination of radiation exposure. Moreover, we assert this standard is not to be applied broadly. Rather, the risks and benefits must be evaluated in the context of an individual clinical scenario. When a procedure is appropriate, providers should minimize exposure while maintaining image quality.	*Thank you for your comments. No further changes to key question 2.*
13	3) What is the differential effectiveness and safety of the tests of interest according to such factors as age, sex, race, or ethnicity, comorbidities (e.g. obesity), tested population (e.g. suspected vs. known CAD), underlying prevalence of CAD, presence of multi-vessel disease, stenosis threshold, scan vendor, type of assessment (i.e. quantitative vs. qualitative), type of radioisotope, and type of stressor (e.g. adenosine, exercise)?	*Thank you for your comments. No further changes to key question 3.*

	Comment	Response
	Age, sex, race, ethnicity—Overall, no significant differences between stress echo and MPI are demonstrated in the literature. Women have a higher incidence of "false positive" exercise ECG findings than do men, but both stress echo and nuclear imaging improve upon this to a probably similar degree. Elderly patients, as a group, are less likely to be able to exercise and achieve target heart rate than are younger patients. For those unable to exercise, pharmacologic stress imaging with MPI is preferred to pharmacologic stress echo testing with dobutamine. Pharmacologic stress echo imaging (with dobutamine) generally is more time consuming, requires the presence of the provider during the test, is associated with more side effects, and requires a longer recovery. Logistics generally prevent one from being able to convert an exercise echo test into a pharmacologic test immediately, whereas that is usually possible with MPI. For patients with resting wall motion abnormalities of any type, MPI imaging is also preferred. Comorbidities (obesity, diabetes)—MPI is generally preferred in obese patients, as image quality is less compromised that is often seen with stress echo. Techniques such as PET myocardial perfusion imaging can be of value in these individuals. Several studies have demonstrated MPI to have superior sensitivity in diabetics (as compared to nondiabetics). It is not clear whether this finding reflects the higher frequency of coronary disease (and single vessel disease) in the diabetic population, or is related to other imaging factors. Resting ECG abnormalities—Patients with left bundle branch block, pacemakers, and ICDs should generally undergo pharmacologic stress MPI imaging to reduce the incidence of imaging artifacts, and there is general agreement this approach is superior to stress echo testing, as well as exercise MPI. Patients with resting wall motion abnormalities, such as prior MI or cardiomyopathy, should also generally undergo MPI imaging, since MPI does not depend upon wall motion for diagnosis. Suspected vs. known CAD, single vs. multi-vessel disease—patients with known CAD have a higher incidence of single vessel disease, and MPI has an advantage in sensitivity in these patients, as compared to stress echo. Patients with prior MI or other known wall motion abnormality also have an incremental benefit with MPI. Underlying prevalence of CAD—Both MPI and stress echo	

	Comment	Response
	imaging are best utilized in patients with an intermediate pre-test probability of disease, and differences between the two are not apparent. Stenosis threshold-- Multiple studies have shown that MPI is more likely to demonstrate ischemia in territories with a 50-70% stenosis at angiography, as compared to stress echo. Scan vendor—If the imaging equipment meets specifications required by the accreditation bodies (ICANL or ACR for MPI, ICAEL for echo), no differences would be anticipated. Quantitative vs. qualitative assessment—Most software for MPI studies provides both quantitative and qualitative analysis, and both are generally utilized by the interpreting physician in finalizing the study interpretation. True quantitative analysis with stress echo testing is uncommon. Differences between the MPI and stress echo are not anticipated on this basis. Type of radioisotope—MPI generally uses technetium based agents, generally sesta MIBI (Cardiolite) and tetrofosmin (Myoview). Pricing is generally competitive and determined by institutional contract. There is no general agreement that the two agents differ in sensitivity or specificity. Tetrofosmin is associated with more rapid hepatic clearance, which can result in faster imaging times in some patients. Outcome differences would not be anticipated, however. Type of stressor (pharmacologic vs. exercise)—In patients who are able to exercise, MPI testing with exercise is preferred, due to the ancillary information which one obtains (presence of angina, heart rate and BP response, exercise capacity, presence of exercise induced ECG changes, presence of exercise induced arrhythmias). Patients with left bundle branch block, pacemakers, and ICDs should generally undergo pharmacologic stress imaging (rather than exercise imaging), due to a lower incidence of artifacts related to intraventricular conduction delay. Patients with a mobility assistance device (cane, wheelchair, walker), or who demonstrate difficulty ambulating from a chair to an exam table, generally should undergo pharmacologic stress imaging.	
14	4) What are the costs and cost-effectiveness (e.g. cost per correct diagnosis, cost per cardiovascular event averted) of the imaging modalities of interest? MPI is more costly than stress echo imaging, generally about 1.5 to 2 times more	*Thank you for your comments. No changes to key question 4.*

	Comment	Response
	costly. Specific costs to Medicare, Medicaid and third party payers are readily available. Total patient testing time is also longer with MPI (about 3-3.5 hours with MPI, vs. 1-1.5 hours with stress echo). In the circumstances outlined above, MPI offers imaging advantages in terms of accuracy. However, analyses such as cost per correct diagnosis are generally not performed, due to the limitations described above (see "Outcomes of Interest—Sensitivity and Specificity", paragraph 2). It is not at all realistic to expect a DIAGNOSTIC test to demonstrate the ability to avert cardiovascular events, it is less realistic to calculate a cost per cardiovascular event averted, and less realistic still to expect such a calculation to be available for direct comparison between two diagnostic tests.	
15	Summary Both stress echo and nuclear myocardial perfusion imaging remain excellent diagnostic tests for determining the presence or absence of obstructive coronary disease, as well as a variety of other indications related to cardiac risk. Both have Appropriate Utilization Criteria (AUC) which have been rigorously developed, have been endorsed by multiple specialty societies, and have been utilized by the physician and the payer community successfully for years. In some states, adherence to these AUC is all that is required for imaging reimbursement and pre-authorization is not required. In Washington, many payers require pre-authorization for these imaging studies, which are based upon these AUC, and these approval processes generally work well. Most are on line, approval is relatively prompt, denials are rare, and direct physician to physician discussion is seldom required. When a patient is referred to a cardiology office for imaging, and documentation of AUC is inadequate, most cardiology offices require cardiology consultation before an imaging request is submitted for approval. These AUC have reduced inappropriate utilization of imaging dramatically, particularly since older practices (such as annual testing of patients with established CAD but no symptoms) have been declared inappropriate. There are certainly circumstances where patients referred for imaging may meet AUC for both stress echo and myocardial perfusion imaging. Selecting the appropriate test in these circumstances is generally best left to the ordering physician, using the factors described above, along with their knowledge of the individual patient. We disagree with the WSHCA attempting to define a selection algorithm between two appropriate and indicated tests, and ask that algorithm to	*Thank you for your comments. No further changes to key questions.*

	Comment	Response
	improve upon the judgment of the ordering physician, while lowering costs and improving outcomes. To date, such an algorithm has not yet been published in the literature, has not yet been developed or implemented in any jurisdiction, and has certainly not been prospectively validated. We would therefore feel such a development at this time appears unwise.	
Neal S. Perlmutter, MD, FACC, Nuclear Cardiology Director, Overlake Medical Clinics and Chair, Advocacy Committee, Washington Chapter, American College of Cardiology		
1	*[complete comments are included following table of responses]*	*As Dr. Perlmutter's individual comments appear to be essentially identical to the comments submitted by multiple specialty societies above (of which Dr. Perlmutter is a co-author), no separate response to comments is provided.*
James H. Caldwell, MD, FACC, FAHA, Director of Nuclear Cardiology, UW Medicine; Marko Yakovlevitch, MD, FACP, FACC, Clinical Assistant Professor of Medicine, UW Medicine; William P. Shuman, MD, FACR, Vice Chairman and Professor, Department of Radiology, University of Washington School of Medicine; and Hubert Vesselle, MD, PhD, Director of Nuclear Medicine, UW Medicine		
1	We object to the statement "The comparator test of interest will be stress echo, the historical standard for visual assessment of myocardial perfusion". In our mind, this statement reflects the biases of the group who wrote the key questions. SPECT myocardial perfusion is the historical standard for visual assessment of myocardial perfusion and has been for the past 30 years. a. Stress echo as performed in routine clinical settings does not assess myocardial perfusion. It uses the development of abnormal systolic myocardial contraction as a reflection of abnormal perfusion. The sensitivity/specificity of this technique is enhanced by visualization of the LV cavity by contrast. Myocardial perfusion assessment with contrast echo is still considered mostly a research technique and not routinely used in most echo laboratories. Only radionuclide or cardiac magnetic resonance imaging (CMR) with contrast measure perfusion routinely and directly.	*Thank you for your comments. We have reworded the description of the comparator section to reflect the inclusion of stress ECHO and ETT as other common non-invasive tests to assess myocardial ischemia, without reference to any historical standard.* *We have corrected this description in the text.*
2	We object to the statement "Fractional Flow Reserve (FFR) is the gold standard for myocardial perfusion measurements". FFR is one method for measuring the ratio of stress blood flow	*Thank you for your comments. This has been clarified in the text.*

	Comment	Response
	to rest blood flow. Quantitative rest/stress PET and rest/stress CMR both measure the same concept, just express the values differently. FFR was originally validated against PET in the clinical arena.	
3	The concept of determining prognosis as a result of imaging is totally ignored in this review and is a major limitation of the Scope since understanding the extent and severity of myocardial ischemia is just as important as the diagnosis of coronary artery disease (CAD). Prognostic information guides further evaluation and therapy and prevents unnecessary procedures and provides cost savings.	*Key question 1 has been revised to clarify the populations and uses of these tests of interest for this evaluation, including prognosis.*
4	The entire concept of diagnostic accuracy and the "gold standard" of stenosis severity for comparing a non-invasive test to an invasive one is a false one. As has been shown in the FAME trial and by Naya et al, among others, that stenosis severity does not equal physiology except when the stenosis is > 90% and even then there is not a perfect correlation (see Figure 1 in Tonino 2010). Moreover, physiology is more important than anatomy with regard to outcomes (death/myocardial infarction). The investigator who established the general relationship between coronary stenosis severity and its effect on myocardial blood flow believes physiology should be the gold standard. Thought leaders within the cardiology community believe we need to move away from "critical" coronary stenosis to the most central concept of myocardial ischemia.	*We have revised the scope to incorporate this change of thinking. As noted previously in response, diagnostic accuracy studies will now only be included if a functional reference standard is used; historical data based on anatomic reference standards will be included for background purposes only, and the change in conceptual thinking will be highlighted in the review.*
5	CT angiography has very high negative predictive value for excluding CAD in low-intermediate risk populations as demonstrated in multiple studies. However, in intermediate or higher risk populations, that positive predictive value is limited. CT angiography can be combined with PET myocardial perfusion to provide excellent diagnostic accuracy. In a study by Kajander et al, using an intermediate (30% to 70%) pretest likelihood of coronary artery disease population and invasive FFR as the unifying standard, PET and CT angiography alone both demonstrated 97% negative predictive value, CT angiography alone was suboptimal in assessing the severity of stenosis (positive predictive value, 81%). Perfusion imaging alone could not always separate microvascular disease from epicardial stenoses, but hybrid PET/CT significantly improved this accuracy to 98%. The radiation dose of the combined PET and CT protocols was 9.3 mSv with prospective triggering.	*We will continue to seek evidence on hybrid modalities, such as the study cited here. We will continue to exclude from our scope studies focused solely on tests that provide anatomic information only (e.g., CT angiography).*

	Comment	Response
6	No review of coronary CT angiography perfusion has been done since it is currently very much a research effort.	*Thank you for your comments. CT perfusion testing has been excluded from our scope given its status as an emerging technology.*
7	A summary of the diagnostic accuracy of SPECT, PET, cardiac MR and stress echo might conclude that one can do a meta-analysis that supports the author's biases. A more generous summary would be that on the basis of currently available and widely used technology, PET and cardiac MR are probably a little better than SPECT and Echo.	*No further changes to key question 1.*
8	2. Documented and Potential Harms: a. Stress modalities: i. Nuclear (SPECT) and echo can use exercise, vasodilator and dobutamine for stress agents. Exercise can be used with PET (at the expense of losing the ability to quantify absolute myocardial blood flow and flow reserve) but generally vasodilator or dobutamine are the preferred stress agents. CMR can only use vasodilator or dobutamine stress. The risks of these agents do not vary among modalities. Selection of which stressor to use depends on the individual patient. Those with LBBB, ICD's for example should have vasodilator stress rather than exercise or dobutamine because of false positives that can occur with LBBB or ICD discharges at high heart rates. b. Radionuclide myocardial perfusion tracers: i. There is no documented or potential direct physical harm from the radionuclide radiotracers and in the concentrations (tracer doses) used for myocardial perfusion imaging. ii. There is no short-term radiation risk for the clinical myocardial perfusion imaging tracers, i.e. no-skin burns or other soft tissue damage that can occur with CT or coronary angiography done improperly. There is a theoretical cancer risk from radiation used in cardiac imaging. Radiation dose is one of the cancer risk components and depends in part on the radiotracer used. 1. For a low/high dose SPECT scan using 99mTc-tracer which would be the standard protocol for an individual with a normal or minimally abnormal body mass index (BMI) radiation dose would be 10-15 mSv. For reference background radiation dose in the Pacific Northwest is ~ 3 mSv. 2. For a 2 day high dose rest/stress using 99mTc-tracer, 13-18 mSv. 3. Rest/Stress 13N-NH3 PET: 3-4 mSv including the low dose CT scan used for attenuation correction.	*Thank you for your comments. No further changes to key question 2.*

	Comment	Response
	4. Rest/Stress 82Rb PET: 10-15mSv including low dose CT for attenuation correction. 5. Rest/Stress 201Tl or rest 201Tl /Stress 99mTc-tracer studies should probably not be used because of the higher radiation dose associated with the 201Tl. 6. Solid-state detector imaging cameras for the 99mTc-tracers are entering the clinical practice of Nuclear Cardiology. These cameras reduce the radiotracer dose required by 2-3 fold with concomitant reduction in radiation dose down to the 2-4mSv range or a 3-4 fold decrease in imaging times. There is no loss of diagnostic accuracy with these cameras. For some of the devices, images can be acquired with the patient sitting which improves patient comfort. iii. Theoretical Cancer Risk: 1. Cancer Risk can be estimated by using a number of different assumptions although there is little/no data to demonstrate that there is a true event rate. Using a readily available tool (http://faculty.washington.edu/aalessio/doserisk2/index.html) representative Lifetime Attributable Risk (LAR) of developing cancer and cancer mortality for a 40 and a 60 y/o female and male are shown for rest/stress MPI using the radiation doses for 99mTc-tracer and 13N-NH3 but as can be appreciated are incredibly low, particularly when used appropriately. c. There is no radiation risk from stress echo or stress CMR. However, there is a small risk associated with the contrast agents frequently used with echo in order to have adequate myocardial visualization and are required for stress CMR imaging. i. For echo, complications from the contrast agents are uncommon but can occur. 22 There have been too few stress perfusion image echo studies done to have an assessment of any associated risks. ii. For cardiacMR, the risks (excluding the standard exclusions for MRI such as pacemakers, ICDs' and other implanted devices) are largely those of Nephrogenic Systemic Fibrosis from the Gadoliniumbased contrast agents in patients with chronic kidney disease (CDK). Risks of NSF increases significantly in patients with Stage 3 and above CKD. Incidence is approximately 5 % in those with Stage 5 CKD.	
9	3. Differential Effectiveness a. Gender Differences: Early studies suggest there might be gender differences in the diagnostic accuracy of both stress MPI and stress echo. Recent studies, including a meta-analysis	*Thank you for your comments. No further changes to key question 3.*

	Comment	Response
	suggest this is not the case. b. Age Effect: A recent meta-analysis of stress MPI and stress Echo in patients > 65 (mean 75.5 yrs) found that an abnormal stress MPI had an almost 4 fold higher ability to predict cardiac death and/or non-fatal myocardial infarction than did stress echo. Abnormal compared to normal stress MPI odds ratio (OR) is 11.8 (95% confidence interval [CI] 7.5 to 18.7) compared with stress echocardiography OR 3.2 (95% CI 2.6 to 3.9). c. Obesity: Although in the early days of stress MPI using thallium, the belief was that sensitivity/specificity was reduced in the obese compared to more normal BMI. More recent SPECT studies using 99mTc-tracers indicate no difference. Moreover, the new detector technology with improved sensitivity and spatial resolution demonstrates excellent results even in the morbidly obese (mean MBI 39+/-7 kg/m2.28 PET is even better in this population demonstrating a significant improvement in diagnostic content in patients with equivocal SPECT (see Table 6 in Yoshinaga reference. Dobutamine stress Echo with cavity contrast can also be performed in a significant fraction of this population. However, we are unaware of studies providing sensitivity/specificity data. d. Hypertensive populations: A recent meta-analysis of stress MPI and stress Echo (compared to coronary angiography) for detecting CAD in hypertensive patients found that stress MPI had a sensitivity of 0.90 [95% confidence interval (CI) 0.82-0.95] and a specificity of 0.63 (95% CI 0.53-0.72). For stress MPI, the area under the curve (AUC) at the summary receiver-operating characteristic (SROC) graph was 0.83 (95% CI 0.80-0.86). Stress echocardiography had a sensitivity of 0.77 (95% CI 0.69-0.83) and a specificity of 0.89 (95% CI 0.83-0.93). For stress echocardiography, the AUC at SROC was 0.91 (95% CI 0.88-0.93). e. Qualitative vs Quantitative Assessment: See comments under Diagnostic Accuracy	
10	4. Cost Effectiveness Data on cost effectiveness remains somewhat limited for all modalities. Perhaps the best are summarized as follows. a. Summary from 2010 analysis by the Ontario Canada Health Technology Assessment Service states “stress echo is generally not cost-effective in comparison to other non-invasive strategies for the diagnosis of CAD in either stable outpatients or acute inpatients. Stress echo appears cost effective only in specific situations where other more cost-effective technologies are unavailable”. The same group stated “stress echo with contrast has a higher diagnostic accuracy in the	*Thank you for your comments. No further changes to key question 4.*

	Comment	Response
	diagnosis of CAD than stress echo (without contrast). Stress echo with contrast seems to have a similar diagnostic accuracy to 99mtechnetiumSPECT. The addition of contrast to echo in patients with suboptimal echo images significantly improves interpretability of the results". b. Mowatt et all, in an analysis of ungated SPECT studies concluded "There was a considerable variability in terms of measurement of outcomes, management, setting and patient characteristics, however the direction of evidence tended to favour SPECT in terms of test sensitivity, although these conclusions are based on a relatively small number of diagnostic studies. SPECT, in a variety of settings and patient populations, provided valuable independent and incremental prognostic information to that provided by stress ECG and/or coronary angiography that helped to risk-stratify patients and influence the way in which their condition was managed." They also concluded "Further research is needed on the effectiveness and cost-effectiveness, diagnostically and prognostically, of (a) gated and attenuation-corrected SPECT compared with standard SPECT, (b) standard SPECT compared with stress echocardiography and (c) the uncertainty surrounding the results presented in the cost-effectiveness analysis." It is very important to emphasize that this analysis was largely (75%) based on thallium studies and did not include gated SPECT which is a critical component of image analysis in today's environment as it improves interpretative accuracy and provides incremental identifiers for multivessel disease. c. Merhige hypothesized that PETMPI with 82Rb would reduce downstream utilization of diagnostic arteriography, compared with SPECT, in patients matched for pretest likelihood of coronary disease (pCAD). RESULTS: Arteriography rates were 0.34 and 0.31 for the external and internal control SPECT groups and 0.13 for the patients studied with PET ($P < 0.0001$). pCAD averaged 0.39 in patients studied with PET MPI, and in the external SPECT control group, and 0.37 in the internal SPECT controls. Revascularization rates were 0.13 and 0.11 for external and internal SPECT patients and 0.06 for the PET group ($P < 0.0001$; $P < 0.01$), with a cost savings of 30% noted for PET patients, with no significant difference in cardiac death or myocardial infarction at 1-y follow-up. CONCLUSION: PET MPI in patients with intermediate pCAD results in a >50% reduction in invasive coronary arteriography and CABG, a 30% cost savings, and excellent clinical outcomes at 1 y compared with SPECT. d. Sharples et from the UK Medical Research Council at Cambridge compared SPECT, stress echo and CMR. They concluded that between 20 and 25% of patients can avoid	

	Comment	Response
	invasive testing using functional testing as a gateway to angiography, without substantial effects on outcomes. The SPECT strategy was as useful as angiography in identifying patients who should undergo revascularization and the additional cost was not significant, in fact it would be reduced further by restricting the rest test to patients who have a positive stress test. MRI had the largest number of test failures and, in this study, had the least practical use in screening patients with suspected CAD, although it had similar outcomes to stress echo and is still an evolving technology. Stress echo patients had a 10% test failure rate, significantly shorter total exercise time and time to angina at 6 months post-treatment, and a greater number of adverse events, leading to significantly higher costs. Given the level of skill required for stress echo, it may be best to reserve this test for those who have a contraindication to SPECT and are unable or unwilling to have MRI. Further research, using blinded reassessment of functional test results and angiograms, is required to formally assess diagnostic accuracy. Longer-term cost-effectiveness analysis, and further studies of MRI and new generation computed tomography are also required. e. In the acute chest pain setting of the Emergency Department, it is likely that coronary CT angiography is more cost-effective than stress perfusion imaging, whether with radionuclides or echo. One cost analysis has been reported comparing coronary CT. angiography with SPECT in individuals without known CAD. The CT patients were matched to a cohort of patients already existing in a large clinical database. These authors concluded that individuals without known CAD who underwent multidetector CT as an initial diagnostic test, compared with those who underwent myocardial perfusion SPECT, incurred lower health care costs with similar rates of myocardial infarction and CAD-related hospitalization. Caution should be applied in interpretation since the study was performed in an institution where CT angiography was likely much superior in quality than can be obtained in smaller centers with low volumes.	

References

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