Washington State Health Care Authority
Health Technology Assessment

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Health Technology Clinical Committee Public Meeting
September 20, 2013

Craig Blackmore: Good morning, everyone. This is a meeting of the Health Technology Committee of the Washington State Technology Assessment Program, and we have a quorum of committee members, so I'm going to call the meeting to order. I'm Craig Blackmore, the chairman of the committee, and the public is welcome. Everyone is welcome. We're gonna start the program with updates on the HTA program.

Josh Morse: Good morning. I'm Josh Morse. I'm the program director for the Health Technology Assessment program. I'll do a short overview. Today's topics are cardiac nuclear imaging and carotid artery stenting. The meeting is being recorded. If you have comments today, we're going to ask you to please use your microphones, so we can get a clear recording, and state your name.

A little background on the Health Technology Assessment program. The Health Technology Assessment program is located within the Health Care Authority, a state agency in Olympia, Washington. The program was created through legislation in 2006 and it's charged to use evidence reports and a panel of clinicians. This group, the Health Technology Clinical Committee to make coverage decisions for selected medical procedures and tests based on the evidence for their safety, efficacy, or cost effectiveness. Multiple state agencies that purchase health care are involved in this program and participate to identify topics and implement the policy decisions that are made through this process. They include the Health Care Authority, which manages the Uniform Medical Plan and the Medicaid program in the state of Washington, the Department of Labor and Industries, and the Department of Corrections. Implementation by the agencies of the determinations is done within their existing statutory framework. The purpose of the program is to pay for what works, to ensure that medical treatments, devices, and other services paid for with state healthcare dollars are safe and proven to work. The program provides a resource to the state agencies that purchase healthcare. We develop scientific evidence-based reports on medical devices, procedures, and tests, and we staff this committee to determine which of those devices, procedures, and tests should be covered and under what conditions. Some of our objectives are transparency. We strive to minimize bias. We strive for consistency, to be cyclic, and to evolve, all to achieve better health for Washington citizens.

This is a brief overview of the Health Technology Assessment process. The director of the Health Care Authority selects technologies. Those are nominated, reviewed, and put out for public input and prioritized. We contract for health technology assessments with technology assessment groups. We draft key questions, publish those key questions for comment, finalize those, and the entire process takes between two and eight months. We then bring this information to this committee in public meeting for a decision. Agencies then implement these decisions.

The primary key questions from the legislation are, is it safe, is it effective, does it provide value, and is it cost effective? Again, these are our values. We value transparency. We do publish all of our topics, criteria reports, and draft work products. We strive to seek the best available scientific evidence and we use an independent clinical committee to make these decisions. The basis of the decisions for this group include objective factors for evidence consideration, including the nature and source of the evidence, the characteristics of the studies or trials on which it is based, and how consistent the outcomes are in comparable studies. Additional factors include the recentness of the information, the relevance, and the bias present in that information.

Here is an overview of some of the topics in the past year and looking forward. Today we have… we are about midway through this, on cardiac nuclear imaging and carotid artery stenting. Looking ahead to November 15th, the next meeting, we will be bringing a re-review of hyaluronic acid and a re-review of hip resurfacing. Into 2014, topics include facet neurotomy, non-pharmacologic treatments for treatment-resistant depression, and proton beam therapy.

How to participate with this program? We have a website on the Health Care Authority webpages at hta.hca. We have an error on this slide. I apologize. You can join our stakeholder list. We have an e-mail address up there, SHTAP, or State Health Technology Assessment Program, where we send out information to all of our stakeholders who are signed up to be notified on program publications and meetings. Anyone may comment on proposed topics, on key questions, on draft and final reports, on draft decisions, and at the public meetings. Thank you.

Craig Blackmore: Thank you, Josh. So, first items on the agenda are to deal with business from our previous meeting. The first item is to approve the minutes from the previous meeting. The minutes have been provided to the members of the committee, and they are also within your packets, committee members. So, I will solicit either discussion or concerns on the minutes, or I will accept a nomination to approve the minutes. Do I have a motion to approve the minutes?

Seth Schwartz: I move to approve the minutes.

Craig Blackmore: A second?

Joann Elmore: Second.

Craig Blackmore: Alright, so we will just have a show of hands, approval of the minutes from the last meeting.

Josh Morse: Seven approved.

Craig Blackmore: And you're abstaining because you're not present. Alright, the second item of business is to finalize decisions made at the previous meeting. The committee makes decisions and then following the meeting, the staff members formalize that in writing, and we have the opportunity then, at the following meeting, or the subsequent meeting, to give final approval for the decisions that we made.
There were two decisions at the last meeting, the first of those was regarding cochlear implant, and the draft decision document has been distributed and is within the packet. Again, I will accept a motion to approve the draft findings and decision document on cochlear implants.

Joann Elmore: So moved.

Carson Odegard: Second.

Craig Blackmore: Alright, I would like again a show of hands for approval of the draft decision on cochlear implant.

Josh Morse: Seven approved, two abstain.

Craig Blackmore: Alright, and then finally we have a decision, draft decision document on catheter ablation procedures for supraventricular tachyarrhythmia, and again, I will accept a motion to approve.

Joann Elmore: I had a question about the responses, right, that were received.

Michelle Simon: I did, too.

Joann Elmore: And, um, it seems as if, I was especially impressed with [inaudible] email citing it. I appreciate it, because this was the one email that cited a few specific articles. Is it the committee members' thoughts that perhaps there were just some more recent articles in late 2012, 2013 that might address this and further substantiate an atrial tach, or were we missing some [inaudible], do the committee members think, in our previous review? Because our previous review was based upon an ARC folder review, and then they just did a followup.

Craig Blackmore: They did an update of it.

Joann Elmore: So, I would appreciate the other committee members' thoughts on this, because I was impressed with the number of responses.

Craig Blackmore: Does anybody have thoughts?

Kevin Walsh: I would… I wouldn't be willing to re-assess the vote unless we spent significant time asking the vendor, first of all, to validate the studies that are… that are mentioned here to decide if they're worth inclusion, and then evaluating them and using the same process we always use.

Joann Elmore: So, in other words, can we delay a vote on it and ask for additional evidence?

Craig Blackmore: Well, that would be one approach. I am not sure if that is what you're…

Seth Schwartz: Personally, I feel like the charge to the vendor is to look at the literature, give us the best evidence there is. If we trust that that happened, then we, we make a decision based on that. That's what we did. This is a… this is an assertion that the best evidence was missed, and that goes back, in my mind, to the vendor, not to our process. So, I would stand by the process and say we can relook at this in the future, just like we're re-looking at hip resurfacing, because it seems that new evidence has come out that requires us to do that.

Carson Odegard: The other alternative is, we could vote on it and come back when we do get more information, like we did with cardiac stenting, and then re-vote it at that time. I forget exactly what we did with that, but we, we did vote at one point and then came back.

Seth Schwartz: I wasn't on the committee then. So, you all remember, obviously better than I do, because I wasn't here, but it seems like at the time, you had questions about that, and that was why you asked that be done. We didn't have questions. I mean, we didn't have enough questions about this at the time. We voted on it and felt comfortable voting on it. So, it's a little bit different.

Carson Odegard: Yes. Yes, it is different, but I'm just saying that that's another alternative.

Michael Souter: I have to say, I concur with Kevin, because I think that if we do otherwise, we are in danger of seeing our process derailed by what may be… what may ostensibly look like a credible communication at every decision point we make, and I think we've undertaken the process. There is a process for revision, should new data need to be evaluated or present itself, and I think we should stick by that process.

Craig Blackmore: I guess in my understanding of, of this, I mean, I'm not sure we have, we've provided coverage for atrial flutter, symptomatic atrial flutter and symptomatic atrial fibrillation, and that is certainly a substantial subset of what he is describing in his concerns around focal atrial tachycardia. So, I think, you know, this was encompassed in our decision. This was based on the evidence we had at the time. This is how we defined the limitations, and I think I'm with Kevin that I think we had the best available evidence that was vetted through the process and I am not seeing any articles here that were subsequent, possibly one, that were subsequent to when the evidence vendor completed their work. So, I think… well, I guess it's up to the committee to decide. Does anybody else want to weigh in on this?

Marie Brown: Did, in any way, our decision leave the option for people to make individual cases for appeal or classic… a particular patient with a specific case that might be appropriate based on… especially the new 2013 study?

Craig Blackmore: I mean one, one could always appeal. One could also suggest to the committee that a given topic be either considered or reconsidered if more evidence comes to light and we're required to reconsider if new evidence comes to light.

Seth Schwartz: I would like to point something out. This is a quote. "This form of SVT has been targeted for ablation for over two decades with remarkable success, and it has had a major impact on the lives of many patients in the US and the state of Washington over the years." This isn't new evidence. I mean, what he's saying is, it's been around for a long time. Well, there wasn't evidence that we felt was compelling for a long time to support it. So he's not basing his request on some groundbreaking article that's just come out. He's saying this is kind of standard of care, you know, get on the bus, and we said, well the evidence isn't there to get on the bus. So, I…

Craig Blackmore: I mean, what I think, what we said is if, if this focal atrial arrhythmia becomes atrial flutter or atrial fibrillation, and it's symptomatic, then we'll cover it, but if you find something that isn't symptomatic or, you know, isn't causing one of these defined arrhythmias then it's not covered.

Kevin Walsh: Well, his assertion that it's been around for 20 years, in my mind, means we have had plenty of time for someone to have generated the evidence that there's value, and we didn't see that.

Seth Schwartz: I guess I'm just trying to understand, if we're not covering what they're talking about, because he's talking about focal arrhythmias that are symptomatic, and we said we're

going to cover symptomatic atrial fibrillation. So, I'm not sure that we're not covering, already agreeing to cover what he's talking about.

Kevin Walsh: I think he's implying covering symptomatic atrial tachycardia.

Richard Phillips: Yeah, tachycardia.

Seth Schwartz: Tachycardia instead of atrial fibrillation, okay.

Craig Blackmore: Okay, well I guess we have two options. We can approve the document as it stands, or we can go through one of several pathways to reconsider. What I'd like to do is take a vote on approving the document as it stands and if we decide not to approve the document as it stands, then we would talk about what the next steps might be. So, again I would like a show of hands to approve the draft findings and decisions, as presented. So, please raise your hand if you're in favor of that. Okay, and one abstention? Okay, so, we are approved.

So, next on the agenda is new business, and the first topic for consideration today is around cardiac nuclear imaging and the first item on the agenda for that topic is the public comment period scheduled in an open public comments. Do you want to take over?

Josh Morse: So, for each topic, we have the opportunity for comment before the committee. If you'd like to comment today and you haven't signed up previously, there are signup sheets right outside of this door over here. We have two commentors who scheduled in advance for presentations, and we'll start with Dr. James Caldwell. Christine, can you get Dr. Caldwell's slides? Thank you.

James Caldwell: Do I have slides?

Christine Masters: Yes, you do.

Craig Blackmore: So for, for all of the speakers while we grab your slides, just the ground rules are, we need you to, we're being recorded. So, we need you to introduce yourself. Tell us who you are, and then tell us if you are representing yourself or if you're representing some larger organization or group of people, and also if you could tell us, please, if you have any financial conflicts of interest that might be relevant to the topic under discussion.

James Caldwell: Thank you. Let me introduce myself. I'm James Caldwell. I'm a clinical cardiologist, have been doing it for almost 40 years. I've been chief of cardiology at the VA. I've been chief of medicine at the VA. I've been chief of cardiology at the University of Washington. I have had a long career there. I still contend on the inpatient intensive care unit. So, I see patients on a regular basis, as well as do a little outpatient clinic. I am also chief of nuclear medicine, excuse me, the chief of nuclear cardiology for the university. I've been doing that for about 15 years, but to go back, I've been doing nuclear cardiology almost 40 years also. I was involved in the original development team that developed SPECT myocardial perfusion imaging, mostly on the technology side, and I've continued my research with almost 90 publications in cardiovascular imaging since that time. I've served on a number of university, as well as national committees, including NIH study sections related to myocardial perfusion imaging. I have no conflicts. In all our development of the technology, we've never received any remuneration for that. It's always been done out of NIH dollars.

I also want to introduce Dr. Lori Sonia, the nurse practitioner who works with me, has for 15 years, and has done a lot of the data analysis that you will see in my current presentations.

I want to start with just to say that you were introduced to the appropriate use criteria in the review, the nuclear medicine review section, and I want to point out that it does work. In the… I don't know if I have this, is there a pointer on this?

Christine Masters: Oh, yes. There's a small laser pointer on the end of the clicker.

James Caldwell: It's not working. In 2005, the appropriate use criteria were published. Dr. Sonia looked at our data from 2005 for the previous three years, and we found that we weren't doing very well. Approximately 30% were inappropriate. At that point, we started introducing appropriate use, and you can appreciate that we've been able to reduce our utilization almost 40%, since 2005. I also bring in our use of cardiac rest/stress PET perfusion imaging, which is a small fraction of what we do but a critical fraction, and this growth in cardiac testing is driven almost exclusively from two referral groups, our interventional cardiologists who use it to help define significant stenosis in patients in whom they're trying to make decisions about revascularization. Some of these patients have already been in the Cath Lab and have fractional flow reserves measured, which you referred to in the review session, and they're equivocal. So, they ask us to do rest/stress PET in those patient populations.

The other patient population is our post-cardiac transplant population, which we are somewhat unique in this state for, but these patients develop transplant vasculopathy, which is a diffuse disease process, and it can occur in, the patients tend to be asymptomatic or have very atypical symptoms because they have been de-enervated. So, people have tried to use stress SPECT, stress echo to evaluate these patients, and it's uniformly been nonuseful. So, what we do is measure stress, rest stress PET with absolute measurement of myocardial blood flow and coronary flow reserve, which is the equivalent of a fractional flow reserve and watch for patient's development.

Now, the rest of the time, I would like to talk briefly about decision analytic model and the, and I'm a big believer in decision analytic modeling. I've used it on my own publications, but, there are limitations to it, and the first of these that people talked about was that it was assumed that all patients are fit enough to go exercise, to do exercise stress testing. You can appreciate in our university setting, less than 50% of our patients are able to do stress, treadmill stress testing. So, we have to do other things, and I also point out a fair member of these patients don't have a… are unable to reach their target heart rate, and that brings us to the dissection, decision analytic model. We had 23% who didn't reach their target, and if this had been a stress echo, that would have been a nondiagnostic study, and they would have had to stop and convert the patient over to a dobutamine stress echo at an additional cost to the system, whereas with nuclear the patient can be running on the treadmill. If they're unable to reach it, we can inject a very potent vasodilator with the patient still exercising and then follow that by injection of the radiotracer and get a complete study, a diagnostic study and in addition, we've got all the physiologic information that we would get from a stress test. As I said, this happens in about 23% of our population.

The decision analytic model assumed 100% specificity and sensitivity for invasive coronary angiography as the gold standard, but I point out that they've got two big paragraphs in it saying that it's not a very good gold standard. So, I would ask that if we

don't have a good gold standard, how are we going to use this in our decision analytic model appropriately?

The other thing they talked about was PET cost, and I agree, PET costs are high, and that's driven because we're currently the only place in the state still doing, or doing cardiac stress PET imaging. So, our costs are high, because we have low volume. It takes, you know, we spend $1,000 a day just for sterility testing and to meet the FDA requirements, no matter how many studies that we're going to do.

See, I need to wrap this up. So, I'm going to skip the patient that I was going to show you about how PET allows us to measure absolute coronary blood flow in patients who have virtually no heart remaining, and you can't do this with SPECT or stress echo.

So, in summary, I actually think the data review is very appropriate and very thorough and I contribute… I did a lot of reviews on this, and I think it's gotten a lot better over time, and I am very satisfied with it. However, I do think that it's inappropriate, the assumption, some of the assumptions in the decisional analytical model have significant limitations in terms of the results, and I'm told I have to stop at this point. Thank you.

Craig Blackmore: Thank you Dr. Caldwell.

Josh Morse: So, our next commenter is Dr. Neal Perlmutter. You have five minutes, doctor.

Neal Perlmutter: Thank you, good morning. Dr. Neal Perlmutter. I've been a practicing cardiologist in Bellevue, Washington for the last 24 years. I'm the director of nuclear cardiology at Overlake Medical Clinics and the advocacy chair for the American College of Cardiology, Washington chapter. I have no conflicts.

Dr. Caldwell did an outstanding job summarizing the data, but I would… and I don't have slides that are pre-prepared, although I did prepare written remarks that were submitted to the committee earlier. I'd point out that the appropriate use criteria alluded to earlier are rigorously developed. They're endorsed by eight specialty societies, and the process involves primary care physicians, general cardiologists, imaging specialists, and third party payers. Imaging specialists are a minority of members when these appropriate use criteria are developed, and this process prevents these appropriate use criteria from being perceived as a document that justifies and expands technology amongst the imaging specialists promoting their technologies, and they work. They're widely accepted by third-party payers, and the process in the state of Washington to date has worked very well.

I would also point out that under the provisions of the Affordable Care Act, there are going to be major advances in terms of credentialing requirements for all nuclear cardiology laboratories in the state. All laboratories are going to need to be credentialed by one of the credentialing bodies and these credentialing processes include inter-observer and intra-observer variability assessments, comparisons to angiography when both studies are done, and standardization of reporting to avoid equivocal interpretations or misleading interpretations.

Much of the evidence generated by the evidence vendor points out the comments that I've agreed with in the written report, as far as where myocardial perfusion imaging tends to favor, tends to come out favorably, as compared to stress echocardiography, including single-vessel coronary disease, prior myocardial infarction, abnormal resting ECG, inability to achieve target heart rate, left bundle branch block, pacemaker, ICD,

other conduction delays, or other resting ECG abnormalities, as well as poor echo image quality. The problem with defining these things in advance is that one cannot identify these patients in advance. The committee and the evidence vendor have asked for a diagnostic test to improve outcome or improve mortality, and there's no clinical trial that's been done to demonstrate such differences, in spite of the fact that these imaging technologies are not new. They've been around for a long time, and a number of very smart people with a lot of resources have had the ability to do such trials, if they're possible to be done. There are simply too many variables beyond the initial noninvasive diagnostic study in a patient with chest pain that no clinical trial could control for, and asking to come up with something such as a cost per correct diagnosis or a cost per cardiovascular event everted is not possible to do in spite of all that effort, particularly given that the evidence in the literature in terms of people who are going to have an intervention that prevents a myocardial infarction or prevents cardiac death. In general, they're going to present with unstable symptoms and are going to go directly to coronary angiography. Most patients who undergo either stress echo testing or nuclear imaging tend to be more stable patients, in whom symptom control is going to be the main goal.

In summary, both stress echocardiography and myocardial perfusion imaging have rigorous appropriate use criteria. They've been utilized by physicians and by payer communities for years, and they're working. They are decreasing utilization dramatically and they are encompassed in the American College of Cardiology's Choose Wisely campaign as one of the five principles for not doing an appropriate imaging, for example, annual testing in patients with known coronary disease who are asymptomatic, is clearly not appropriate. The current process utilizing appropriate use criteria, it works, it's online, the approvals are prompt, and the deterrent effect is that denials are rare. In a practicing cardiology office, if documentation for appropriate use criteria is inadequate, the office generally will insist the patient be seen by the specialist before an imaging study is scheduled. It's true that some patients will meet appropriate use criteria for both stress echo and myocardial perfusion imaging, and in that case the selection is best left to the ordering physician who has the knowledge of the individual patient. Since no such algorithm attempting to define which patient should get which imaging study has been developed or published in the literature has been implemented in any jurisdiction or is prospectively validated, I feel that such implementation would be unwise, and since this whole process is evidence based, I don't think that such criteria should be made up. Thanks very much.

Craig Blackmore: Thank you. So, those are the scheduled public comments that we had, and this is a public meeting, and we welcome anyone who has not told us in advance that wishes to address the committee. There is a signup sheet outside, which, did we have anybody sign up?

Christine Masters: There were the two [inaudible].

Craig Blackmore: Okay, and then we'll also check on the phone and see if anybody who has called in wishes to address the committee. While you're doing that, I am going to introduce our clinical expert, Dr. Redberg. Actually, I'm going to ask Dr. Redberg to introduce herself. Alright, the phones are un-muted, so this is the Health Technology Clinical Committee, and this is the public comment period on cardiac nuclear imaging. So, is there anyone who has called in that wishes to address the committee at this time? Okay, I'm going to close the open public comment period. I'm going to ask Dr. Redberg to introduce herself to the committee, please.

Rita Redberg: Sure. I'm Rita Redberg. I'm a cardiologist at the University of California, San Francisco, and I have participated in appropriate use criteria work with the American College of Cardiology on multi-modality imaging and also in the evaluation of CT that was done in 2007, as well as some efforts that were jointly done with the American Society of Nuclear Cardiology and American Society of Echo, particularly focused on use of imaging in women.

Craig Blackmore: Thank you, and could you also share with us if you have any financial conflicts of interest related to the topic at hand?

Rita Redberg: I have no financial conflicts of interests.

Craig Blackmore: Thank you. So the, the clinical expert is here because the committee members, our field is in evidence-based medicine, and that's why we're selected for the committee, but we're not necessarily experts in cardiology. So, throughout the course of the morning's proceedings, we will doubtless have questions for you and you will be able to provide insight and the goal… your job is not to provide us with a summary of the evidence. That's why we have the formal evidence summary and vendor, but there will be doubtless clinical questions, and we want to make sure that we understand the context appropriately and the techniques appropriately, and so, thank you for being here.

Rita Redberg: Pleasure.

Craig Blackmore: Alright, we will proceed then. The next item on the agenda is a report from the Washington State agency representative, that is Dr. Nobuhara.

Kerilyn Nobuhara: Morning. I'm Kerilyn Nobuhara. I'm the senior medical consultant with Washington Medicaid and again, on behalf of the agency medical director workgroup, we'd like to thank the committee for their time and deliberation on this topic, which is cardiac nuclear imaging. We'll hear more background information from the vendor, but the topic at hand this morning is noninvasive assessment of myocardial perfusion, SPECT imaging in particular, allows for spatial and temporal resolution. The technologies continue to advance quite rapidly. SPECT imaging is widely utilized. There are a number of different perfusion scans available, mainly SPECT, PET, and hybrid modalities. The workgroup did understand that a direct comparator is actually not available for this particular type of nuclear imaging. The comparators that were chosen were the stress echo examination, which is actually a functional evaluation and coronary angiography, which is an anatomic evaluation. There are no other direct comparators in terms of perfusion scans, in terms of these nuclear tests.

SPECT scanning is more widely available, as Dr. Caldwell had already mentioned. It does not provide a quantifiable estimate of blood flow, which PET scanning does. SPECT scanning is subject to attenuation artifacts. In general, PET imaging is higher resolution and also, as already mentioned, also much higher costs.

For all of the evidence reviews, there are risk assessments included for symptomatic and asymptomatic adults. In the evidence reports, you'll notice that the scoring systems vary slightly. I just included the slide so you do understand there are some different clinical criteria when assessing for low, intermediate, and high risk groups.

Also, as already mentioned, there are appropriate use criteria published in the literature and widely available. The guidelines are available online. The most recent publication was in 2009. This is a multisociety appropriate use criteria guideline. The risk

assessments used for these appropriate use criteria are the Framingham, Diamond, Forrester, and ATP-III.

For the state agency utilization data from PEBB, you'll see that there was a total expenditure of $10.8 million between the years of 2009 to 2012. The average paid amount per encounter, if PEBB was the primary payer, was $1,300. The average encounters per patient was just over 1, and there were some outliers in terms of multiple tests performed per patient.

For the Medicaid data, the expenditure for Medicaid, again from years 2009 to 2012, was $3.1 million. The average pay per encounter $351. If Medicaid was the primary payer, the average paid amount was $438. Average encounters per patient was just over 1, and there were a few outliers in terms of max number of tests performed per patient over the four-year period.

From L&I, the expenditures from 2009 to 2012, total expenditures of about $500,000. The average paid per test was about $1,000. The average encounters per patient, or number of tests per patient just over 1 with relatively few max encounters in terms of three per patient.

For the PEBB, Medicaid, and L&I populations, you can see the number of patients and their ages with, as would be expected, the majority of patients falling in the 50-64 year age-range for all agencies. For PEBB, the 65 to 79-year-old group is much larger. Remember that Medicaid becomes the secondary payer for the majority of patients who are 65 years or older.

General trends, again from 2009 to 2012, for both SPECT and stress echo. You can see that there is a slight downward trend for SPECT utilization 2009 to 2012 in PEBB with relatively stable use in terms of stress echocardiography. Cardiac MRI was also included just because it was chosen as one of the relative comparators in the evidence report. For repeat SPECT procedures, there are a few outliers in terms of certain patients who received multiple tests. The majority received, at most, two or three tests over the four-year period.

Current state policies, I will just outline some of the disparities. The agencies are primarily agreed in terms of which of these tests require prior authorization. Presently, Washington Medicaid does not cover PET perfusion scanning, and some of the agencies cover stress echocardiography without prior authorization. There is a national coverage determination in place that is actually pertaining to PET scanning and not SPECT scanning, although SPECT scanning is mentioned in this particular NCD, and primarily you can see the wording in the upper point. In the case of myocardial viability, FDG PET may be used following a SPECT that was found to be inconclusive. However, SPECT may not be used following an inconclusive FDG PET performed to evaluate myocardial viability. Again, there is no NCD addressing SPECT scanning itself. There is an LCD in place. The LCD has a myriad of clinical criteria. These clinical criteria are very much in line with the appropriate use criteria that are published.

From the workgroup perspective, as the key questions were being formulated and passed onto the vendor, safety was considered as a medium rank, efficacy medium, and cost is a high concern.

For safety concerns, these are primarily involving radiation exposure and radiation exposure with repetitive testing. There is also a concern about whether or not

downstream effects of the SPECT imaging or PET imaging itself leads to an increase or decrease in referral to coronary angiography, which of course has its own risk associated with that test.

Effectiveness was a medium concern, and the question was whether or not comparative value could really be generated between exercise treadmill testing, echocardiography, SPECT, and PET imaging. The second question raised by the workgroup was whether or not adherence to the clinical guidelines actually improves clinical outcomes, as well as decrease rates of utilization.

Cost was a high concern, primarily because of volume and widespread use of the SPECT scans.

Other agency considerations, there is a higher quality of evidence supporting comparative value of SPECT imaging versus PET imaging for myocardial perfusion imaging. The vendor report in general, supports the appropriate use criteria for most of the targeted populations, except for one, which is for asymptomatic patients at high risk of coronary artery disease for this particular patient population. This is ranked as appropriate by the joint technical panel. However, the vendor report suggests that the evidence is somewhat inconclusive. There is very limited evidence available addressing the use of PET as a primary study versus SPECT imaging.

So, the recommendations from the agency directors workgroup is to cover with conditions for symptomatic patients at low, intermediate, or high risk of coronary artery disease for patients with known coronary artery disease that have a worsening in symptoms, to not cover for screening for patients with known coronary artery disease who have no changes in symptoms, or for screening for asymptomatic patients at low, intermediate, or high risk of coronary artery disease. The second recommendation would be to cover with conditions for PET scan if SPECT scanning is inconclusive or not technically feasible.

Craig Blackmore: Thank you. Questions from the committee?

Michelle Simon: I have a question on slides 6, 7, and 8 on the state agency utilization data, the max encounters per patient. Can you just clarify for me, is that actually people getting successive SPECT scans, or are those encounters or other things related to the same ICD-9 code?

Kerilyn Nobuhara: It's for the same CPT code.

Michelle Simon: Same CPT code.

Kerilyn Nobuhara: Yeah.

Michelle Simon: OK.

Seth Schwartz: I'm curious if cost is the major concern and we're seeing fewer patients having tests, and the costs of the tests not going up over time, why this is being raised now?

Kerilyn Nobuhara: I don't think cost was necessarily the primary concern. It was a high concern.

Seth Schwartz: It was the, it was the one that, it was the highest concern you mentioned.

Kerilyn Nobuhara: Right, mainly because of volume, but we didn't have the actual agency cost data before those key questions were generated.

Seth Schwartz: But the volume's going down.

Kerilyn Nobuhara: Yes, it is.

Female: Right, if anything, I think the state agency utilization data is heartwarming, and it's impressive and makes me proud of the Washington State physicians in that they are reducing the utilization and perhaps appropriately ordering these. It was a little bit scary seeing that there is one patient who had 11 SPECT procedures in a four-year period, but if you look at each of your slides, Medicaid, L&I, and PEBB, each successive year, the total number of procedures has been going down, which I think is reassuring.

Kerilyn Nobuhara: I agree.

Craig Blackmore: Which is a nice lead in to… oh, go ahead.

Joann Elmore: And it sounds like a lot of that, or some of it, may be due to there's a fairly good consistency across clinical guidelines and that there's adherence to clinical guidelines.

Kerilyn Nobuhara: Well, the agencies have SPECT scans on prior authorization. The criteria used for that prior authorization process differs among the agencies, but I would agree that yes, the general trend is downward for volume in terms of ordering of these tests.

Craig Blackmore: So, in terms of the preauthorization criteria, how do they align with the appropriate use criteria that the multispecialty panel came up with?

Kerilyn Nobuhara: So, I can only speak for L&I and Medicaid, because we have an external contractor, which is Qualis that uses the InterQual guidelines. I can't disclose the InterQual guidelines, but they are very much in line with the appropriate use criteria.

Craig Blackmore: They're proprietary, is that the…?

Kerilyn Nobuhara: Yes, they are proprietary.

Craig Blackmore: And the, your slide number 14, which myocardial perfusion imaging and then it says parenthesis L31072, I may have missed this, but these are the criteria for the local coverage decision. Is that right?

Kerilyn Nobuhara: Yes.

Craig Blackmore: And these are largely aligned with the AUC?

Kerilyn Nobuhara: Yes.

Craig Blackmore: Okay.

Michelle Simon: Has there been any change in the past four years in the way that prior authorizations are determined?

Kerilyn Nobuhara: I can only speak for Medicaid, and Medicaid placed SPECT scanning on prior authorization, I believe, in 2011. Our guidelines have not changed. I cannot speak for the other agencies.

Craig Blackmore: I just want to circle back, and this is not directed at you, but, am I to understand then that there are appropriate sort of, there are preauthorization criteria that the State of Washington uses for this test that they can't share?

Kerilyn Nobuhara: Yes.

Gary Franklin: We're doing the UR together. It's the first time in the country that Medicaid and Worker's Comp are doing anything together for UR, and most of the decisions in that UR program are transparent, based on transparent guidelines that we have used. A minority of the decisions are based on the intercore, InterQual criteria, which are proprietary. So, in this case, they are proprietary, but a high priority for us is to make everything transparent.

Craig Blackmore: Thank you. Any other questions? I guess one other question. How long has the state been doing preauth for these? Has this been longstanding or is that a new phenomenon?

Kerilyn Nobuhara: So, for Medicaid again, it was 2011 that it was started for SPECT scanning. I don't know about L&I or PEBB.

Craig Blackmore: Can anybody speak for PEBB or L&I? I know you don't do a lot of these, but, we don't know how long that preauth has been in place.

Gary Franklin: I'm sorry. I missed the question.

Craig Blackmore: So, how long has preauth been in place for these procedures in U&P? Do you know the answer to that?

Gary Franklin: I don't.

Craig Blackmore: And L&I, you don't do a lot of these, right?

Gary Franklin: No. It'd only be a firefighter or a policeman with a presumptive coverage for cardiovascular disease, that kind of thing.

Craig Blackmore: Okay, thank you. Okay, next on the agenda is the evidence report.

Daniel Ollendorf: Great, thanks Christine. Okay, thank you to the committee. Thank you to the agency for allowing me to present the information from our comparative effectiveness review and comparative value review of cardiac nuclear imaging. My name is Dan Ollendorf. I'm the chief review officer at the Institute for Clinical and Economic Review. I'm also wearing progressive lenses for the first time, so if my eyes start to kind of go in different directions, bear with me.

So, this brief overview… what was that?

Craig Blackmore: Speak up.

Daniel Ollendorf: Oh, okay, sorry. We'll talk about the scope and comparators, the outcomes of interest that were undertaken during the review. We'll talk about the major results from the review, as well as our comparative value analysis. ICER has its own evidence rating system, which we will describe, and I will share with you what the ratings were for these comparators. We will also look at what major clinical societies are saying in terms of clinical guidelines, as well as payer coverage policies, some of which you've already seen, at least on the federal front.

So, I won't belabor the point, in terms of the background. Certainly, coronary artery disease is common and a significant cause of morbidity and mortality in the US. This has already been alluded to previously, but historically, the gold standard for evaluation of the severity of coronary artery disease has been anatomic in nature using invasive coronary angiography, which does come with some risks. Not surprisingly, there has been interest in the development and use of noninvasive technologies. There is also the possibility of functional assessment through the identification of location of defects in myocardial perfusion and blood flow to the heart. The correlation of anatomic and functional data is, in fact, quite weak. Obstructive lesions are often not functionally important, except when the blockage is nearly complete. This has been demonstrated in recent studies and clinical trials. However, it is the case, and we will come back to this a little bit later, that anatomic findings from angiography are still used to guide many treatment decisions despite these findings.

So, there are multiple techniques to test for the presence of ischemia. Some of the common tests outside of the nuclear imaging sphere are stress electrocardiogram, also known as the exercise treadmill test, we'll use the abbreviation ETT in this presentation, and stress echo. These do not measure perfusion specifically, per se. Ischemia is indicated on an ETT through the presence of abnormal electrical signals, and on a stress echo through abnormalities in the wall motion of the heart. So, cardiac nuclear imaging tests have been developed to more precisely measure myocardial perfusion.

In terms of nuclear imaging tests, as you've already heard, the most common test in use, that has been used for quite some time, is SPECT. PET imaging has also been used for quite some time, but in terms of its frequency of use, is considered an emerging technology. These allow for 3D imagery of myocardial perfusion. There are protocols that employ putting the patient under stress only, as well as stress and rest. Multiple stressors can be used, treadmill, bicycle, or pharmacologic stress, which has already been discussed, and through the use of radioactive tracers, areas of good and poor perfusion are then highlighted. So, in this particular example, which is a cross-sectional image of different areas of the myocardium, there is a comparison of rest versus stress images, and the area of potential ischemia is highlighted by the arrows.

So, other tests include coronary computed tomography angiography. Although this is described in our review, it's not actually analyzed as a comparator, because we did a CCTA review for the agency in 2008, and there was a decision made. Cardiac magnetic resonance is also mentioned, but because its use is still small, it's an emerging technology, it was not considered as a comparator for our review, as well. However, we did look to find evidence on hybrid imaging. So, hybrid imaging is essentially the use of a perfusion test like SPECT or PET combined with CCTA or MRI technology to provide anatomical information and the results of both tests are fused into a single report.

So, the policy context around the topic of interest is that on a national basis, there has been increased utilization of cardiac nuclear imaging. Now, I will say that the study that indicated this is a bit dated, in terms of the publication of the appropriate use criteria.

So, updated numbers may, in fact, tell a bit of a different story, but over a six-year period, from 1999 to 2005, there was over a 50% increase in the use of cardiac nuclear imaging nationwide. Another study documented something else that was interesting in that at one large academic medical center in New York, over a couple of decades of experience in five-year increments, there was a significant drop in the rate of abnormal findings on cardiac nuclear imaging tests so that questions were raised based on this finding. Certainly there have been changes in the medical management of patients at risk for cardiovascular disease and other changes in the demographics of the population, but questions were raised based on this study around whether there is a lower threshold to send patients for noninvasive testing now and other concerns, as well. In addition to these issues, there are also concerns about, generally, about differences in costs, risks, and availability among the diagnostic strategists.

So, we've talked a bit about the populations of interest already through the other presentations, but our key questions focused on asymptomatic patients at high risk of CAD due to existing comorbidities like diabetes, as well as symptomatic patients at low, intermediate, or high risk of CAD, and patients with known CAD who either do or do not have changes in symptoms. There is a key question around the potential risks of these tests, including contrast, radiotracer and, in fact, pharmacological stressor reactions, radiation exposure, and other concerns. Several subgroups were brought up as of interest during the formulation of the key questions including demographics and comorbidities, clinical setting in which the test is performed, whether the test is ordered by a primary care or specialty physician, and then other concerns regarding the vendor, the type of assessment of perfusion, the type of radioisotope used, and the type of stressor. Then finally, information on costs and cost effectiveness from published studies and our own decision analytic model were used to address key question four.

So, we've talked about the project scope in terms of population already. Our focus in terms of nuclear imaging was on SPECT, PET, and hybrid tests. Major comparators included ETT and stress echo. Outcomes of interest, cardiovascular related and all cause mortality. The incidence of major cardiovascular events, which could have included MI, stroke, revascularization, or other cardiovascular related hospitalization, health-related quality of life, referral for subsequent and downstream testing, as well as clinical impression and/or decision making. Does the use of the test change decision making in practice?

So, our literature search focused on a period from January 1996 to February 2013. Importantly, we focused on comparative studies only. So, we were looking to see what the impact of nuclear imaging tests would be relative to a comparative strategy, and that could have included studies of different groups receiving different tests, including some RCTs, a single group that received multiple tests, and/or comparisons of testing to no-test strategies. We did look at diagnostic accuracy as a secondary measure, but we decided to focus only, in part in response to public comments, to focus only on studies that used a functional reference standard. So, most of the diagnostic accuracy literature has focused on angiography results in terms of anatomic data, but there are measures, such as the fractional flow reserve, that measure cardiac function, and so we included accuracy studies if that was the measure.

We used well-accepted and validated tools to assess the quality of individual studies, and we also used four general domains to assess the overall strength of evidence for each population. The risk of bias, i.e. what kinds of studies were used and what their quality was, and consistency were the findings generally consistent in terms of their direction and magnitude. Directness was their direct comparison of the major tests of

interest and/or direct measurement of the key outcomes of interest or were surrogates used, and precision, the confidence interval, essentially, around the estimates of effect. So, was it wide or narrow?

I won't go into detail here. In fact, I can't even see the detail here. So, I'll just tell you that there 55 studies that made it into our sample. We'll talk in general about the studies that focused on clinical outcomes primarily, but we also included studies that focused specifically on harms, as well as economic evidence, etc.

In terms of quality and type of evidence, this will differ somewhat from the full Prisma diagram in the report, because the 14 RCTs and comparative cohorts that are listed here were those that focused on clinical outcomes alone. Other studies did look at other concerns, as well. Of those 14 RCTs, most were good or fair quality. Information on PET was extremely limited. We found three studies in our entire sample that focused on PET imaging, and there were no comparative studies of asymptomatic patients with known CAD. So, that subset of the key question that focused on asymptomatic patients with no changes in symptoms, we found no comparative studies for that particular population. Interestingly, of those 14 studies, most of them were in what we ended up calling mixed population. So, these were populations that included symptomatic and asymptomatic patients, patients with suspected and known CAD, patients at differing levels of risk for CAD, so it was a bit of a mixed bag. Because of this heterogeneity, we decided to focus our efforts on qualitative results and not do quantitative synthesis of data.

So, key question one. With a focus on that first population of key question one, asymptomatic patients at high CAD risk. There was one RCT identified with approximately 1,100 individuals with diabetes examining the impact of one-time SPECT screening versus no screening in this population with a followup of about five years. There were no differences in mortality or major cardiovascular events between the two groups. In terms of downstream testing and clinical decision making, there was a higher rate of referral to angiography in the SPECT group, not surprisingly, because they got the screen, and there was a somewhat higher rate of downstream stress testing in the no screening group, but in fact, downstream stress testing over five years of followup for clinical indication was substantial in both groups. We found no studies of PET or hybrid tests in this population and no studies measuring health-related quality of life.

Moving to symptomatic patients at low to intermediate risk, one RCT and three cohort studies, approximately 25,000 individuals in these studies. For SPECT compared to a variety of tests, we found mixed evidence of its benefit relative to exercise treadmill testing. Mixed evidence comes because there was one RCT conducted in women at low to intermediate risk of CAD comparing SPECT and ETT, again finding no differences in rates of mortality or cardiovascular events. There was another study, however, that showed significantly better prognostic ability of both SPECT and echo relative to ETT in clinical parameters in this population. In terms of downstream testing and clinical decision making in that RCT, there was actually a higher rate of repeat testing in the SPECT group. So about 9% of individuals got another SPECT test during the study followup period and 3% of ETT patients got another ETT, but there was also a significant amount of crossover from ETT to SPECT in this RCT. About 18% of ETT patients required a SPECT during followup. Quality of life is also measured in that RCT using the Seattle Angina Questionnaire. No differences were found between treatment groups. Again, no studies in this population focusing on PET or hybrid testing. Do you have a question?

Michelle Simon: Do you know [inaudible] follow-up was in that study?

Daniel Ollendorf: I can look it up when we go through the question period. I believe it might have been two years, but I'll double check.

In terms of symptomatic patients at high risk of CAD, again, one RCT and three comparative cohort studies, about 4,000 patients. Here, as risk moves up the continuum, we find studies showing a reduced revascularization rate of SPECT in comparison to ETT, comparable results in comparison to echo. One study evaluated risks and downstream testing in patients receiving SPECT, PET, and CCTA in a registry format and found that revascularization in terms of SPECT was higher than for PET in this population, but other measures, other outcome measures were not significantly different. In terms of downstream testing and clinical decision making, again studies showed a reduced rate of unnecessary angiographies that essentially had a false-positive result, or showed a false-positive result for the noninvasive test relative to ETT for SPECT versus ETT and again mixed evidence in downstream testing in comparison to PET, although not a focus of our analysis, CCTA. There were single studies of PET. I've already talked about the PET registry. Another study looking at hybrid testing focusing on images that matched versus those that did not. So, essentially the functional image and the anatomic image either showed abnormality together or one showed abnormality and one did not. Probably not surprisingly, from a clinical standpoint, the matched images were much more correlated with clinical outcome than the unmatched images were, but we considered that design of a study and that outcome to be insufficient. No studies of health-related quality of life in this population.

In terms of patients with known CAD, so there were two cohort studies of about 5,000 patients, and again, this is known CAD with symptoms or without symptoms. From a comparative standpoint, we found very little data. There was one study that looked at the sequence of use of SPECT with angiography, whether it was done before angiography, whether it was done after angiography, or whether it was not done at all, and findings suggested that the highest rate of revascularization occurred in patients who got angiography alone, because essentially the authors concluded that the anatomic data were driving the decision, and there was no functional data available, and lower rates for SPECT either performed before or afterwards. Another study queried physicians about their clinical plans for patients before receipt of PET perfusion data and then looked at actual management after the PET data were received by the clinician and found large-scale changes and a large increase in the percent of patients who receive medical management and a large decrease in the percent of patients who were referred for angiography between these two decision points with a single study. For health-related quality of life, no studies, and no studies of hybrid technologies.

So, moving to our largest population, the mixed population. So, here we had two RCTs and six comparative cohorts, relatively small numbers of patients, however, about 5,000 patients studied across all studies. Here, we found moderate evidence to suggest that in comparison of SPECT to echo, there were results that were comparable in some circumstances. In one RCT, there was a higher rate of readmission to hospital in the echo group. This was an RCT performed in the UK, and the authors attributed the difference to the complicated course of a couple of echo patients who were repeatedly readmitted and also described the fact that in fact, in the UK, SPECT is a much more established modality than echo is for this particular use. There were cohort studies comparing to PET showing no differences in major cardiovascular events, but some differences in downstream testing, which I'll talk about in a minute. In this population, generally there was more prognostic information available around mortality for SPECT, as compared to ETT. In that study I referred to comparing PET to SPECT. There was a reduced revascularization rate in the PET group as compared to two SPECT control

groups. No other differences in clinical outcomes that I just mentioned, however. Another study in this population, again, looking at matched versus unmatched images on hybrid testing, similar results found, so an insufficient body of evidence from our perspective. In terms of downstream testing and clinical decision making, no differences in the studies that compared to SPECT versus echo. That RCT also included a comparison to cardiac magnetic resonance and direct referral to angiography, but studies did show superiority to ETT in terms of reduced unnecessary referrals for angiography in this mixed population. PET was superior in that one comparative study for reduced referral to angiography relative to SPECT in that one study. The RCT comparing SPECT to multiple modalities did also evaluate quality of life using both the Seattle Angina Questionnaire and some generic quality of life instruments, like the SF36. No substantial differences were found in quality of life across any treatment, or any testing category.

So, moving quickly to diagnostic accuracy, we found a total of eight studies that assess the accuracy of SPECT or PET using a functional reference standard typically fractional flow reserve primarily in populations with a history of CAD. The issue with trying to do anything with these studies in term of drawing conclusions was that the threshold for fractional flow reserve actually varied across studies and in some studies, the use of either a functional reference standard or an anatomic reference standard constituted positivity, making it, again, difficult to draw conclusions. That being said, there was a wide range of reported sensitivity and specificity across the studies, wider with the SPECT studies than with the PET studies, but they're presented here.

So, moving to risks. I'm not going to spend a lot of time on this slide, because the risks that were described in comparative studies in our set were minimal, in terms of their description, and there were no substantial differences seen between the testing groups, in terms of the risks of testing.

So, the big question on everyone's mind is radiation exposure with these tests, and here we've, this is in the report as well. There's a reference table we've prepared that sort of puts the radiation exposure in context relative to other tests used in this population, as well as other tests that do emit radiation, as well. So, you see a wide range of radiation for both PET and SPECT. There were, initially, some lower rates of radiation estimated for PET that came directly from manufacturers, but in fact experience during the studies has shown the radiation exposure to be a bit higher, and the issue, of course, with radiation exposure is that it's a poorly understood phenomenon from an epidemiologic perspective. A latency period in terms of secondary malignancies can be anywhere from 10 to 40 years. So, they really need to be considered in the clinical context of interest. So, if you're talking about a 75-year-old man who is getting tested once because of suspected CAD versus a 50-year-old person who's had a procedure and is potentially a candidate for serial imaging after the procedure, those are the kinds of things that, that need to be thought about when trying to look at this radiation exposure, but it is also the case that patients can be exposed to radiation through these tests, as well as other tests, including invasive angiography that exists along the diagnostic pathway.

In terms of key question three, differential impact of nuclear imaging in key subgroups. Again, I am not going to spend a lot of time on what we actually found in our study sample, because, in terms of comparative effects, there really wasn't much available. We did also look at tests, studies of individual tests, so not compared to another strategy, and we found comparable performance for SPECT and even for echo in many of these studies, according to demographic characteristics and certain comorbidities, such as diabetes and hypertension. SPECT has been more widely studied in populations

that vary by body weight and several meta-analyses suggest that the performance of SPECT is comparable in obese, overweight, and normal weight populations. There was not information available on PET in these subgroups, however. Analyses of SPECT ordering versus those appropriate use criteria that have already been described to you suggest that inappropriate ordering is more common among nonspecialists. So, one multicenter study and several single-center studies suggest that primary care physicians tend to order more inappropriate tests than specialty physicians, cardiologists primarily. Most of the inappropriate ordering that does occur occurs in women, asymptomatic individuals, and younger patients.

So, moving to economic impact. So, in terms of prior published evidence, there is a single decision analysis, and I note that this is published before the DIAD Study, the RCT that looked at SPECT screen versus no screening. So, this was positing based on studies of individual modalities what might occur. We found that the one-time screening was slightly more effective, increasing quality adjusted survival by ten days over a lifetime. So, that is slightly more effective, and slightly more costly versus no screening, but when repeat screening at intervals less than ten years were introduced to the model, the additional benefits were minimal, but the additional costs were substantial. So, those results do differ in some respects from the results of that RCT that suggested no differences in outcome. Findings from economic studies in symptomatic low to intermediate risk population, some of these studies were actually the RCTs and cohort studies in our sample that also measured cost suggested that studies in low to intermediate risk populations that used treadmill testing before nuclear imaging may be cost saving or cost neutral versus SPECT first. That's not withstanding any differences in outcome, but again, this is a population in which we found mixed evidence of benefit of initial SPECT versus initial ETT. In mixed populations, we found one study, a study that compared PET versus SPECT control groups and actually found lower costs for PET over time due to a lower referral rate for angiography.

We also undertook our own decision-analytic model, which you've heard something about already to try to examine the tradeoffs and try to display them for you that might be apparent during the diagnostic phase for different testing strategies. So, we looked at SPECT, PET, treadmill testing and echo as stand alone tests and also the use of ETT first and then those three noninvasive tests as a second test. Definitive diagnosis was provided by angiography and harkening back to what I said initially, the only evidence base that we could use to show essentially the gold standard for angiography results that had information available for all of the tests in our model were those older studies that looked at anatomic data. So, recognizing the controversy that exists over the use of anatomic data alone to guide treatment, still felt this was a way to compare all of the testing strategies on a relatively even playing field and, in fact, still does represent how, in many cases, the data are used to guide treatment. We based costs on data provided from the agency.

So, I'm not going to go through the outcomes in detail here. I'll just show you those on the table. Key assumptions, you've heard about some of them already, the ability to exercise and target heart rate achieved. I will note that to simplify the model, we did make this assumption, and it certainly recognized that many patients cannot exercise and do not achieve their target heart rate, but in terms of our estimates of the model, we actually estimated a higher nondiagnostic rate for both echo and ETT relative to the nuclear imaging tests. So, if a test was positive or nondiagnostic, the patient went to the next test in the pathway. I've already talked about the anatomic issue, and you should think about the PET analyses, given the limitations and our evidence base, it is

very exploratory, because we use diagnostic accuracy data alone to drive this, and as you saw, the evidence base for PET is extremely limited in terms of comparative studies.

So, talking about a high-risk group, so a high rate of underlying CAD prevalence, when looking at this kind of a population, what you'll see with ETT, with treadmill testing, is that you have a much higher number of false-positives and false-negatives in this population. Not surprisingly, it is not as precise a test as the other tests, and you have a lot of underlying disease. PET, based again on that diagnostic accuracy data, produces the highest number of true positives and the lowest number of false negatives, but is also the most costly test and exposes all patients in the pathway to radiation.

Joann Elmore: Would you repeat that sentence?

Daniel Ollendorf: Okay. PET produces the highest number of true-positives and false-negatives in this model but is the highest cost test and exposes all patients to radiation. Hopefully, I repeated it correctly.

Craig Blackmore: You didn't. Try again.

Daniel Ollendorf: Okay. PET produces the highest number of true-positives and false-negatives, but is also the highest cost test...

Group: The lowest number.

Daniel Ollendorf: Oh, sorry. You're right. I'm sorry. Highest number of true positives and the lowest number of false-negatives but is also the most expensive test and exposes all patients through radiation.

Joann Elmore: Okay.

Daniel Ollendorf: And then you see that in this high-risk population it, not surprisingly, is not a good idea to think about treadmill testing as an initial strategy, because it produces an untenably high number of false-negatives relative to use of a more precise test initially.

Moving down the risk continuum, and there are other risk levels provided in the report, looking at a population where only 10% of the patients have underlying CAD. Here, the differences in false-negatives are much more minimal. Again, you have fewer patients to detect, so a lower risk of a false-negative result, even with a less precise test like ETT. However, there are bigger differences in false-positives across the tests. So, you had smaller tradeoffs, for example, in false-positive numbers between echo and SPECT in the 50% population, and those are magnified a bit in the 10% population, so a higher number of false-positives with echo, and that was also the case with the 50% comparison, but it's a wider difference now and a higher number of false-negatives with SPECT, but here it is very minimal. Relative to the false-positive issue though, use of ETT first in this population will produce a much lower number of false-positives, as again, a positive or an inconclusive test on ETT will result in an echo, SPECT, or PET.

So, to summarize, we are feeling like this model is a way to visualize the tradeoffs between tests that vary depending on the underlying prevalence of CAD. Concerns with false-negatives increase with increasing prevalence, differences in false-positive rates are magnified with decreasing prevalence, and those two test strategies performed best at lower prevalence levels. Yes?

David McCulloch: Can I just ask you, how would you determine if somebody's in a 50% [inaudible]?

Daniel Ollendorf: Well, these are hypothetical cohorts. So, we're basically assuming that truth in 1,000 patients in a 50% cohort is at 500 have CAD.

David McCulloch: Oh, I see.

Daniel Ollendorf: And in the 10% population, 100 have CAD, and truth in this case is determined by angiography results.

So, the limited data on PET accuracy suggests reduced false-positives and false-negatives but at a substantially higher cost, and there are other tradeoffs to consider. Radiation exposure is a major one. There are other measures that were included in these tables that I'm not going to focus on in detail, like incidental findings, propensity for findings outside of the heart, that need to be considered, as well.

So, moving to ICER's integrated evidence rating matrix, this is the matrix here, and it's described in detail in the report. For those four populations of interest, asymptomatic high-risk individuals, we found that SPECT in comparison to no screening produced comparable results, but this was not an explicitly modeled population, but because SPECT introduces a cost that does not exist with no screening, we judge that its value would be low value in this situation. All other populations and comparisons, there was insufficient evidence to create an evidence rating. For symptomatic patients at low to intermediate coronary artery disease risk, because SPECT produces comparable results in some studies and incremental results in other studies in comparison to ETT in this population, we rated the technology as comparable or better, but again, because it is a higher cost test, as demonstrated by both the studies in our sample and our model, we considered its value to be low economic value. In terms of SPECT versus echo, comparable results from the clinical studies were produced for both tests. We felt that SPECT was a reasonable value in this situation. It is somewhat of a higher cost test, but the cost differences are smaller and again, insufficient evidence to evaluate PET or hybrid testing.

In symptomatic patients at high CAD risk, we found that SPECT actually produced incremental benefits across all studies in comparison to ETT, so we call this incremental or better, and that it produced a reasonable value. In at least some of the studies, the cost offsets associated with reduced unnecessary referral to angiography represented a reasonable value. Again, the same rating in this population comparing SPECT to echo, and insufficient evidence for PET and hybrids. For known CAD without symptoms, that's noted by the asterisk at the bottom, we felt that the evidence was insufficient for asymptomatic populations with known CAD, because we found no comparative studies. In known CAD with new symptoms, there were no comparisons of SPECT to ETT, so that was insufficient. The comparisons of SPECT versus echo that were available were felt to be comparable and of reasonable value, and insufficient evidence for PET and hybrids.

So, clinical practice guidelines. We looked at a variety of sources to summarize clinical practice guidelines, including appropriate use criteria, as well as the Choosing Wisely campaign, which has statements from multiple societies. In asymptomatic high-risk individuals, in contrast to what the conclusions of our evidence review were, guidelines state that SPECT is generally considered appropriate for detection of CAD or risk assessment in these patients. In symptomatic patients at low to intermediate risk, recommended for diagnosis in patients with an intermediate pre-test probability and an

un-interpretable EKG, not indicated as an initial test in low risk patients who have an interpretable EKG and can exercise.

In symptomatic high-risk patients, the universally-recommended nuclear imaging for diagnosis and risk stratification in patients at high risk who have an uninterpretable EKG and even in some patients who have an interpretable EKG but have low physical functioning. In known CAD, recommended for risk assessment in patients who are candidates for revascularization or in those who have deteriorating symptoms after procedure, not recommended in asymptomatic patients post-procedure unless at least five years after CABG or with evidence that revascularization was incomplete.

Statements from Choosing Wisely, the American Society of Nuclear Cardiology essentially says many of the same things. Asymptomatic patients should not have imaging unless high-risk markers are present. Cardiac imaging should not be done in patients who are at low risk. Routine followup cardiac imaging, nuclear imaging, should not be done in asymptomatic patients, and wherever possible, use methods to reduce radiation exposure. Statements from the Society of Nuclear Medicine and Molecular Imaging and the ACC generally follow along with these.

Payer coverage policies, you've already actually heard from the agencies on both the NCD and the local coverage decisions. In terms of what private payers are saying about SPECT, generally cover for patients with known or suspected CAD who have an uninterpretable EKG and an inability to exercise, covered for follow-up testing with time limits. So, at least two years following an event or a percutaneous intervention, at least five years after CABG, not covered for asymptomatic low-risk patients or in high-risk patients who have hemodynamic instability. PET is generally covered only when SPECT is inconclusive or in patients at risk of attenuation artifacts on SPECT, so very obese, women with dense breast tissue, etc., and hybrid imaging, in terms of private payers, is generally not covered, considered experimental or investigational.

So, to summarize, the comparative evidence that we've reviewed suggests that SPECT provides incremental diagnostic and prognostic information over ETT generally in higher-risk patients, but at least in some studies in patients at any level of CAD risk, performs comparably to stress echo in symptomatic patients, is of lower or uncertain benefit in asymptomatic patients at either high CAD risk screening patients or with known CAD, in terms of followup. There are important tradeoffs to consider in terms of costs, radiation exposure, and other considerations in comparing these testing strategies, evidence on PET and hybrid imaging is currently insufficient, in our view, to determine its comparative clinical effectiveness and value.

So, we also had discussions with several clinical experts in the production of the report, and we found that in their views, this was not scientifically tested, some areas of potential nuclear imaging overuse included serial imaging in asymptomatic patients, again something that's not supported by appropriate use criteria and that may be having an impact, in tests ordered by nonspecialists. One cardiologist told us that it was his feeling in dealing with primary care that oftentimes there is a need to have an image. It does not necessarily, it's obviously not completely the case across all clinicians, but there is a need to have an image when the test is referred to the cardiologist, and the cardiologist in some cases may not have wanted to do the test. If there is a need to do initial testing in symptomatic patients at lower risk, there should be some consideration of those tests in patients who do not have contraindications that do not involve radiation exposure and are potentially less expensive. So, I will take your questions over there. Does that make sense?

Craig Blackmore: Thank you. Questions from the committee on the evidence report?

Richard Phillips: Yes, I have a question about hybrid testing. Obviously in the patient populations that we're discussing, you either found very few tests, very few studies or no studies at all. Were those tests, I mean, just to consider as a committee, those tests were included in the other studies and they are just so small that they did not appear?

Daniel Ollendorf: We actually found very few studies that even evaluated hybrid testing in comparison to another testing strategy. So, that was really the reason. It wasn't that we were not using data that was available. It just wasn't… the studies were not there.

Richard Phillips But in some of the direct tests between the other tests between SPECT and PET, there were some hybrid findings in there, as well? Is that?

Daniel Ollendorf: I'm not sure I'm following you.

Richard Phillips: Let me think what slide that was.

Daniel Ollendorf: There might have been some confusion, because there was one study that examined PET, SPECT, and CCTA as individual modalities.

Richard Phillips: Yes, yes. Right. That's what I was looking for.

Daniel Ollendorf: So, there was no hybrid interpretation of any of those tests.

Richard Phillips: Oh, okay, alright. Yeah, thank you.

Daniel Ollendorf: And getting back to the question on the DIAD Study, there was a question about the duration of followup, and it appears that, oh, no, that was, I'm sorry. The DIAD Study was five years. One more second. So, in the women's study, that was the comparison of SPECT to ETT in low-risk women, that was a two-year followup.

Kevin Walsh: I have a question about slide 23. When the… when you're talking about the direct effects, you say reduce from vascularization rates. So, just to clarify, that means the likelihood of patients in each group having a procedure for revascularization, so angiography?

Daniel Ollendorf: Right, that's correct.

Kevin Walsh: And then, so then I'm curious. What was the effect size, or do you have any assessment of the effect size, of the difference between those groups?

Daniel Ollendorf: Well, so we, because we didn't do a quantitative synthesis, there is no pooled estimate of effect size. I can certainly look up what the results were in particular studies, though.

Kevin Walsh: At least in the one randomized trial if I could have, if you knew that information.

Daniel Ollendorf: So, in the high risk population?

Kevin Walsh: Yeah.

Daniel Ollendorf: Yeah. I'll look that up and get back to you.

Kevin Walsh: Thank you.

Chris Standaert: I had a question, just on the model. These models always trouble me, because you make so many assumptions in them, and some of is clear and not totally true, and every time you make a model and you introduce assumptions, you introduce error, and everytime I see the data, there's no sense of the margin of that error, so I get a finite number. I know those numbers are probably nowhere near accurate, but I don't know what my error is. So, I just fundamentally have that problem, but my question is, it looks like we were given, from the agencies were given multiple different scoring systems for low, moderate, and high-risk patients and what the actual probability of having that cardiovascular disease, either symptomatic or significant cardiovascular disease, do we have any idea of sort of these different categories? Has anybody ever written about the actual rates of coronary disease in these categories by the way their stratified so we know whether we're talking, because every time you change by a few numbers, you dramatically shift your equation. Is low really 10%? Is moderate really 50? Is high really 90? Do we have any idea?

Daniel Ollendorf: So, essentially, our guiding principle going into the review was to think about the populations in terms of pretest probability. So, using the Diamond and Forrester classic rankings for pretest probability, which were, Diamond has written about this extensively. So, these were models, nomograms that were evaluated, validated, and tested in research populations, but there was a recognition when they were published that they tend to overstate substantially, in some cases, actual prevalence in the community. So, what we attempted to do with the model was to come up with approximate underlying prevalence figures that would relate to those categories of pretest probability, and there's not a, sort of a clear guiding light to say that high risk is 50% or is 60% or is 70%, but at the same time, from a decision-making standpoint, and maybe Dr. Redberg can comment on this, as well, it's less important to think about whether intermediate risk means 30-70% or 10-90%. It's more important for the clinician to think about the information available. So, I guess the conclusion is that the measure of underlying prevalence in comparison to pretest probability is not exact, but it was our best approximation.

Chris Standaert: Meaning that 50% is moderate, or 50% is high, or?

Daniel Ollendorf: High.

Chris Standaert: High. So, moderate is somewhere around...

Daniel Ollendorf: But we also, we produced results for 2%, 10%, 30%, 50%, and 70% so that you could see how things changed over the range, in the report.

Craig Blackmore: Do you want to comment, Dr. Redberg?

Rita Redberg: Sure. I think, you know, Dan gave a fair assessment of it. The problem is, probably clinically people don't rate risk the way it's done here, and overall we're probably testing patients on the much lower risk ends of the spectrum. I mean, the national data, and I think maybe we'll get into it later, shows that, and you alluded to it when you showed how… how much, um… how tiny the percentage of abnormal findings is, in terms of the overall nuclear tests. The national studies show that somewhere between where you're looking, 30-60% of patients getting nuclear testing are asymptomatic. So, you'd have to say that we're looking at a very low risk part of the spectrum. So, I think

the estimates of pretest probability are fair. They are based on coronary angiography, because that is considered the gold standard in most of the studies, but that overall clinically what we're looking at are on the low-risk end of that spectrum, and some of those scores, like the Framingham and the Reynolds, they were designed to be used in asymptomatic patients, which are, by definition, less than 10% CAD prevalence.

Craig Blackmore: Other questions? Well, I happen to like decision analysis models, because I think they help understand complex concepts that you can't summarize in a simple 2x2 table. So, it always helps me to put things in context. That being said, I was a little unclear on, in the model, which is driven by accuracy data and purely anatomic data as I understood it, and you had talked about the PET piece, and again, being driven by the accuracy in the PET data, but I also got the sense from some of the other things you said that the PET data was pretty limited. So, I wanted a better feel for the strength of that accuracy data around PET.

Daniel Ollendorf: So, essentially, there's a couple of connections to make here. So, we focused our literature search on comparative studies of PET to other modalities. We limited our analyses on the clinical side to diagnostic accuracy studies that used a functional reference standard. So, we found three PET studies of outcome and three PET studies of diagnostic accuracy. There are many more PET studies with diagnostic accuracy that use anatomic reference standards, and because we were trying to evaluate all of these testing strategies in the model, we could only find anatomic data for all of them. So, we had functional reference standard data for PET and SPECT, but not, and a little bit for echo, but not for ETT. So, we had to go back to large scale meta-analyses using an anatomic reference standard to get information for all strategies. That's really why I tried to use the cautionary language around exploratory with PET, because it wasn't really, that evidence base was not a focus of our review.

Chris Standaert: I had a question on the radiation thing, radiation fees? The ranges in the radiation exposure for these studies are ginormous. I sit there and I think about risk, you know, trying to compare the risk of, you know, less than a CT scan or maybe a couple of x-rays versus a mile from Hiroshima, you know? Your range covers that whole thing. So, what is the reality here? I mean, does in current clinical practice, not studies from 20 years ago, not, but in current clinical practice, and by current standards of radiation studies and radiation exposure, where are we in the doses required for these tests, because I really don't know, and the range is huge. I'm not sure how to assess that in my head very well.

Daniel Ollendorf: So, the range is, in fact, wide. There are dose-sparing protocols that are used with a number of these tests, and some of them are used by certain centers and not by others. There is the inter-, I didn't really mention this during the presentation, but the use of CT to correct for attenuation artifacts actually introduces additional radiation exposure, as well. There's another table in the report that looks at radiation exposure, specifically for SPECT. This is a table that's adapted from another study, and it appears at the higher end of the range where SPECT is for thallium SPECT testing and I think predominantly in the U.S. it's sestamibi or Tetrofosmin, if that's how you pronounce it, that's used, which has a lower effective radiation dose, and maybe you can speak to this, too.

Rita Redberg: So, you've identified a really huge clinical problem, because there is a huge range, and not only do patients not know how much radiation they're getting with any particular test, but the ordering physician generally doesn't know. I mean, there have been surveys done of physicians, including radiologists, and they have no idea, and it's even harder than that, because, you know, there have been studies published. There was in

the archives of Internal Medicine about a year or two ago where they actually measured the radiation exposure for a very, this was for CT, but it would certainly apply to myocardial perfusion imaging, for a variety of tests done at different institutions around the Bay Area, as well as the same test at the same institution, and the range was up to 30-fold for the difference in exposure for the same tests at the same institution. So, it's a very big issue. It's not just that there's variability in the tests, but, you know, as we know from the kind of problems that came to the surface with some of the lawsuits over brain perfusion imaging, you know, things go wrong that we don't, there are attempts now by the society, you know, the radiology societies and a little less by the FDA and the government, which after those articles came out in 2009 held a hearing on radiation and talked about a lot of things they were going to do to kind of make sure that these very high exposures weren't occurring without anyone knowing about it, but the truth is that nothing has actually changed very much. So, there's just a wide variability in radiation exposure that is very hard to quantitate, and patients and physicians don't know, besides the inherent variability in the technique.

I had a question on slide 23 that just… did you only include the revascularization rates in the summary of mortality and risk of cardiovascular event, because those were the only events that were reported. Those are generally considered soft outcomes, and I'm wondering if there were any hard outcomes like MI or death?

Daniel Ollendorf: There were hard outcomes. So, in some studies, the definition of major adverse cardiovascular events included revascularization. So, when there's a mention of revascularization, it's typically when that's the only outcome that differed between strategies. So, there were no differences in MI or stroke or other events like that, and it's just not described on that summary table.

Craig Blackmore: Other questions from the committee? Okay, we're going to take a short break. I've got 5 of 10, so we will resume at 10 past 10 for further committee discussion.

I'm going to ask the committee members to resume their seats, and we will… or take their seats, and we will resume the meeting. How's that?

Marie Brown: Has it always been the case that we weren't able to see some criteria for prior authorizations for other kinds of things, or that they weren't public?

Craig Blackmore: It's always been the case that companies have proprietary [inaudible], and it's a great mechanism to deny because everybody knows what the rules are.

Marie Brown: So, you can't challenge them.

Craig Blackmore: Okay, we are back in session, and I am going to give the committee, if they have any questions they've come up with in the break here that they want to ask either the agencies or our clinical expert or our evidence group, this would be a good time to do it? Any other questions from the committee? And then Daniel, did we get all, were you checking some things for us, or did we get all that? Maybe we got it all.

Daniel Ollendorf: I think I answered everybody's questions, but if anybody has another one?

Kevin Walsh: I'd asked you about the effect size for that one randomized trial.

Daniel Ollendorf: Oh, right. Sorry. I will look that up.

Craig Blackmore: Okay. So, it is useful, as we start our discussion, we're into the committee, our time, this is when we make our decisions. It's always useful to have somebody sort of kick us off and give a perspective on where they think we're headed and use that as an anchoring point as we start to make our decision. So, I think we're faced with a number of different clinical scenarios here. I am going to see if I can find the right clinical questions and we're going to have to do some level of lumping and splitting how many of these different groups we're considering, high risk, low risk, different modalities separately and together. Alright, I need a copy of the clinical quest-, of the key questions, which should be in the...

Josh Morse: They're on the slides.

Craig Blackmore: …slides. Sorry. I know it's here somewhere.

Seth Schwartz: Page 5 of ICER.

Craig Blackmore: Okay. So, key questions. So, we are asked to address, basically, SPECT, PET, and hybrid imaging modalities in different groups of patients, asymptomatic, low to intermediate, and high risk, known/unknown coronary artery disease, and I said symptomatic versus asymptomatic. So, can I get a volunteer from the committee to start us off on the discussion, maybe with perspective on how we might lump or split here?

Daniel Ollendorf: Craig, can I just, I just want to get back to the question about the effect size in that high-risk RCT. So, in terms of revascularization, in the SPECT arm, the proportion of patients who were referred for angiography that then were revascularized was 66%. In the ETT arm, the proportion referred to angiography who were revascularized was 38%. That was statistically significant at 0.005. In terms of any further diagnostic testing after the initial test, the rates were 74% for ETT and 16% for SPECT with T-value less than 0.0001.

Kevin Walsh: Thank you.

Craig Blackmore: I'm sorry. I didn't hear that interchange.

Kevin Walsh: I asked if the numbers for subsequent testing was separate, really was 74% for SPECT and 16% for...

Daniel Ollendorf: Other way around.

Kevin Walsh: Okay, 74% for treadmill testing and 16% for SPECT.

Daniel Ollendorf: In this particular situation, subsequent testing could have been angiography or echo after the initial test. So, 74% for ETT included a portion of patients who received echo and others who went straight to angiography.

Kevin Walsh: Okay, that's not very helpful.

Chris Standaert: I just have one quick question in the scope of the review. So, in the project scope, you guys note that your population is asymptomatic, high risk, high risk patients was included, but when I go to the agency recommendations that they are looking for, they say screening for asymptomatic patients at low, intermediate, and high risk. Did you look for data on screening of asymptomatic patients at low and intermediate risk, or was that not part of the scope of what you did?

Daniel Ollendorf: The scope, as we discussed with the agency medical directors, was focused on asymptomatic at high risk.

Chris Standaert: So, you didn't look for information on asymptomatic low-to-moderate risk individuals, so we don't have that data if it exists?

Daniel Ollendorf: Right.

Chris Standaert: I just wanted to make sure.

Marie Brown: So, if there's nothing for high risk, there wouldn't be as much for, there wouldn't be things for lower.

Chris Standaert: They didn't look though.

Marie Brown: Right, okay.

Craig Blackmore: Alright, does anybody want to take a stab at starting us off here?

Seth Schwartz: Sorry, Craig, can I ask just one more question?

Craig Blackmore: Absolutely.

Seth Schwartz: I'm just curious about the, the health-related quality of life assessment. I'm trying to understand how they actually did that assessment. What were they really comparing in those groups? I mean, did everyone who got SPECT, did they just do a quality of life assessment in everyone who got SPECT and everyone who got ETT and then, and at what point did they do the assessment of quality of life? I'm just trying to figure out what that piece of data even means for this kind of testing.

Daniel Ollendorf: Yeah, these occurred primarily in the RCTs that were part of the sample, and essentially they were done like they would have been done in any other RCT of any other intervention. There was a baseline assessment done with the patients and then when they came for followup at various timepoints, it was done again. So, these were analyzed as change scores, essentially, from baseline, a change in quality of life from baseline for every patient in each arm.

David McCulloch: Craig, I would… I think we can dispense with asymptomatic patients quite quickly, since I don't think there is any evidence that these studies are helpful in asymptomatic individuals in theoretically low, moderate, or high risk, and I think our ability to identify high risk people is very weak. I mean, I can't, it's interesting that up to 30, or over 30% of these tests are now being done in asymptomatic individuals. Diabetes is very often picked out as a great example, because it's a "cardiac risk equivalent," which of course it isn't. The amount of increased risk of heart disease you have, having diabetes, depends mass-, entirely on how long you've had it, how poorly controlled it's been, and a whole bunch of different factors. So, I mean, it's one of these weaknesses when it's used in Framingham or any other study, because it's just present or absent. You can have two 42-year-old individuals with diabetes with massively different risks. So, I just think our ability to identify low, medium, and high risk in asymptomatic individuals is [inaudible] and I don't see any evidence that these tests would help, so I think we can dispense with that and say that none of these tests should not be covered for asymptomatic individuals.

Craig Blackmore: Okay. So, sort of in the big picture, we can divide into symptomatic and asymptomatic, as you're proposing, and so why don't we start with the asymptomatic, and we have a starting point. Do other people have thoughts on where the data leads us in the asymptomatic group, or are we all on the same place here?

Seth Schwartz: I agree with David. I looked at the one study that I thought was interesting was the Young Study, it was on page 47 of the review. It was comparing SPECT based one time screening to no screening, RCT of 1,100 asymptomatic patients with diabetes followed for five years, no difference.

Craig Blackmore: You said 47?

Seth Schwartz: Well maybe I got the page wrong. I'm always looking at the top, instead of the actual page.

Michael Souter: 94. There's a discussion of the Diad Study, [inaudible], the Diad Study, page 94.

Seth Schwartz: Thank you.

Craig Blackmore: And then that was also summarized in the...

Michelle Simon: It's on slide 21 of the ICER.

Craig Blackmore: 20, yeah, okay, 21.

Michael Souter: The only difference was in the rate of revascularization, which was higher in the screening group, therefore indicating that if you look for something you're going to do something about it.

Craig Blackmore: You're gonna find it. Any other thoughts on the asymptomatic? I'm willing to move on unless I get difference from other members of the panel, or?

Carson Odegard: Well, some of the, some of the guidelines mention asymptomatic patients with, you know, higher than 80% stenosis. Obviously, those patients have been detected as a risk… as a high risk.

Craig Blackmore: So, presumably you did something to that patient or you wouldn't know that.

Carson Odegard: Something had to happen. Something had to happen, yeah.

Seth Schwartz: Isn't that followup in asymptomatic patients. I mean, I guess that's the one difference. Are we talking about asymptomatic at baseline versus patients who have had some form of treatment and are asymptomatic?

Craig Blackmore: Well, right.

Chris Standaert: If there's a known cardiac [inaudible].

Craig Blackmore: Known cardiac disease.

Seth Schwartz: I mean, I think those are different.

Craig Blackmore: Okay, so we're, we're talking about asymptomatic initially. We're talking about asymptomatic, no known coronary artery disease, so not, right. Okay, and then, okay, any other thoughts on this particular group? Alright, how about if we get into symptomatic, and of course symptomatic means symptoms that may or may not be referable to your coronary artery disease if you have it, and then we get into low risk and low, intermediate, and high risk, etc. Where are we on symptomatic? Nobody will make eye contact with me, and that's not a good sign.

Chris Standaert: That's not a good sign, no.

Craig Blackmore: Seth, what do you think?

Seth Schwartz: Well, again, I'm just looking at slide 22 at, you know, for the mortality risk factor. It looks like there is moderate level of evidence and some improvement relative to ETT mixed versus echo in the intermediate to low risk group. So, you know, there's something there. I don't want to really, and again, I'm struggling with what to make out of this quality of life data. I think, you know, when you look at the likelihood of events in all these populations is very, very low. I don't know, we're looking at, I think it's somewhere around 2 to 3% of actual event. So, when you're looking at differences versus, in groups of 1,000 patients and you're trying to quantify a difference of, you know, a fraction of a point on a scale of a quality of life questionnaire, I just don't think that's a… it's just not valid for what we're looking at. So, the only outcome I think we have to really look at is mortality. It's hard to know what to make out of downstream testing, because it's the same problem that we have with screening, which is if you look for it, you're going to find it, the same kind of thing. If we have a test that's more likely to show us something, you're going to get more, you're going to do more testing afterwards. So, I'm struggling what to, what to do with that data, as well, but it looks like there is some small amount of evidence to suggest that using SPECT as a first line treatment in symptomatic patients with low to intermediate risk may improve mortalities by some small amount.

Kevin Walsh: But when you looked at cost data, when you factored that in, as well, I thought that the benefit kind of disappeared, and they posited the value of a two-test strategy using treadmill testing and then moving on to SPECT, as perhaps a more cost saving approach.

Seth Schwartz: I think, you know, one of the other questions here is, that I'm trying to figure out clinically, not knowing much about this is, it seems to me that's essentially what's happening. If patients can undergo a successful or at least you would assume that they could have a successful treadmill test, that that's a reasonable place to start, and so we're talking more about the patients in whom you don't think you could do well with that test. So, for instance, if they're unable to exercise or if you don't think their EKG is interpretable, then it doesn't seem, then that two-test strategy seems not so good anymore if the first test is not likely to be doable.

Kevin Walsh: Yeah, I was kind of assuming that.

Seth Schwartz: Yeah, so, I think that's a reasonable point.

Craig Blackmore: So, is, I'm sorry. I can't see Dan too well. Can you help me to understand slide 22, sort of where we are? The symptomatic patients at low, intermediate risk. So, the one RCT here, is this, this is the women's study?

Daniel Ollendorf: The women's study, yes.

Craig Blackmore: And the women's study is, I'm looking on your report, page 94, it seems that it actually didn't show a difference, is that correct?

Daniel Ollendorf: Correct.

Craig Blackmore: And that's why you say here, mixed evidence.

Daniel Ollendorf: Right, there was no...

Craig Blackmore: So, moderate strength. We've got some good data but what we find is, in fact, not at all clear one way or the other. Is that?

Daniel Ollendorf: Right.

Craig Blackmore: Or am I reading this wrong?

Seth Schwartz: You had mentioned a second study.

Daniel Ollendorf: There's a second study. There's a cohort study by Olmos and colleagues.

Craig Blackmore: So, there's one randomized trial and then there's some cohorts, is that right?

Daniel Ollendorf: Right. The Olmos Study is a large comparative cohort study that showed the incremental benefit of, or examined the incremental body of SPECT information, echo information over ETT in clinical parameters alone and showed a significantly higher area under the curve for both SPECT and echo, in fact.

Seth Schwartz: I guess I would have a question about that same study, the women's study from our clinical expert. It was a two-year followup. That seems fairly short in terms of if you're evaluating a low to intermediate risk group trying to look for a difference. Do you have any sense of, you know, what would be an appropriate duration of followup to really see differences in that group? Dr. Redberg?

Rita Redberg: How long you would need for followup?

Seth Schwartz: Yeah, for, I mean, for...

Rita Redberg: Well, as you said, with a [inaudible] so low that you need a very large cohort with no long follow-up. So, I suspect that even with long followup, you're not going to see big differences, because it's a low risk group to start with. So, I mean, if you wanted to look at it from a different point of view, you know, a number needed to test, it would probably be very high, because you're looking at number to test to prevent one event. The other point I'm going to say is important, because, and Dan was very comprehensive in the tables and included the comparison to treadmill or to echo, but those are slightly different, because most of the diagnostic accuracy numbers were similar for both imaging tests, and then you're just talking about what ends up to being individual preference for a lot of labs, you know. I think overwhelmingly people choose nuclear, but if you're looking at costs, you know the cost of echo is about half the cost of nuclear, and there is the other big factor, to me, is the radiation issue, which can be quite large. There was an Einstein publication from JAMA a few years ago where they looked at their own experience at Colombia in myocardial perfusion...

Craig Blackmore: So, I'm, I'm sorry. Was that a publication part of your…?

Rita Redberg: You know, this one only looked at radiation dose, so it wasn't looking at accuracy. So, I don't think it was.

Daniel Ollendorf: It's an earlier, an earlier Einstein publication. I'll take a look.

Craig Blackmore: So, this is about dose, is that what you want to share with us?

Rita Redberg: Yes, is that okay?

Craig Blackmore: Sure, yeah, sure.

Rita Redberg: Only to put in context. It said, as Dan presented in the introduction, that the overall medical radiation in the U.S. has increased six-fold from… they looked at a 20-year period from the 1980s up to 2006 and that 22% of the effective radiation dose from medical sources is from myocardial perfusion imaging. So, one-fifth of all medical radiation is MPI, and it's estimated to account for more than 10% of the entire cumulative effective dose to the U.S. population is myocardial perfusion imaging. So, that's something to consider. The last thing I'll say is, the IOM report on breast cancer identified medical radiation as the number one environmental cause of breast cancer in the U.S.

Craig Blackmore: Yeah, you can't… I'm just saying, we could spend all day talking about radiation dose, but you certainly cannot make a concrete linkage between medical radiation and any diagnosed cancers, because it's, there's… it's… the evidence is very indirect. It doesn't mean it doesn't happen. It just means you can't make such conclusions. Okay.

Chris Standaert: I just, I want to try and clar-, and so we're still on the… we're in the low to intermediate risk symptomatic, yes?

Craig Blackmore: We are symptomatic low to intermediate risk.

Chris Standaert: So, I'm trying to go back to the user model to help me, right? So, theoretically, you know, an echo or an ETT would seem to have advantages over SPECT or PET because they're cheaper, and there's no radiation. When you go to your model and you give a very low prevalence of CAD, you have very high false positives in ETT. If you have high false positives, it seems that those people go get something else. They get a cath. They get a something, because they're, but that's the, they're overwhelming outnumbering the true positives. So, the data you gave us was somewhat mixed in terms of downstream decision making, but there wasn't a lot of data on it. So, you know, you can save money in radiation up front with a test that's cheaper, but if it really has a very high false-positive rate and leads to more stuff, then it may well wind up being more expensive and more risk provoking, because it accounts for more things being done, but...

Kevin Walsh: How can it be more risk provoking?

Chris Standaert: Well, the false-positive rate is so much higher.

Kevin Walsh: I know, but you're starting with a...

Chris Standaert: In the low risk population.

Kevin Walsh: …you're starting with a nonradiation based test, as opposed to a radiation-based test as a screening test.

Chris Standaert: Yeah, but your false-positives are a third of the people being screened, at least.

Kevin Walsh: But the radiation test might be the subsequent downstream test you do.

Seth Schwartz: But it's not just radiation. I mean, angiography is the other thing.

Chris Standaert: Angio. They're going to go cath.

Seth Schwartz: And that, isn't that like a 1% stroke risk? What's the, do we know what the stroke risk or risk of negative events from catheterization? That's pretty high too?

Daniel Ollendorf: About 1%, yeah.

Seth Schwartz: So, I mean, 1% risk of stroke versus this theoretical risk of risk of radiation, I mean, you know, there's bad things either way.

Craig Blackmore: So that's all encompassed on slide, page 19, whatever it is. I mean, we've got a number of patients who are referred for angio. We've got the estimated deaths from angio. We've got the number who are getting exposed to radiation, whether it's from the initial test or all subsequent tests.

Daniel Ollendorf: Keep in mind that the high false-positive numbers in that low prevalence population are for treadmill testing with referral directly to path for positive or equivocal results. If you move over to the right and you look at treadmill testing as a negating test before another noninvasive test, you see a much lower number of false positives.

Chris Standaert: Okay, say that again.

Daniel Ollendorf: So, if you go to the right three columns.

Chris Standaert: Oh, you're doing it sequentially.

Daniel Ollendorf: Yeah.

Chris Standaert: If you did them sequentially.

Joann Elmore: Yes.

Daniel Ollendorf: Yes.

Chris Standaert: And that's assuming you're SPECT'ing the people with the normal ETTs. Is that how that algorithm works?

Daniel Ollendorf: Abnormal or equivocal, yeah.

Craig Blackmore: So, instead of SPECT'ing everyone, you SPECT a subset basically.

Joann Elmore: Right.

Chris Standaert: So when you're, in your other terms of use, terms like an uninterpretable EKG, do you mean uninterpretable ETT? Or do you mean just a standard EKG, for the noncardiology people here?

Daniel Ollendorf: So, ETT...

Chris Standaert: Because you talk about uninterpretable, so now you just said you have an equivocal ETT. Is that what you mean when you go to the other table and you say an uninterpretable EKG?

Daniel Ollendorf: Right, although, if you look at the coverage policies, when they talk about uninterpretable EKGs, they are talking about resting, a standard resting EKG, yeah.

Chris Standaert: Okay.

Daniel Ollendorf: So, in this case, this is an ETT that was determined to be equivocal or nondiagnostic or shows abnormality. In either case, you go to the next test.

Chris Standaert: And then you go to the next SPECT. Okay.

Rita Redberg: Because the professional guidelines suggest you should start with a treadmill test alone for people that have an interpretable ECG, and so, and that's with the uninterpretable. Like, if you have a left bundle at baseline, then you wouldn't, because a treadmill test you're only reading the ECG as the result.

Chris Standaert: Right.

Rita Redberg: Although in practice, that's not what occurs, and I think 90-95% of patients getting a stress test are getting an imaging test in the U.S., but our guidelines state that if you have an interpretable ECG, you know, a normal ECG, [inaudible].

Chris Standaert: You just measure. You just watch the ECG. You wouldn't get an imaging component to it, too.

Rita Redberg: That's right, and that's what's recommended in the guidelines.

Chris Standaert: And so it isn't typically what happens.

Rita Redberg: And there's been a shift to use imaging lately.

Chris Standaert: So, either echo or radiation.

Rita Redberg: Either echo or nuclear [inaudible] in people with this accuracy.

Craig Blackmore: So, in terms of the professional guidelines or sort of common practice, which of these approaches is, sort of, more standard, ETT straight to cath, or ETT to some other sort of imaging modality like echo or SPECT, or is it just all over the map?

Rita Redberg: I think most people go from ETT to an imaging test and not straight to cath. They would only go straight to cath if it was felt to be a true positive test, and that's kind of on your clinical impression. The other point, which is hard to look up in the models, is testing is thought to be most useful in a population of intermediate probability, and so when you

start looking at any test in this very low probability population, it's very hard to have a test that performs well.

Chris Standaert: Right. They're all bad.

Rita Redberg: And here, the question really is, do these people do better with no test at all because they're so low risk and there's very little you're going to do with any of this that will make any impact on outcomes.

Craig Blackmore: So then you start looking at the randomized trial data, which we have very little.

Kevin Walsh: I can't remember the last time that I sent the patient for a treadmill who didn't get an echo in my community, and I'm sure my in is miniscule, but I am out in the real world, so I was struck by the lack of difference between the ETT to echo and ETT to SPECT numbers in slide, the slide at the bottom of page 19.

Chris Standaert: Well all I got there is being, other than radiation, they seemed relatively close.

Kevin Walsh: Right, the radiation exposure is significant.

Chris Standaert: They seem relatively equivalent otherwise, going to echo over SPECT using that model.

Kevin Walsh: But, that's in the low prevalence population.

Craig Blackmore: Low-intermediate.

Seth Schwartz: To clarify what's happening clinically here, so, I just heard it referred that there is a 90-95% chance of getting an imaging study if you get an ETT. Is that only if you have a positive ETT? So, if you have a negative ETT, those patients, sorry, those patients are not going on to get additional imaging, or are they?

Rita Redberg: I'm sorry, what I said, if you look at overall use of stress testing in the U.S., most people are now getting an initial test that includes imaging.

Seth Schwartz: So, this… the concept of this, which is, you get an ETT and if it's negative, nothing else happens, is not what's happening.

Rita Redberg: I think that is happening. It's just that very few people, I think if someone goes for a treadmill test and it's negative, they're not likely to get more testing unless they continue to have symptoms, and then...

Seth Schwartz: Okay, so then...

Rita Redberg: …of course they would get more testing. It's just that most people are not being sent, initially, for a treadmill test alone. There is a tendency, just as Kevin I think just said, to have a treadmill test with some kind of imaging as the initial test, even in patients that, by professional guidelines, are recommended to start with a baseline treadmill test.

Chris Standaert: They come combined.

Joann Elmore: And even though the clinical guidelines don't suggest that, starting with a combination, okay.

Seth Schwartz: And then Dan, for the appropriate use criteria, do we note that, which does that specify? Does that specify ETT alone for the low-risk group, as far as the…?

Daniel Ollendorf: So, some of the clinical guidelines speak to intermediate risk, and do describe imaging tests as appropriate in intermediate risk patients. Those that specifically call out low-risk patients do also talk about treadmill testing first.

Rita Redberg: The appropriate use criteria are separate by modality, so they are not comparing. There are appropriate use criteria for echo, and then there's appropriate use criteria for nuclear.

Chris Standaert: And do our studies compare SPECT to ETT with echo, I mean, but being done as a combined, if we consider ETT as a singular test only using the ECG versus combined with, by definition, an echo, they come together, which seems to be in clinical practice what happens much of the time, is what we're hearing, but the studies don't look at that. They look at isolated just an ETT or just a stress echo of some sort?

Daniel Ollendorf: You're talking about?

Chris Standaert: The studies you gave us here comparing…

Daniel Ollendorf: The studies will compare exercise SPECT to exercise echo. Yeah, there are studies that do that. So, exercise echo, essentially, is ETT with echo. There are also studies comparing pharmacologic SPECTs to pharmacologic echo, as well.

Chris Standaert: And so, in your tables when you say ETT as your comparator, you mean just ETT, or do you mean ETT with echo?

Daniel Ollendorf: In the model, we were...

Chris Standaert: In your tables, in your data tables.

Daniel Ollendorf: In the model tables, we are considering ETT alone.

Chris Standaert: The data tables where you talk about the study.

Daniel Ollendorf: In the evidence tables.

Chris Standaert: Yeah, the evidence tables.

Daniel Ollendorf: So, in...

Chris Standaert: If it says ETT, it means ETT alone.

Daniel Ollendorf: If it says ETT, it's just ETT, yeah.

Chris Standaert: Okay.

Craig Blackmore: So, the local coverage decision on slide 50, and this is a summary I assume, says the SPECT is covered when a stress test or EKG is abnormal in symptomatic patients undergoing revascularization. Of course, I don't know how you would know they were undergoing revascularization before you tested them, but, and in patients with known coronary artery disease who have new or significant symptoms. So, that would seem,

again, this is just a summary, but that would seem to imply that you're supposed to have a stress test first, or an abnormal EKG, which would seem…

Rita Redberg: I would suggest that these coverage guidelines are not what actually is covered. I think that a lot of asymptomatic patients undergoing MPI are actually covered under Medicare and other private insurance.

Craig Blackmore: Well, that's what we're here to deal with.

Rita Redberg: You know, they don't use, in most of these cases a preauthorization.

Chris Standaert: And this is, I mean, this is, I assume, this is LCD, I assume it is a cover, a summary of LCDs, and LCDs are all very distinct depending on…

Craig Blackmore: This is our LCD. Well, it's, Dan, on your slide 50, it says LCDs for coverage criteria.

Daniel Ollendorf: Yeah.

Craig Blackmore: So, does that, that may not, is that our LCD or is that just a, sort of a qualitative assessment of LCDs?

Daniel Ollendorf: We looked at those for this region and those for others. There was actually a lot of congruence in this case across them.

Craig Blackmore: Okay. So, we, one of our of charges, one of our responsibilities is that we're required to, when we make a determination, reconcile it with national coverage decisions for Medicare, and we should at least consider local coverage decisions for Medicare and other insurance policies.

Kerilyn Nobuhara: We have the local coverage decision under the state agency slides on page 7.

Seth Schwartz: Right, slide 14.

Craig Blackmore: Yeah, slide 14, you're right. So, number three is abnormal standard stress test, nondiagnostic or inaccurate standard stress test. We may have to look through all of these, but it sounds like this is getting, again, the approach that you should have an ETT first.

Kevin Walsh: This is for intermediate risk we're talking about, correct?

Craig Blackmore: I'm… well, I'm just looking at the local coverage decision, which doesn't say one way or the other.

Kevin Walsh: But look at that first one. Look at the first criteria.

Craig Blackmore: Abnormal EKG with a high likelihood of coronary artery disease or strongly suggestive symptoms.

Kevin Walsh: Right. So, I think we have to parse out intermediate risk and high risk as we try to discuss this.

Craig Blackmore: Yeah, I'm not, we'd have to also understand how we interpret that first bullet point. Does that mean you have to have an abnormal ECG or does it mean abnormal ECG or high clinical suspicion?

Kevin Walsh: I think it means with.

Craig Blackmore: I think it means with. That's not an and.

Craig Blackmore: So, both of these, both one and three, would mean you had either an abnormal EKG or an abnormal stress test, which is basically an abnormal EKG under stress. Right?

Kevin Walsh: Well, I think, I guess the point I'm trying to make is one, saying if you're high risk, an abnormal ECG is enough to get you the SPECT test.

Craig Blackmore: If you're… isn't that the same as an abnormal stress test, though?

Chris Standaert: No.

Kevin Walsh: No. I think that's a resting ECG.

Chris Standaert: A resting, ECG, yeah.

Kevin Walsh: Number one, in my mind...

Craig Blackmore: Right, no I understand that.

Kevin Walsh: …the first two are resting ECG, and number three refers to an exercise treadmill test.

Chris Standaert: I assume they're talking about abnormal ECG and high likelihood of coronary disease or it strongly suggests that you're in the high risk categories is, I think, what they're trying to describe.

Kevin Walsh: Right.

Chris Standaert: So, he's a high risk patient [inaudible].

Kevin Walsh: That's why I'm advocating that we separate it out.

Craig Blackmore: Okay.

Chris Standaert: Low and intermediate versus high?

Kevin Walsh: Correct.

Chris Standaert: Yeah. I would agree.

Craig Blackmore: Okay.

Chris Standaert: Things… the data seems to change a bit when you get to the high-risk group.

Craig Blackmore: Okay, so for procedure, if we're in, I'm going to lump low and intermediate. Does that work? And we're going to lump high, symptomatic, and, um… so what do we do in low intermediate? Kevin, what are you advocating here?

Kevin Walsh: Well, I think that Chris had accurately pointed out that there's not a whole lot of… the only difference that you see is that there's higher radiation exposure for a group of patients.

Craig Blackmore: From the model, yes.

Kevin Walsh: In the model. There's also a cost difference. So, I, when I look at the data that the ETT, as an initial required, an abnormal ETT, then get you a radio-based study. That seems to me to make the most sense. When you try to factor in the numbers, in terms of effectiveness, cost, and risk.

Craig Blackmore: Okay, so there's two issues. One is the idea of ETT as a gate to get you to...

Kevin Walsh: And this is ETT for people who can perform the ETT.

Craig Blackmore: Right.

Kevin Walsh: For people who can't perform the ETT, the 40% that was referred to, they get a pass. They would go right to the...

Craig Blackmore: Okay, so there's two issues. That's the first issue, and then the second issue is, are we differentiating between the stress echo and the stress SPECT, in essence? So, you have your ETT first, and then there's still two pathways, right? There's the stress echo pathway and the stress SPECT pathway, or the SPECT rest stress. So, what are you saying there? Are you saying that we'll leave that up to the...

Kevin Walsh: Well, I'm saying that the radiation exposure, yeah, I mean, that's a good point, and maybe I mis-spoke. I mean, that would, if you just look at the radiation exposure difference for those two groups of people, the echo is probably the safer test.

Craig Blackmore: So, I'm not, so I think the first thing is the concept of you have to have an abnormal ETT/EKG or you can't do exercise before you are allowed to have the imaging. So, let's talk about that first and then talk about if we want to have it specified among choices of imaging. So, what are our thoughts on having an initial filter based on having an abnormal treadmill test, having an abnormal EKG, or being unable to exercise before?

Kevin Walsh: Yeah, I wouldn't lump an abnormal treadmill test and an abnormal EKG as being equivalent for intermediate risk patients, because I think that the abnormal EKG, the prevalence of those is high enough, and now you're looking at a population where the actual disease incidence is low.

Craig Blackmore: Okay.

Kevin Walsh: So, I would throw out abnormal resting EKG and say abnormal exercise treadmill test.

Craig Blackmore: Okay.

Kevin Walsh: Okay.

Craig Blackmore: So, and we can fine tune, but conceptually, I want the big picture. You have to have… we don't just do this on everybody. We do it on people that meet certain criteria around the endotracheal, endotracheal. I'm still thinking ETT. I think endotracheal

tube. I'm sorry, the exercise treadmill test, we have a gateway built around the ETT plus some other criteria and whether you can exercise or whatever else it is. So, is that, how does the committee feel about that concept, because I think that...

Marie Brown: Without an echo, ETT alone.

Craig Blackmore: Before you get to the next, before you image.

Marie Brown: Right.

Chris Standaert: Well, we can't come in a… we're not talking about echos. We're talking about the radionuclide.

Marie Brown: Right.

Chris Standaert: So, we're only talking about SPECT and PET.

Craig Blackmore: Because there is a risk, and the risk is you make it easier to get an echo than a SPECT study and so everybody just gets an echo.

Chris Standaert: So, if we, can we go back to the data and see where those studies…?

Craig Blackmore: Yeah.

Chris Standaert: So, we have this little category, right? Low to intermediate, and this is different than high, and it's not stunning that ET, that their comparators, in the downstream testing, they compared to have ETT and an ETT with echo, which is probably not our current clinical standard of care. You don't get… there isn't a lot of difference, it doesn't look like.

Michael Souter: What are you looking at?

Chris Standaert: Page 11. So, we're looking at...

Craig Blackmore: And again, this is ...

Chris Standaert: …slide 22, page 11.

Craig Blackmore: ...this is the women trial, it's the RCT, and then there were some other cohort, and in the women trial and supported by the cohorts, there is moderate evidence, there is reasonable evidence that's out there, but there's not any real difference.

Chris Standaert: Right, and [inaudible] somewhat short-term follow-up for this risk category, which is two years, which is not a long, not very long for low to intermediate risk patients, I wouldn't think. So, our evidence isn't phenomenal one way or the other, but there doesn't seem to be any glaring evidence that says one is superior? Is that how… that would be my reasoning.

Joann Elmore: Except for SPECT has a higher rate of referral to angiography.

Craig Blackmore: Versus echo?

Seth Schwartz: And what does that mean?

Joann Elmore: I don't know.

Seth Schwartz: What does that third column mean for the downstream testing? That people who got SPECT got more downstream testing? When it says downstream testing and clinical decision making?

Kevin Walsh: No, he said, he said 9%... 9% of people got SPECT, so this was crossover I guess, and 18% of the abnormal ECT, ETT, or 18% of the ETTs ended up getting a SPECT. So, it's 9% versus 18%.

Chris Standaert: 9% of the SPECT got another SPECT.

Daniel Ollendorf: So, in the women's stud, 9% of SPECT patients got a repeat SPECT, 3% of ETT patients got a repeat ETT, and 18% of ETT patients crossed over to SPECT during the two years.

Craig Blackmore: So, this was ETT versus SPECT. So, we don't have echo in the picture?

Daniel Ollendorf: Only in comparative cohorts. Not in the RCT.

Craig Blackmore: And in the comparative cohorts, was there a difference in utilization of downstream angio and revascularization between SPECT and echo?

Daniel Ollendorf: Between SPECT and echo? No.

Seth Schwartz: Okay, can I just try to understand that a little bit. Why would people get a repeat SPECT? I mean, I'm just trying to, I mean, is there a reason, or is there an indication? What would be the indication for getting a repeat SPECT?

Daniel Ollendorf: I can look at the study report and see.

Seth Schwartz: Within two years.

Daniel Ollendorf: It may have been that the initial SPECT was nondiagnostic.

Seth Schwartz: And then you had more symptoms.

Craig Blackmore: Yeah, something changed.

Daniel Ollendorf: Something changed. I'll take a look and see.

Richard Phillips: Something changed.

Rita Redberg: It's all kinds of those, and there are doctors that recommend annual SPECT. I've had patients come to me and say, it's time for my annual SPECT.

Kevin Walsh: But this is a randomized trial. I'm just trying to think, in a randomized trial setting, why that would be happening.

Craig Blackmore: So, am I hearing support for the gate/gatekeeper concept thing here?

Group: Yes.

Chris Standaert: No, yeah, I think we should, if we phrase it in terms of our data. If we go to the data and we view the data as somewhat limited, the women's study is all female, which limits the population a bit. The other cohorts aren't. They seem to be relatively equivalent in this population in terms of predicting additional bad things, and you don't seem to get a lot more for the SPECT, and then you would, in our decision model tool, you would decide that, and you get down to cost and safety, and you have to decide which is, and if you're just looking at ETT, perhaps it's cheaper. I suppose if everybody is getting ETT they are also getting echo. By the numbers we have it probably isn't much cheaper than just getting a SPECT frankly. So, you get down to the radiation issue, it would be the safety issue, but in our tool of how we think about these things, that's how I would start to think about it. So, in absence of difference in efficacy or benefit of the test, you start thinking about the harms of the test.

Seth Schwartz: Especially when the costs are relatively equivalent.

Craig Blackmore: And so we're stuck in a little bit of a practical quagmire, because our goal, I think, would be to say you should have ETT before you have an imaging study, but our charge is only to look at the nuclear piece. So, we could require this ETT before nuclear, but we can't require before echo, because that's outside of our scope. So, the easiest pathway then might be just to go to echo, which would be unintended consequencing.

Seth Schwartz: But I think that's, I mean, it sounds like [inaudible]

Chris Standaert: It sounds like that's what's happening already.

Seth Schwartz: I think I kind of agree with Chris. I mean, our question is, is SPECT more… is SPECT a better test than ETT or is it more effective than ETT, and what we're seeing here, as far as the data is, there's no conclusive evidence that it's a better test, right? So, that's question number one. Number two is, okay, if you have two tests that are equivalent, then how do you decide which to do? Well, if one has more harm and is more expensive, then that's less, then that's not going to be the way to go. So, then you can say, okay, well that's been, you know, ETT certainly favors as the first test, but it's because of… it's equally effective, less harmful, and cheaper.

Craig Blackmore: Right.

Seth Schwartz: At least in this population...

Chris Standaert: Right.

Seth Schwartz: ...we're talking about now.

Chris Standaert: Then SPECT becomes something you consider when you can't do the ETT, or you can't… or it's uninterpretable or something for some reason.

Craig Blackmore: Second line.

Chris Standaert: It's a second-line test.

Daniel Ollendorf: Just to respond to the question in the women's study about the repeat SPECT, so the overall rate was 9%. The rate in women with normal, mildly-abnormal, and severely abnormal initial SPECT results were roughly the same. So, about a third of women who got a repeat test had normal results.

Craig Blackmore: Okay.

Kevin Walsh: Did you mis-speak there. Not a third of women got a repeat test, but a third of the women who got a repeat test were in the normal range.

Daniel Ollendorf: A third of women who got a repeat of the, a third of the 9%, 3%.

Chris Standaert: A third, a third, a third.

Craig Blackmore: Okay, what about high risk? So high risk symptomatic, page 23 of the report.

Marie Brown: What's our confidence in how high risk is defined in the clinical population?

Craig Blackmore: I guess I can't answer that, but I would say, how is it defined in the study?

Marie Brown: Research, yeah.

Craig Blackmore: Which we can get at. Dan, do you know how it is defined? So, we are now onto maybe the Sabharwal? I'm sure I'm not pronouncing that correctly, but single-center RCT in the U.K., 457 patients with suspected coronary artery disease intermediate to high risk. We'd have to drill down to understand how they define that, and I'm page 95 of the actual report, slide 23.

Joann Elmore: Is that included in any of the clinical guidelines, how high risk is defined?

Craig Blackmore: Probably.

Michael Souter: They usually don't.

Seth Schwartz: Can we ask Dr. Redberg? Do you know the Diamond guidelines?

Rita Redberg: Yeah, the...

Seth Schwartz: Aren't they, isn't it chest pain and hypertension?

Rita Redberg; It's age, sex, and type of chest pain. So, Diamond and Forrester, age and sex are the big drivers. Women, in general, have lower risk and then, of course, as you get older your chance of coronary disease increases and then the biggest driver is the kind of symptoms you are having. So, if you have classic angina, then you're in the high pretest probability depending on age and sex. If you have what they call atypical angina, so some features of angina but not all of them, then you're in the lower intermediate risk, and then if you're in the atypical chest pain, then you're generally a low pretest probability. So, for example, for a 50-year-old man who had atypical angina, the pretest probability of having coronary disease is about 18%. So, if you did ang-, and that's why angiography, if you took all of those patients and they had angiography, 18 out of 100 would have an obstructive lesion at angiogram. For women who have atypical symptoms and you did angiography, it would be 6%. So, that's how they, and then those numbers would, of course, go up with an older population, because coronary disease is higher prevalence.

Seth Schwartz: Thank you.

Daniel Ollendorf: In the one RCT in this set, it was pretest probability that was used to define high risk.

Carson Odegard: So, what you're saying is that one of the guidelines here says that for symptomatic patients at low to intermediate risk, it is recommended SPECT for intermediate pretest probability. So, that intermediate pretest probability is defined as the Diamond intermediate chest pain or angina of some sort.

Rita Redberg: That's right, and...

Seth Schwartz: In the right, in the right gender and the right age.

Carson Odegard: In the right gender and right age and not the atypical chest pain.

Rita Redberg: That's right. The American College of Cardiology and American Heart Association guidelines actually have a little table in them that they show pretest probability that's based on Diamond and Forrester, and the way the table is divided, it's men and women, ages, and type of chest pain, just like I told you. So, most men who have atypical angina or typical angina are going to be intermediate or high test probability. Like, a man who has typical angina, they have a 95% chance of having coronary disease.

Carson Odegard: Oh, you know, okay.

Rita Redberg: But for a woman, it's much lower.

Carson Odegard: So, the age really steps it up there.

Rita Redberg: Sex. For women.

Carson Odegard: I mean sex.

Rita Redberg: Women are almost...

Carson Odegard: ...and age.

Rita Redberg; ...always in the intermediate probability. It's very hard for them to get into high probability until they get to be age 70 to 75.

Carson Odegard: Okay, thank you.

Craig Blackmore: Okay, so another question that has come up is postevent monitoring. We talked about low risk. We talked about high risk. We talked about symptomatic. We talked about asymptomatic, and the other scenario described is posttreatment monitoring, and I'm going to try to find the slide that refers to that. If somebody gets there first, let me know.

Chris Standaert: Are we still talking about symptomatic high risk or we're there right now?

Kevin Walsh: He moved on.

Craig Blackmore: We can go back.

Chris Standaert: Did we figure out, did we come to a solution then? Did I miss it? I don't remember missing the solution.

Craig Blackmore: No. Solutions come later.

Kevin Walsh: He diplomatically skipped on.

Marie Brown: Moved the discussion along.

Chris Standaert: Would you like to move elsewhere or do you want to start with symptomatic high risk?

Craig Blackmore: No, we can talk symptomatic. What's your proposal?

Chris Standaert: So, the symptomatic high risk gets a little more perplexing, it looks like, because it looks like the disadvantage of SPECT in terms of radiation and perhaps cost starts to get minimized, because ETT becomes less specific, frankly. You get a higher false-negative and you get more trouble and you wind up with higher cath rates, which then start to outweigh the benefit of sort of avoiding the more radiation exposure costly tests in the first place, and things start to pile up on you, as you move up into a high-risk category. The limitations of ETT become more profound compared to the other modalities, and then the risk benefit ratio switches when you start thinking about adverse events and exposure.

Craig Blackmore: So, what do you think?

Chris Standaert: So, it looks like a more SPECT in somebody with higher risk where the whole point is if you had an abnormal ETT, you're going to get a SPECT anyway, but if you already think you're going to have a high risk. I mean, you jump, you're just adding steps that you probably don't need to do. I don't know. I don't treat this stuff, but, it would seem that the data would suggest that certainly SPECT is more favorable in the high-risk group than the low to intermediate risk group, as an initial test.

Marie Brown: Right.

Chris Standaert: Because, not because of the test, per se, but because of what comes after it. So, consequently the test, because of the rates of intervening on these people are so high in the first place. The rates of them going to cath, going to, something else happening to them are high.

Kevin Walsh: Well, and the, if you look at slide 23.

Chris Standaert: Yeah, that's what I'm looking at.

Kevin Walsh: Right, so the revascularization rate is reduced with SPECT compared to treadmill, but there's no difference compared to echo.

Craig Blackmore: So, is there anybody who feels we should be restricting the use of SPECT in high-risk symptomatic people?

Chris Standaert: I mean, the study, this Sabharwal study from 2007, it's ETT, it's not echo. It's ETT and SPECT, but it's, you know, you have a lot more people going to angio from the ETT group, 47 versus 16, and 71% of the people who got ETT got some other test of some sort. I assume, they're getting SPECT, they're getting echos, they're getting something else along with it, and that all washed out any sort of cost benefit of the ETT.

Craig Blackmore: So, I'm hearing that you don't think we should be restricting SPECT in the high-risk symptomatic patients. Is that not?

Chris Standaert: I am saying we need, it looks we need to think about it differently and do the calculations separately and decide, is it again for the same reasons you might choose not to have SPECT initially in the low to intermediate might you actually choose to have it as a top choice in the high-risk group based on what I read, but…

Craig Blackmore: Does anybody feel differently?

Joann Elmore: Except that women would be less likely to be in the high-risk group.

Craig Blackmore: True.

Seth Schwartz: Well, if you go to the ICER matrix...

Chris Standaert: Well, that goes back to the definition of high, low, and intermediate, which are...

Seth Schwartz: If you look at the ICER matrix on page 41 and then look at slide 43, so SPECT was better than ETT, but comparable, in terms of effectiveness, to echo and a little bit better in terms of comparative value. So, I guess that supports the notion that we shouldn't have a gate for SPECT for high-risk symptomatic patients, but it's not overwhelming.

Craig Blackmore: Does anybody feel differently? Okay, so the next sort of little group, if you will, or maybe it's a big group, I don't know, is the followup group.

Chris Standaert: Patients with known cardiac disease.

Craig Blackmore: Yeah, and I want to, I think there's actually more than one followup group, and I'm trying to find my spots here. I'm trying to get back to the key questions. Okay.

Chris Standaert: What they list on that review are patients with known CAD to guide treatment selection and postprocedure and postevent monitoring for the populations that they looked at in the report.

Craig Blackmore: Okay, so are we going to treat those separately or together is sort of my question.

Chris Standaert: Although the key questions are sort of patients with CAD who have seen, who are changing and patients who have CAD who are not changing are the key question populations.

Craig Blackmore: Okay, so...

Marie Brown: No changes, yeah.

Craig Blackmore: Dan, can you help me out? If we're looking specifically at the post-treatment group, did we, did you give us a slide on that group or a summary on that group?

Daniel Ollendorf: So, we gave you one slide on all studies in patients with known CAD.

Craig Blackmore: Okay, so they're lumped together.

Daniel Ollendorf: And that's slide 24. Our initial intent was to break out those with changes in symptoms versus those who did not have changes in symptoms. We didn't find enough information to do that breakout. We found no studies focused on asymptomatic patients post-procedure or event.

Craig Blackmore: And then of the… so of the ones that are in the slide 24, these are basically patients who had some change?

Daniel Ollendorf: Some symptoms, yeah.

Craig Blackmore: Yeah, there's not a lot here, is there? Okay, so if we isolate to the group, the sort of postprocedure group, the postprocedure followup group if you will, we're hearing that there isn't any real useful evidence on that group.

Seth Schwartz: Can I just ask a clinical question about how this would go down? So, Dr. Redberg, if you have a patient who has known cardiovascular disease and develops new symptoms, say you got, it looks the comparator groups were either SPECT or angiography. So you got, say you got SPECT, and it was positive. Will those patients go immediately onto some form of revascularization, or would they also then have a diagnostic angiogram before they went on to revascularization?

Rita Redberg: That's generally one procedure, the angiogram and the revascularization. They're done at the same [inaudible].

Seth Schwartz: Well, what they're doing, what they're comparing here is, well I'm not sure what they're comparing here. It says SPECT versus angiogram, so I'm, on slide 24, it says for the mortality when they're assessing it, SPECT versus angiogram. I was presuming that meant diagnostic angiogram, but would that then be if they were doing diagnostic angiogram for that patient, would that be the same procedure when they do revascularization, versus the SPECT population where if it was positive that would then go on and have revascularization procedure?

Rita Redberg: So?

Seth Schwartz: I'm trying to understand whether there's addition, whether those groups are going to differ and how much additional testing might happen if they had a positive test.

Rita Redberg: So, somebody who has known CAD, whether it would make a difference if they had the SPECT?

Seth Schwartz: No, no. They have known CAD.

Rita Redberg: Yeah.

Seth Schwartz: They develop symptoms again.

Rita Redberg: Okay.

Seth Schwartz: And what it's looking like they're showing us here is, those patients either went on to have a SPECT, or they went on to have an angiogram. So, if you have a patient who has a… and I guess that's what I'm trying to figure out is, are they having a diagnostic angiogram, or are those patients really going on to have a therapeutic angiogram, and they're just telling us what the diagnostic results were?

Rita Redberg: Right. So, I don't think most of those are having a diagnostic angiogram, because they have known CAD, so we know they have coronary disease. So, if they're having an angiogram, it's generally with, I think, the idea of doing another revascularization.

Joann Elmore: At the same time.

Rita Redberg: At the same time. You'd almost...

Seth Schwartz: So, the only question for Dan would then be, what are the, what does this actually, what happened in this study. What are they actually telling us, because it seems like they're two very different interventions. Either these patients were symptomatic and you simply said we're going to treat you, or they were symptomatic and we said, let's get a SPECT and find out what's going on and then only treat the ones that have a positive SPECT. So, those seem like two very different treatment strategies, so I'm trying to figure out what they're actually comparing in this study.

Daniel Ollendorf: So, this is, this was a difficult study. This was a cohort study examining patients with CAD and left ventricular dysfunction and basically the angiography, so the patients were included in the study based on angiography being performed, and then they were stratified based on whether nuclear imaging was performed in the six months prior to or after the angiography. So, to be honest, I'm not sure how useful it will end up being in this discussion.

Craig Blackmore: So, can I make a proposal and then you guys can shoot it down, or not, but I mean it seems to me there are sort of two clinical scenarios here. There is, we know somebody has disease, so we're following them every year for whatever reason, whether they have change in symptoms or not. Then, there's another group that has some sort of change in symptoms, and that's going to be a very heterogeneous group and the appropriate care for that person is going to be variable. So, you know, I would say based on what we've seen and heard there isn't any real data to suggest that following people without a change in symptoms, even if they have known disease or they had a revascularization procedure, or whatever it is, doing SPECT on them has not been demonstrated to be of any value, whereas the group that has a change in symptoms is just way beyond our ability to try to parse out what we should and should not be doing.

Seth Schwartz: There's no evidence either way.

Chris Standaert: For what?

Seth Schwartz: For that group.

Kevin Walsh: The group with known CAD who have changes in symptoms. There is, I mean, there's one study, and it was looking retrospectively at what diagnostic studies had been done before angiography. We can't make a decision based on that.

Chris Standaert: Can I ask a question? Well, there's a [inaudible] Study with 100 patients. It's a PET study, not a SPECT study, and it just said people who basically got a PET wound up with much lower rates of stuff being done to them. They shifted over to a much higher rate of medical management after their PET than the, versus the people who were suspected. It said, where's the initial description of that study?

Marie Brown: Something like 28% before...

Chris Standaert: So, PET, PET angio, before PET angio is recommended in 62% of people in medical management and 28%, and then they did a PET and it changed to 78% of patients, medical management was then recommended in 76% of patients. So, it flipped. It went from 62 were going to angio to 28...

Kevin Walsh: I forgot that.

Chris Standaert: ...medical after they did a PET and then they flipped totally from 23 angio, CABG, whatever, and 76 medical management. So, in that population, the PET dramatically flipped management.

Craig Blackmore: Okay, but let, let's stay on SPECT for the time being, just to, because we, we haven't talked about that yet.

Seth Schwartz: Was there any data like that for SPECT? I mean, that would be a 50% reduction in angiogram rate. That's pretty substantial. Is there any data like that for SPECT or even any studies like that?

Daniel Ollendorf: There were some comparative studies. We didn't find any other than the first study I described.

Chris Standaert: Let's not, but this one study, this 3,000 patient cohort, it's confusing, because I'm wondering why, you know, it seems like angio is done regardless of what the SPECT showed. The angio and SPECT are independent decisions, which seems like a weird thing to be doing looking at all this, but it did look like the people who got a SPECT in one way or the other, along with their angio within that timeframe of a year had lower rates...

Kevin Walsh: But I don't, I don't think that's...

Chris Standaert: ...than angio.

Kevin Walsh: ...but that's, you can't separate those out. In other words, if you're looking for people who had SPECT and had angiogram, then you may be selecting the patients who had positive SPECT to begin with.

Chris Standaert: I'm sorry. It's rates of revascularization. So, they looked at people who got angio. Some of them had SPECT before and after and some of them did not have SPECT at all, and the revascularization rates were a lot higher in the people who did not get a SPECT. So, SPECT, there's no study of SPECT affecting angio rates, it was affecting revascularization rates, and what it suggests is that having the SPECT data, for some patients, along with your angio, will lower the rate of revascularization, because you may see some… you may see… I assume that's the point of SPECT in this population. You see obstructive lesions, but they don't have a physiologic consequence you can pick up on SPECT, so you're less inclined to send them. Is that how their logic would go?

Rita Redberg: Yes, I think. There's a much lower threshold to go right to angio in someone with known CAD.

Chris Standaert: Right.

Rita Redberg: So, I think the patients that are getting any kind of stress testing and SPECT in this case probably had very funny, peculiar symptoms, and so people wanted confirmation that there really was some relationship between these funny symptoms and functional current ischemia.

Kevin Walsh: I'm having trouble...

Rita Redberg: So, it's a different population.

Chris Standaert: A different population.

Kevin Walsh: It seems like it should go the other way, though. I mean, if you have, presumably if you had a negative SPECT, you wouldn't have then gone on to have angio, so you would have suspected that if you had a positive SPECT, then you would have had higher revascularization rates in the population that had SPECT. So, I'm confused as to what advantage SPECT would have offered at all in these patients, unless there's a whole other huge group who had SPECT who then didn't end up having to go on and have angiogram, angiography. So, the whole thing is kind of confusing.

Rita Redberg: I don't think we can learn that much from this study, because it's such a mixed population. We don't know why they had the tests. Some of them had SPECT before angio. Some had SPECT after angio. I don't think...

Michelle Simon: And we're only looking at the patients who did have angio.

Rita Redberg: ...we're going to get a lot more.

Seth Schwartz: Right.

Michelle Simon: So, the ones who had SPECT alone, we never even, we knew nothing about them.

Craig Blackmore: Okay, so, if I get back to this breakdown again of, sort of, no change in symptoms, routine annual follow-up, are we in agreement on that group that we don't need to be doing SPECT?

Marie Brown: Yes.

Craig Blackmore: Okay, and then what about the people with known disease, already imaged, change in symptoms? Do we restrict the use of…

Chris Standaert: It seems like that's what this...

Craig Blackmore: ...the imaging...

Chris Standaert: ...it seems like that's what this data suggests. You have somebody who has known CAD, something changes, and you're trying to decide is that physiologically significant. You know you're going to cath them and it's not going to be normal, and you're trying to figure out should you do something once you've cath'd them, and that is where you would use the SPECT to help you decide the physiologic significance of what you're about to find on your cath.

Kevin Walsh: So, in the hypothesis that your positing, are you supposing that you're going to have a femoral catheter in the right side of your heart and find abnormal vasculature and pull it out and run them off to the SPECT lab?

Chris Standaert: No.

Kevin Walsh: And then bring them back?

Chris Standaert: No.

Craig Blackmore: This is known disease. This is I already had a bypass or last year I had a...

Chris Standaert: No, that's not what I'm saying at all.

Craig Blackmore: ...I had a PCI and now I'm...

Kevin Walsh: Right, but we're talking about doing angiography.

Chris Standaert: But you're getting somebody who is having changing symptoms. They have known CAD and they are getting changing in their symptoms...

Kevin Walsh: Right, right, right.

Chris Standaert: ...are they cardiac?

Kevin Walsh: I'm just, I'm just thinking, if I was the person with the cath, you know, who was pushing that catheter up there, I'm already there. I can do...

Chris Standaert: No, we do the SPECT...

Kevin Walsh: ...I can do a stent in...

Chris Standaert: ...but do you let them do the SPECT...

Kevin Walsh: ...two minutes.

Chris Standaert: ...the question is, do you let them do the SPECT before that, if they want to do the SPECT? So, do we restrict them from getting a SPECT before their cath, if that's what they want to do, to sort out the significant, they know it's going to be, you know, I assume, the logic is that you know your cath is going to be abnormal in some way, because you did it before and it was abnormal, and you already did something to them probably.

Marie Brown: What new information, though, would the SPECT give?

Kevin Walsh: Well, but the...

Marie Brown: That would make a difference in the angio.

Kevin Walsh: ...but the, that's what the, that's what evidence is showing that if you do the SPECT ahead of time it flips how many people get medical therapy versus revascularization.

Chris Standaert: Right, but if you count that, but if you count PET and SPECT in the same thing, the idea is...

Kevin Walsh: Oh, that's right. I'm sorry.

Chris Standaert: ...that the, the physiologic data you get from that...

Kevin Walsh: We're supposing that.

Chris Standaert: ...allows you to determine the significance of the abnormalities that you may find knowing your… they have known it's not going to be a normal cath, and you're trying to figure out do you revascularize if you go intervene.

Kevin Walsh: Right, but that's PET.

Craig Blackmore: So, in the absence of data, because we don't have data, do we accept using SPECT in that circumstance?

Kevin Walsh: That's the question.

Craig Blackmore: That's the question, and we maybe can infer something from PET or not. You can make that decision, but, you know, personally I don't, I think it is such a com-, you know, multivariable, you know, there's so many different levels of complexity to that, that I'm more comfortable allowing the use of the test in that circumstance than in trying to define ways in which it would be restricted.

Michelle Simon: Well, we're also talking about a test that has...

Richard Phillips: It's missing a physiological piece that I'd want to know. I mean, otherwise, it's [inaudible] information.

Craig Blackmore: Theoretically, it could improve the appropriate use of PCI.

Joann Elmore: Yes. Right, theoretically.

Craig Blackmore: There's no data, but, so we're going on a theoretical argument, and we're not… we try not to do that, but sometimes we do.

Chris Standaert: Well, there's, there's not high quality there. There's relatively poor data that does sort of fall in that arc, so it's not totally...

Craig Blackmore: Unreasonable.

Chris Standaert: Yeah.

Seth Schwartz: It's not totally out of thin air. There's something in there that sort of suggests that it's not very high level data.

Michelle Simon: I still think we have to keep in mind that without the compelling evidence, there is a safety issue with this test, and we're not talking about radiation much anymore, but I think it's still important to keep in mind, that that's a factor of this decision.

Seth Schwartz: What I'm struggling with is that we have no evidence from this that SPECT is improving our ability to decide what to do with the angiogram or affecting angiography in any way, and yet it's a test has some costs and has some risks. What I'm concerned about is, we have no idea if SPECT is being used in this setting. Maybe it's decreasing the number of patients that are getting angiography, and those patients are totally thrown out of this. There's just no data looking at that, at all. So, by restricting SPECT in this situation, what we may be saying, what we may be doing is compelling a lot more people to be getting an angiogram, and we just don't even know. So, I think it's really hard to know what to make out of what we have, because we don't have, I mean, to even make a theoretical argument here is difficult, because we're extrapolating from nothing basically.

Chris Standaert: Right. I mean, if you back up our logic and say SPECT in high-risk patients, SPECT can be a preferred treatment over just a straight stress test, people know and see they are clearly are high-risk patients. They are beyond high-risk patients. So, why would you change your logic necessarily on that group, and then exactly what you just said. Why would you reverse and say we can get them if they're high risk, but once you know they have heart disease you can't do it again once they become symptomatic, because then you're going to wind up in this sort of, you get yourself, you box yourself in essentially, and you cath them all.

Craig Blackmore: So, do I, do I have any other views on the committee towards restricting the use of SPECT in this group, meaning known coronary artery disease change in symptoms of some sort?

Carson Odegard: No. In fact, I would say just the opposite. I think there's a real need to risk stratify and knowing the amount of myocardium in jeopardy is a major decision, major information that the interventionalist has to have.

Rita Redberg: I would just suggest that what you're saying applies to all stress imaging. I know you're talking about SPECT, but you know, as the data showed comparative effect, you know the accuracy was the same in downstream testing. Everything else was pretty much the same for echo and SPECT.

Craig Blackmore: Yeah, we're not allowed to look at echo. This is, you know, you have to deal with the parameters of the way things are structured. So, that's another question. I'm not disagreeing with you, but it, it's just beyond the scope of what we can… what we're ruling on today. Today, we're just looking at SPECT and PET. Okay, so, let me get back to my list of categories? Are we through the categories or not?

Chris Standaert: I think so.

Craig Blackmore: I can't make a ruling on something I don't understand. Okay, so those are the four main groups. So, we talked about SPECT. Now, we need to go back through and talk about PET. In PET, there's a lot less data, but there is. So...

Kevin Walsh: Can I make a suggestion?

Craig Blackmore: Yeah.

Kevin Walsh: Since we've talked about SPECT that we vote on SPECT?

Craig Blackmore: Sure.

Kevin Walsh: And then we go through the PET?

Craig Blackmore: Sure. Is that…?

Kevin Walsh: Because my short-term memory loss will leave me.

Craig Blackmore: It's still better than mine. Okay, so that's a good suggestion. So, we'll work towards voting. So, we have three choices, as always, and they are never cover the test, always cover the test, or cover the test with conditions, and the purpose of the last hour has been to sort of narrow us down and it is useful, I think, to take a straw vote, which means no cards please, and I am going ask people unofficially to raise their hands if they are in the never cover group, or if they are in the cover without any conditions group.

David McCulloch: I'm sorry, Craig. Is this for asymptomatic?

Group: Everybody.

Craig Blackmore: This is for everybody. Is there any condition… is there any circumstance in which you believe we should pay for SPECT?

Chris Standaert: For everybody.

Craig Blackmore: So what we're going to do, I think, is we're going to narrow it down to conditions, and the conditions are going to be you have to symptoms, or whatever they are. So, anyway, we're going through the exercise, but the idea is, I think we're in the cover with conditions group. We just have to appropriately define the conditions, right? So, I'm getting nods. That's good enough. So, we'll go to… or it's going to help us. We're going to get some conditions up here. We can do that first. Chris has pointed out that we have yellow cards, and I should not skip the yellow cards to get to the pink cards. So, I need the tool. I can't find my pink. Does anybody know where my tool is? Alright, here it is, the coverage reimbursement analytic tool. I won't go through all of it, because we're familiar with it. We'll go to the action at the end here. So, have we just sort of, for thoroughness, have we, as the committee members look at the outcomes that we're considering, the safety outcomes, the effectiveness/efficacy outcomes, are there outcomes here… outcomes other than what is on the list, that we felt are important or should be considered, or that we are considering in our decision making? Chest pain, dizziness, I guess I would add safety outcomes. I think if downstream testing is a safety outcome, particularly if you're leaning to angio, and angio has risks. So, I would add downstream testing as a safety outcome. You've got that as an effectiveness outcome, okay.

Daniel Ollendorf: Yeah.

Craig Blackmore: Sorry. So, it's there. Okay, and then special populations. We talked a little bit about gender and age. We talked a little bit about comorbidities. We certainly didn't talk about scans and tracers and stressors, and I think that's beyond our scope to be honest. I don't think we're going to tell people what radioisotope they should use. And then we also talked about cost and cost effectiveness. Is there anything else that we think is important?

Alright, we will move to the first voting question, and these are the tan cards. So, is there sufficient evidence under some or all situations that the technology is effective, and the comparator is going to be an imaging strategy without the use of… we're talking

about SPECT now, so that would mean endotrach-, endotracheal tube, sorry, ETT or some other approach, and basically if you think there is any circumstance where SPECT is more effective than competing approaches, you should say more, and if you believe under all circumstances it is less, you should vote less, and unproven you don't know, and equivalent means it's always equivalent.

Chris Standaert: So, less has to be all circumstances and more can be any circumstances.

Craig Blackmore: Yes.

Chris Standaert: Okay.

Craig Blackmore: Okay, so let's have some cards. Alright.

Josh Morse: 11 more.

Craig Blackmore: And then safety with the same rules.

Josh Morse: 11 unproven.

Craig Blackmore: Alright, and then cost effectiveness.

Josh Morse: 11 unproven.

Craig Blackmore: Okay. So, now I'm going to work with the committee to produce what cover with conditions might look like, should the committee decide to vote that way. So, we're talking about SPECT, and let me just take a stab at this from my notes and then you guys can correct me. So, the first thing is, I believe we were saying they had to be symptomatic, and the second thing is differentiating between low, intermediate risk, and high risk, and now my notes are incomplete. What do we think about the low to intermediate risk group? What did we decide on that? Where are we leaning on that?

Chris Standaert: I believe we were leaning, in the symptomatic, we were leaning towards it being a second-line test. So, for in-patients with an abnormal prior test or whatever that language is. So, in that group we were thinking it was the second-line test. So, it's for people who cannot have the first line test for a number of reasons. They cannot complete an exercise test or in whom the exercise test is abnormal or indeterminate, and other testing is desired.

Craig Blackmore: Okay, so that's going to go under low to intermediate risk. You're going to have to write it in, I'm afraid.

Michelle Simon: Let's restart from scratch, please.

Craig Blackmore: So, under low to intermediate risk, it's abnormal ETT.

Michelle Simon: Or unable to obtain ETT.

Craig Blackmore: Or unable to perform ETT, and then I guess it's abnormal or indeterminate ETT, because it may not be technically adequate or interpretable or whatever.

Michelle Simon: Right.

Craig Blackmore: Was there anything else?

Chris Standaert: So, does an abnormal ECG automatically put you in the high risk category, if your symptoms like have an abnormal ECG, or, no? So, they would, they wouldn't, they would be, the other ones who would go get the ETT.

Seth Schwartz: Oh, symptomatic and abnormal ECG?

Chris Standaert: Were they high risk or were they, they're the ones who would go get the ETT?

Craig Blackmore: Doctor, Dr. Redberg?

Rita Redberg: Right.

Craig Blackmore: Based on accepted criteria, does being symptomatic and having an abnormal EKG put you at high risk or not?

Rita Redberg: It's not that it puts you at high risk, but it makes your treadmill test uninterpretable, because you would be reading the ST. So, for example, if somebody who had left bundle or LVH with repolarization so that they had abnormal ST at baseline. Those are people that generally you would start with the imaging tests.

Chris Standaert: Because there's no, there's just no point.

Craig Blackmore: So, is that...

Rita Redberg: Because...

Craig Blackmore: ...is that all, that's not all, that's not all abnormalities on EKG. There's still...

Rita Redberg: That's right. There are abnormalities that are, like a right bundle, you could still get.

Craig Blackmore: So, if we say unable to...

Rita Redberg: And ECG that major, an abnormality that made ECG uninterpretable.

Craig Blackmore: So, if we say unable to perform ETT, would that cover?

Rita Redberg: No, that is evasive.

Marie Brown: Unable to perform.

Chris Standaert: ECG that prohibits interpretation, accurate interpretation of an ETT.

Rita Redberg: Yes. Uninterpretable ECG.

Chris Standaert: Uninterpretable ECG, yeah. A separate line.

Craig Blackmore: I wouldn't say uninterpretable ECG.

Chris Standaert: ECG abnormalities, does that make it… does that make ETT, uninterpretable, no get rid of that word. We decided we don't like that word. Go back. Back up, just delete.

Joann Elmore: Delete the word uninterpretable.

Chris Standaert: So, ECG abnormalities that prevents accurate interpretation of an ETT, something like that?

Joann Elmore: Or that limits accuracy of ETT. In other words, this goes under the reasons why you're unable to perform ETT. Either you have screwed up EKGs or the patient is unable to exercise.

Chris Standaert: Right.

Craig Blackmore: Okay, does that resonate? Okay, and then if we go up to high risk, we're just covering here, right?

Chris Standaert: Cover.

Craig Blackmore: So, we're good, covered.

Joann Elmore: And how are we defining high risk? I was afraid to ask that all along.

Craig Blackmore: You know, I think...

Joann Elmore: We're going to leave it open?

Craig Blackmore: ...I think it's got to be some accepted, you know, I don't know which model they want to use. We can...

Joann Elmore: It's the [inaudible] criteria, I'm assuming.

Craig Blackmore: ...leave it up to these guys.

Joann Elmore: ...but do we need to specify.

Chris Standaert: I would say they can figure it out.

Craig Blackmore: It's got to be some validated risk stratification tool, and I don't...

Joann Elmore: Is it greater than 90%, or?

Craig Blackmore: No, it's not going to be greater than 90%. I mean, it's got to be what? I mean, I assume the ACC and these groups have accepted...

Rita Redberg: Right, and actually Dan's just pulled up one, the ACC guidelines that define able to exercise, and it's a standard exercise ECG testing is recommended for patients with low-intermediate pretest probability who have an interpretable ECG and at least moderate physical functioning or no disabling comorbidity, which is kind of what we said, and there's also, in this same document, a table with the pretest probability and it's defined low is less than 10%, pretest probability, intermediate is 10-90%, and then high risk is over 90%, and...

Craig Blackmore: 10-90, wow.

Joann Elmore: Yeah, that's why I was asking if we're defining it as greater than 90 here.

Rita Redberg: ...and, and it is defined in this cardiology document.

Chris Standaert: Does the state want us to pick a criteria to use or does the state want to determine the appropriate and evolving categorization?

Kerilyn Nobuhara: I defer to the agencies.

Chris Standaert: So, we can leave this, and you guys would be happy with that?

Kerilyn Nobuhara: Yes, thank you.

Craig Blackmore: Okay, and then let's scroll down. Can you scroll down, please? So, under...

Chris Standaert: Asymptomatic is not covered.

Craig Blackmore: Okay. So, let's get rid of high-risk, low-intermediate risk under asymptomatic and just say not covered, and then no changes in symptoms under known CAD is not covered, and changes in symptoms is covered. Then, can you do me a favor and get rid of all the spaces so we can see it on one screen, and then we'll give the committee a chance to look at it? Single space it. You might have to change the font, too. I just want us to be able to absorb this. That's everything. That's it. So, just think for a minute and let me know if there's other…

Richard Phillips: I'm wondering about the asymptomatic patient, not covered, does that mean that what is covered in an exercise treadmill study and an echo only?

Craig Blackmore: Well, I mean, we're not...

Joann Elmore: We're not saying.

Craig Blackmore: ...that's beyond the scope of our discussion, but those would certainly be options out there.

Chris Standaert: We're saying we don't have evidence to do this to people who don't have any cardiac symptoms.

Marie Brown: To do SPECT.

Chris Standaert: To do SPECT.

Marie Brown: We're not compare… it's not compared to anything.

Richard Phillips: Well, I guess that's what I'm getting at is, you've got to have something to cover those patients. I mean, if you have a patient who's got an amputee with diabetes who has asymptomatic coronary artery disease...

Chris Standaert: They have known coronary artery disease.

Richard Phillips: They have, well...

David McCulloch: How do you have to be symptomatic cardiac-wise.

Richard Phillips: And, you know, most diabetics tend to be asymptomatic with respect to pain, or a good number of them.

Craig Blackmore: So, we didn't, we didn't talk about, oh there it is. Yeah, we've got known cardiac, known coronary artery disease right there.

Marie Brown: I mean, there has to be monitoring if it's known cardiac.

Craig Blackmore: And then known cardiac coronary artery disease would… that would encompass prior procedures, which we should probably specify. So, known CAD and/or prior coronary interventions. Kevin is looking at me funny.

Kevin Walsh: Do you mean somebody who's had a stent?

Chris Standaert: But then they have, they have known CAD.

Kevin Walsh: They have known CAD by definition. They don't need to… you don't need to, hopefully.

Craig Blackmore: I'm just trying to make sure we get at that circumstance where people are doing yearly followup on their stent, but if we think it's covered, it's...

Chris Standaert: A prophylactic stent, prophylactic stent.

Kevin Walsh: What about, what about the populations like transplant or other things. I mean, those patients don't necessarily have coronary artery disease, but they're kind of an exception to everything we've talked about.

Seth Schwartz: There's no evidence.

Craig Blackmore: That's true.

Chris Standaert: You would just SPECT them, even though they seem fine?

Kevin Walsh: No.

Chris Standaert: That seems odd.

Kevin Walsh: No, no, no, but I mean, if you have someone like that who had change in symptoms, who developed symptoms.

Chris Standaert: Well, then they've become symptomatic and they have known risk because they're, you can get rid of those words probably.

Margaret Dennis: Which?

Chris Standaert: Coronary.

Seth Schwartz: But didn't we just hear that those patients [inaudible].

Chris Standaert: The ones we just added. The interventions part.

Craig Blackmore: Would you be more comfortable if we had… okay, other thoughts?

Joann Elmore: I have a question for the group. I was impressed with the high number of repeat exams, and I can envision a patient that is high risk, they are always symptomatic, and they keep rescanning, and obviously, we don't address that, and I'm not certain we can, but I'm just wondering if anyone has any thoughts or suggestions. The repeat testers, I think, was one of the reasons that this was brought to our group's attention.

Man: [inaudible]

Joann Elmore: Everything—utility, cost, patient care.

Craig Blackmore: Apart from, we're doing it every year because we want to, which we do cover, I don't know how to get at that. I mean, I don't know how to, I don't know how to...

Joann Elmore: This obviously doesn't.

Seth Schwartz: We can't.

Carson Odegard: I think part of is we don't, the model that's here doesn't really speak to reality always. For example, echo studies are, about 20% of the time, they're nondiagnostic, technically not valuable to the users. So, they end up having to do a repeat study. Yet, in this model, they're considered to be equivalent, diagnostically equivalent. At least that's the way I read the studies. So, I have, that's one of the biggest problems I've had in interpreting this is that we really… I'm not sure that is true the way it's been represented, but I think that's a, it's a good question, which I believe she brought up.

Chris Standaert: I mean, I guess I understand, but the numbers are actually pretty low. If you look at it, they have, they have 13,000 patients and, you know, 600… 2,000 got two but they're a year and a half apart, so they may well have different symptoms. 604 got three, but then you really fall off. I mean, I don't know you have 20 patients having six or more SPECT in four years. That seems a lot, but there's something very weird about the provider network or the patient, but that's 20 out of 13,000. So, it's a very small number and...

Seth Schwartz: Let's not try to weigh in on that.

Chris Standaert: Yeah. Those are outliers, changing what we did for extreme outliers doesn't make a lot of sense.

Craig Blackmore: Okay. I'm prepared to move this to a vote, unless somebody else wants to comment? Okay, so you have three choices, and based on the evidence about the technology, safety, efficacy, and cost effectiveness… actually before we do that, I want to reconcile with the coverage decisions, because it might be easier to do that before, now rather than later. So, we've had an opportunity to look at all of these, but the national, we don't have an NCD, but we do have a LCD, right? Somewhere? Don't we have an LCD somewhere?

Josh Morse: There is an LCD and it's...

Craig Blackmore: Is that not in my...

Marie Brown: Page 3 of the [inaudible].

Craig Blackmore: Okay, page 3 of the tool, right. So, Medicare's NCD basically defers it to the LCD, and the LCD says SPECT is covered, abnormal EKG, stress test, or inability to complete a standard stress test. So, all that we pretty much have. Patients who are symptomatic following a reperfusion procedure. So, we've got that. Known CAD with changes in symptoms. Intermediate risk patients undergoing high risk surgery, which we haven't talked about at all. Does anybody want to weigh in on that? We certainly haven't seen any evidence.

Michael Souter: So, preoperative assessment was one of the exclusions in the evidence report, I thought. I saw that mentioned that you didn't consider preoperative assessment at all.

Craig Blackmore: Is that true?

Daniel Ollendorf: It's preoperative assessment for noncardiac surgery was an exclusion, yes. So, that was part of a discussion we had with the medical directors when some of the initial agents utilization data was provided, and it was a very small number.

Craig Blackmore: Okay.

Daniel Ollendorf: So it was excluded.

Craig Blackmore: So, then, so in our decision we need an asterisk that says this decision does not apply to preoperative evaluation for noncardiac surgery. Can you get that for us? The fourth one is patients with known CAD with new or significant symptoms. We have that, and then they also have here evaluation of postcardiac transplant. Dan, was that part of our scope, or was that not part of our scope, the cardiac transplant?

Daniel Ollendorf: It would have been if we'd done any studies.

Craig Blackmore: Okay.

Daniel Ollendorf: But we did not.

Craig Blackmore: So, that was part of our scope, and there was no data out there. So, we can… we can either allow it or not mention it.

Chris Standaert: You would think that post cardiac transplant would fall either in the high-risk group or in a known CAD group. I mean, you already… it's not a normal...

Craig Blackmore: Well, but you're not, you're not normal myocardium, but are you normal coronary?

Chris Standaert: I don't know.

Craig Blackmore: Presumably, you could put a heart in there that has flow.

Seth Schwartz: I don't agree with you. A new heart, by definition, means it's a new heart with coronary disease.

Craig Blackmore: Does?

Seth Schwartz: Does not.

Craig Blackmore: Does not.

Seth Schwartz: In my mind.

Chris Standaert: Does not mean it's a new heart with or without?

Seth Schwartz: It doesn't mean that it's a with by definition, because it's a new heart. A transplant does not automatically put you in a high risk category for...

Craig Blackmore: Coronary artery disease.

Seth Schwartz: ...coronary artery disease.

Michael Souter: They screen the donor heart before you transplant it. They screen a donor heart before you transplant it. Isn't that what's one of the criteria.

Craig Blackmore: So, do we want to specifically mention, again, we don't have data. There wasn't any. It's an unusual clinical circumstance. We can allow it.

Chris Standaert: I guess what I'm saying is what if these patients are symptomatic. If somebody is suspecting they have a coronary problem in their transplant patient, don't they just fall in these categories, as opposed to saying you can screen them just because they have a transplant, and they seem fine, but they have no symptoms, so you're going to screen them anyway. That does not seem terribly logical, I agree, but...

Craig Blackmore: Dr. Redberg?

Chris Standaert: ...if they become symptomatic, don't they fall in one of these categories?

Craig Blackmore: Is SPECT used for nonsymptomatic post-cardiac transplant? The heart is denervated, right? So you might not have symptoms the same way you would otherwise?

Rita Redberg: Right, and there is this syndrome of accelerated atherosclerosis in cardiac transplants that is thought perhaps to be related to the immunosuppression they are on. So, I think that, I don't think it's consistent, but there are probably some people that use SPECT to screen in asymptomatic postcardiac transplant for ischemia.

Michael Souter: I just don't think we have enough data to be able to say anything about this at all, and I just think it's going to be a very small number, and I think we should just leave it alone.

Craig Blackmore: Leave it alone meaning?

Michael Souter: Just don't make a coverage decision on it, yes.

Seth Schwartz: Don't speak to it.

Chris Standaert: I mean, to add on that statement or to patients undergoing cardiac, who have undergone cardiac...

Craig Blackmore: Postcardiac transplant.

Chris Standaert: ...transplantation. That just doesn't. They're a different category.

Craig Blackmore: Otherwise, we're pretty much...

Michael Souter: We don't even know how many patients in Washington State it affects?

Craig Blackmore: I don't think we want to cause problems for…

Richard Phillips: I have a problem with the asymptomatic having… being not covered, and I think the high-risk patients… there seems to be some… I think there should be some statement about them that they should have the same, maybe the same thing as we have written up above for low and intermediate risk or symptomatic patients. The problem I have is that if we by not specifically stating the coverage for SPECT, we implicitly endorse the echo and/or exercise treadmill study, which is… which may be inappropriate, and I realize that we do not have a lot of data with which to address that issue, but I think it would be wrong of us to, my personal feeling, it would be wrong to basically say that we don't cover it. I think there's consequences of that, asymptomatic high risk patients, I think, are worthy of some kind of statement for coverage, in my opinion.

Seth Schwartz: One thing I'd say about it is, what we looked at is that, you know, we're talking about screening here. When they looked at screening, they found no advantage of SPECT over no screening. So, it's, we're not endorsing over ETT or echo. We're endorsing it over no screening. So, people elect to do ETT or echo, that's, in my mind, a separate issue than what we're talking about.

Richard Phillips: But if you have a high risk patient who has a left bundle branch block, i.e., can't have an exercise treadmill study, and if you have a patient who is not, who maybe has an amputation and can't exercise, basically you've… this patient can't be covered for anything, because you've already made this, by his criteria, by his risk factors, the patient can't undergo ETT, really will have a suboptimal echocardiogram or stress echo, and therefore the only thing available to him would be a SPECT or a PET, which we've said we won't cover, and that seems wrong.

David McCulloch: It doesn't seem wrong. If they're asymptomatic, we shouldn't be doing it.

Chris Standaert: Right.

David McCulloch: If you take your amputated, diabetic patients and you do SPECT on them, they'll all have abnormalities. It doesn't translate into the fact that an intervention on those patients is going to improve their outcomes. I think it's a… I don't think there's any reason we should be saying that high-risk asymptomatic patients should be… if there's no symptoms, we shouldn't be screening them with these tests. I mean, if you screen them with any test, you'll find abnormalities, but you're not going to prove their outcome with no data that says you...

Richard Phillips: Well, I totally agree that we don't have the data, but I just don't...

Chris Standaert: We do have data. We have an RCT. We have a study on asymptomatic, high-risk patients and it did not find...

Seth Schwartz: And there's no improvement.

Chris Standaert: ...SPECT helpful at all, and what they found was that SPECT had more people going to angio, and people who didn't get SPECT did, more of them got stress testing of some sort, but as a screening tool in an asymptomatic, high-risk population, it doesn't seem like a helpful test. So, once they become symptomatic...

Richard Phillips: We're not talking about this as a screening tool. We're talking about as a coverage. Right?

Michael Souter: Not if they're asymptomatic.

Chris Standaert: But if they're asymptomatic, it's a screening tool.

Kevin Walsh: If they don't have symptoms, it is, by definition, if they don't have symptoms, it's a screening tool.

Chris Standaert: Yeah. So, I'm struggling for a clinical scenario why you would want to do a SPECT on somebody who has no cardiac symptoms whatsoever, whatever their risk factors are, because you're going to wind up in trouble. You're going to wind up doing more stuff to them. What's the whole point?

Marie Brown: And we go back to...

Richard Phillips: No, what I'm...

Chris Standaert: Because the prevalence of disease is so low.

Richard Phillips: ...what I'm saying is that you have certain criteria of patients who cannot undergo any study. That's what you're saying, so you're not going to cover any of them.

Chris Standaert: No. This is SPECT. They're not going to get a SPECT.

Richard Phillips: No, we're not going to cover a SPECT, and therefore, and the patient's not a, doesn't have indications for any other of the stress studies. I mean, you know, know left bundle branch block, whatever.

Chris Standaert: What's the indication for the SPECT?

Richard Phillips: Pardon?

Chris Standaert: Can you help me? What's the indication for a SPECT? Why would you do it? What's the indication?

Richard Phillips: Well, that's… the high risk is totally the indication.

Chris Standaert: Alright, but that's the study we have that says it didn't help.

Marie Brown: It didn't help.

Chris Standaert: And they got more, they got more caths.

Michelle Simon: And they're exposed to radiation on top of that.

Chris Standaert: Yeah.

Joann Elmore: Right. We haven't talked about the radiation part in a while, but that is a major factor.

Craig Blackmore: So, I… we're going to, I'm just going to try to keep things going.

Seth Schwartz: Let's vote.

Craig Blackmore: I think with all respect I think the majority of the committee is favoring the noncoverage in that spot, and can I just get nods or?

Group: Yes.

Craig Blackmore: So, thank you.

Richard Phillips: And I think, I think that the criteria set are fairly restrictive, too, in these studies. I mean, you know, I can see a lot of patients, left heart failure, you know, not just coronary disease, you know? Not just, but I accept that, and it's my personal feeling on that.

Craig Blackmore: So, we're going to move to the vote with the list as we now have it.

Joann Elmore: Can we clean up the footnote?

Craig Blackmore: Yep, so the footnote should say, does not apply to preoperative evaluation of patients undergoing high risk noncardiac surgery.

Joann Elmore: Well, is it noncardiac surgery, or?

Craig Blackmore: Yes.

Joann Elmore: Okay, alright.

Craig Blackmore: By the asterisks, does not apply to patients, does not apply to preoperative evaluation of patients. Okay? Alright, so your choices are cover always, never cover, or cover with conditions as laid out here.

Josh Morse: 11 cover with conditions.

Craig Blackmore: Alright, and we have already reconciled with Medicare, and we've already looked at all the other guidelines that exist, and we're basically in line with Medicare, so I don't think we need to go into a lot of detail as to why we disagreed.

Seth Schwartz: No, you were considering a local coverage decision.

Craig Blackmore: We were considering a local coverage decision, which is, because there isn't a national, okay. Okay, that brings us to PET, and we have the same categories. We have not as much data perhaps. So, who wants to start us off?

Chris Standaert: You know, I found the PET data interesting, because in the limited data we have, it looks like a pretty useful test and actually looks better than SPECT, and it has less radiation, costs more, but there is a lot less data. The radiation in SPECT is really high, and some of those ranges are really high, and PET doesn't get anywhere near that high. So, it looks preferable from a safety standpoint, and it looks like it is actually a more reliable test in the limited data that is there. It looks better than SPECT in the stuff we got. So, it's what to do with it, you know? It's clearly not the first line that people use, but it looks like it could be a useful test, just not the same depth of data.

Marie Brown: And the utilization rates on PET.

Craig Blackmore: So, there's only one center in the state that does it, is that correct? That's the university, and it's not done that much, so utilization rates are fairly low. Whether that would change, I have no idea.

Chris Standaert: I assume that utilization from the state was combined. They didn't break it out, but it looks like it is small.

Craig Blackmore: So, I guess the opposite ends of the spectrum, one would be to say, we don't have data, we're not covering it. The other end of the spectrum… well, maybe not the end of the spectrum, but another approach would be to say, it's the same sort of information you get from SPECT, or at least it's similar, so we would use the same rules that we used for SPECT. I guess the other end of the spectrum would be to say, it's not done that much, so why don't we just cover it. I'm not proposing any of those at this point, but I think those are sort of…

Chris Standaert: Well, where, where in this stuff is the NCD on PET, because there is an NCD on PET, it looked like.

Craig Blackmore: There's an NCD on PET?

Daniel Ollendorf: Page 4. The NCD stipulates coverage for an inconclusive SPECT.

Chris Standaert: Where is that actual, the language?

Daniel Ollendorf: Slide 50 and then [inaudible].

Marie Brown: Covered when SPECT is inconclusive and/or RB82 or a pneumonia radiotracers were used.

Craig Blackmore: Alright.

Chris Standaert: Is that the full, is that the full language, or is there more to it? I mean, do you ac-, do we… in our materials do we have the actual text of the full NCD or no?

Craig Blackmore: So, in your decision tool on page 4...

Chris Standaert: In the first folder?

Craig Blackmore: ...it's in the first folder tab just before all the articles here. I don't know if this is the full or if it's just a summary. So, I guess that's the fourth approach is we would cover it when, under the SPECT rules when SPECT is inconclusive or can't be done for some reason, I guess. Thoughts?

Seth Schwartz: I think that's a sensible approach. The only caveat I would say is that it looks like there is better data for PET than for SPECT in dealing with known coronary artery disease in symptomatic patients. We actually have evidence to say that it is going to substantially decrease the risk of angio… or the need for angiography in those patients, and that's both potentially cost saving and improvement in safety.

Chris Standaert: It's funny when you look at that, again, and compare these models and you look at the models it looks pretty good in the model, as a test.

Michael Souter: Yeah, but that was a, that was just PET. I don't see any data in there to say that it was compared to SPECT.

Seth Schwartz: No, I'm not saying that, but we're, we're separating them out and Craig's done that. What Craig is proposing is that we approve PET in the same circumstances as SPECT, if SPECT was inconclusive.

Craig Blackmore: I'm pulling out the options, I'm not…

Seth Schwartz: I'm saying… I don't think you need to say… I don't think you'd have to do SPECT first in that population.

Michael Souter: Well then, but we have to, that's why I would be concerned about it is if you dropped the threshold for doing PET when it's a more expensive study and then, so we may see circumstances then where people are actually going to use PET rather than, because now they feel more structured about using SPECT.

Seth Schwartz: But what I'm saying is, I don't have a problem with that, because I think the data supports the use of PET in that. You can throw out, disregard PET.

Michael Souter: My point was that the data was looking at PET in that circumstance. There has been no data, we couldn't find anything to see that it's actually been SPECT looking at circumstance. So, we don't know whether PET is better than SPECT.

Seth Schwartz: I think that's true, but I think… but I don't think… so I don't think we should restrict PET use to people who have already had a SPECT when we don't know whether SPECT is better or not.

Michael Souter: I'd like to see more data than just a prospective cohort with 100 patients before we actually make, I'd give full reign to that.

Seth Schwartz: Well, I think that's reasonable, but we just did the same thing for SPECT. We just agreed that SPECT is okay with no data. So, here we have data that PET is better than what is currently being done. So, why would you be more restrictive of that study when it has less radiation? It may be more expensive, but it's less… less radiation and at least there's some data that suggests that it's going to be cost saving.

Michael Souter: Cost saving as compared to just doing angiography or...

Seth Schwartz: Yes.

Michael Souter: ...cost saving in compared to doing, you know, ET, the echo testing? I mean, I just don't see that level of data in that study.

Craig Blackmore: Okay, so that's, that's one narrow circum-, can I get my screen back or not?

Rita Redberg: The other point about PET, besides that I think the data is very limited is that you can't exercise with a PET study. So, you automatically get less data, because you can't exercise, and a lot of your data from an exercise test is from how many minutes did you go on the treadmill? You can't exercise with PET, but it's very limited data.

Chris Standaert: This language confuses me. What does imaging is done, so it's a certain type of radiotracer, then it says rest or rest stress imaging is not conducted in addition to SPECT, meaning that you can do a PET if you don't do an echo?

Craig Blackmore: I have no idea.

Chris Standaert: And you do a SPECT. So, you do a… PET's covered if you also, if you do a SPECT but no echo. That seems sorta weird, or it falls in inconclusive SPECT. I get that one, but I don't get that first criteria.

Craig Blackmore: Well, we would rewrite it or something. I don't know what that means.

Daniel Ollendorf: I have the detailed NCD up. It's basically saying PET is… PET is performed in place of, but not in addition to SPECT.

Michael Souter: Rest or stress...

Daniel Ollendorf: Then it's covered.

Michael Souter: ...imaging in relation to the PET scan rather than to, okay.

Chris Standaert: No, mine says PET imaging, okay. So, it's nothing… it's not in place of SPECT or when you have an inconclusive SPECT and you still want more information.

Craig Blackmore: Alright.

Chris Standaert: But that means with limited data, you could make PET the first line study for people who are high risk, symptomatic patients, which we just said for SPECT, even though we don't have data on that population with a SPECT.

Craig Blackmore: So, I think we've seen the data, such as it is, and I think we're going to have to make a decision on the limited data that we have. So, again, I'm going to try to narrow a little bit. Is there, is there a feeling that we should never cover PET? I'll start off with that, and just give me hands if that's where we think we're heading. Okay, I'm not seeing enthusiasm. Is there a feeling that should cover it unconditionally? That would be the other end of the spectrum. Is there… is that… am I seeing some yeses on that? Does that seem viable to people? That may be an option. Then the other would be to try to define what conditions would look like. Maybe some people would want to have unconditioned. Maybe some people want conditions, and the conditions, it looks to me like one approach is to go with the inconclusive this sort of. You can't… well, it's not this actually, but you can't do a SPECT for some reason or it's inconclusive, which would be a very small subset.

Richard Phillips: They're two different populations.

Craig Blackmore: They are.

Richard Phillips: You've got the patients who cannot have a SPECT, just because of tissue abnormalities, and then you've got the ones who had the SPECT that are going... that are inconclusive.

Craig Blackmore: Right, there's ones you think it's going to be inconclusive, so you don't do it, and then there's one whose already did it, and it was inconclusive.

Richard Phillips: Right.

Craig Blackmore: Yes.

Chris Standaert: That's basically why the agency is suggesting in their comments, too, that it be done in those populations, inconclusive or not technically feasible SPECTs.

Joann Elmore: I think I would eliminate the first one, though, imaging that we don't, we didn't even discuss that.

Craig Blackmore: I would definitely eliminate the first one. I'm with you on that. So, I'm hearing SPECT is not technically feasible instead of that first line.

Joann Elmore: Yes.

Craig Blackmore: So, again, this is one approach, and another approach is to, we could, again, use the same rules we use for SPECT. I just want to make sure we consider all the options here.

Chris Standaert: Maybe SPECT is inconclusive.

Craig Blackmore: This is basically making PET a second-line test used, and I guess we would have to say...

Chris Standaert: Under the same circumstances as SPECT when...

Craig Blackmore: ...under the same limitations of SPECT, which I think we're all, we're all on the same page with that.

Chris Standaert: So, covered under the same conditions as SPECT.

Craig Blackmore: When.

Chris Standaert: Colon, SPECT is not technically feasible or SPECT is inconclusive.

Craig Blackmore: So, this is, again, this is making it a second-line test. Another approach would be to allow it as a first-line test for the same indications as SPECT, is that… I'm soliciting input.

Chris Standaert: Just SPECT is inconclusive.

Marie Brown: The safety issues seem less with PET. So that keeps weighing on me.

Man: It's important to remember that...

Chris Standaert: You mean, as a safer test? Is that what you mean? Less radiation?

Marie Brown: I think that PET had less radiation.

Chris Standaert: Yeah, it seems like PET just needs more work. They need to market it. It may well [inaudible] widely available, and then the cost may go down to, I suppose.

David McCulloch: You know, that's exactly what I'm going… I'm intrigued and fascinated by this potentially being a… at this point based on existing evidence, I would feel nervous about using, based on the very limited data saying just give it all the same criteria then people… but I think it's likely we'll get more data on it, and it will become more mainstream, but at

this point, the… I would favor having it as the criteria [inaudible] as a second-line test. We don't have enough data to say otherwise.

Seth Schwartz: I would agree with that, except the one condition of the patients with known coronary artery disease where, I won't say we have good data, because we certainly don't, but we have at least as good data as we have for SPECT, and I have a harder time restricting it versus SPECT without any reason to do that.

Craig Blackmore: Okay, let me, let's just back off on that for a minute. Is there anybody who does not agree conceptually with we're going to approve this as second line maybe plus or minus exemptions? Is there some other, maybe there's some sentiment to use it as first-line. Have we covered the bases? Is there anything else that I'm not talking about here that we, how we might approach this? Okay, then I want to take a straw vote on PET. We're going to allow the same conditions as SPECT as a first-line. So, this means you can get it for anything that we said you could do SPECT for first-line. So, hands if we think that's where we think we should be. Okay.

Josh Morse: So, have you done your yellow vote for this?

Craig Blackmore: No, no.

Josh Morse: So, give those back?

Craig Blackmore: Probably. Okay, so then I want to get at if we're thinking second-line, do we want to basically make [inaudible] modifications, or do we want to keep second-line for everything? Is that, did I phrase that? Tell us again the situation? So, we're saying second-line for everything except...

Seth Schwartz: Known coronary artery disease in symptomatic patients...

Craig Blackmore: Because of the...

Seth Schwartz: ...new symptoms.

Craig Blackmore: ...because of the study that we saw in here.

Seth Schwartz: Yeah, for what it's worth.

Craig Blackmore: So, by a show of hands, how many would support that rather than second-line for everything? Pro-Seth, Anti-Seth?

Chris Standaert: That one, I sort of follow with Mike that it's a noncontrolled cohort of 100 people, and there's no SPECT in it, and so you just don't… it doesn't have the proper comparator. It's not controlled. It's very small. It's one study, highly suggestive, but boy it's…

Craig Blackmore: So, then, therefore what I'm hearing, not universal, but basically I'm getting support for, you know, get rid of the top line, please, Margaret. I'm hearing support for this. Okay, let's go to the yellow cards. So, is there sufficient evidence under some or all situations that the technology is effective, safe, and cost effective, and if you believe it is more effective under any circumstance, you'll vote more, and if you believe it is less effective, you'll vote less, etc., etc. You know the drill.

Seth Schwartz: And the comparator is ETT in this case?

Craig Blackmore: And the comparative is imaging strategy-based… is diagnostic strategy based on other techniques, which might be ETT, might be SPECT, yeah.

Josh Morse: I see nine unproven and two equivalent.

Craig Blackmore: Safe?

Josh Morse: I see 11 unproven.

Craig Blackmore: Cost effective?

Josh Morse: 11 unproven.

Craig Blackmore: Further discussion. Okay, we're going to move to the second vote. Before we do that, we have the national coverage decision. We had some sort of coverage decision. Let's reconcile.

Josh Morse: You have a link, an electronic link if you have access.

Craig Blackmore: Can you read it?

Josh Morse: I can read it.

Craig Blackmore: Is it incredibly long?

Man: It's short.

Josh Morse: So, indications and limitations of coverage, 1. Rubidium 82. This was effective March 14, 1995. Effective for services performed on or after that date, PET scans performed at rest or with pharmacological stress used for noninvasive imaging of perfusion of the heart for the diagnosis and management of patients with known or suspected CAD using the FDA approved radiopharmaceutical Rubidium 82 are covered provided the requirements below are met: 1. The PET scan, whether at rest, alone, or rest with stress is performed in place of but not in addition to a SPECT (or) 2. The PET scan, whether at rest, alone, or with or rest with stress is used following a SPECT that was found to be inconclusive. In these cases, the PET scan must have been considered necessary in order to determine what medical or surgical intervention is required to treat the patient (for purposes of this requirement, an inconclusive test is a test whose results are equivocal, technically uninterpretable, or discordant with the patient's other clinical data and must be documented in the beneficiaries file). The final bullet for this part 1. For any PET scan, for which a Medicare payment is claimed for dates of service prior to July, 2001, the claimant must submit additional specified information on the claim, including proper codes and modifiers to indicate the results of the PET scan. The payment must also include information on whether the PET scan was performed after an inconclusive, noninvasive cardiac test. The information submitted with respect to the previous noninvasive cardiac test must specify the type of test performed prior to the PET scan and whether it was inconclusive or unsatisfactory. It goes on with the bit about G-codes.

Part 2, and this is for ammonia N-13. This was effective October, 2003. Effective for services performed on or after October 1, 2003, PET scans performed at rest or with pharmacological stress used for noninvasive imaging for perfusion of the heart for the

diagnosis and management of patients with known or suspected coronary artery disease using the FDA approved ammonia N-13 are covered, provided these requirements are met: 1. The PET scan, whether at rest or alone, or rest with stress, is performed in place of, but not in addition to SPECT. The PET scan, whether at rest or alone, or rest with stress, is used following a SPECT that was found to be inconclusive. In these cases, the PET scan must have been considered necessary, in order to determine what medical or surgical intervention is required to treat the patient. For purposes of this requirement, an inconclusive test is a test whose results are equivocal, technically uninterpretable, or discordant with the patient's other clinical data and must be documented in the file. This was last reviewed in March of 2005.

Richard Phillips: It looks like they covered it all.

Chris Standaert: That's more liberal than this.

Craig Blackmore: Yeah, so the...

Chris Standaert: We could use it in place of SPECT is what that says.

Richard Phillips: Yeah, right.

Chris Standaert: Which is not what we're saying, because we don't have that data to say that.

Craig Blackmore: So, the differences are, we don't specify agents, and that's… we just feel that's outside of our scope, and then, like you said, this is less restrictive, and I think our reasons for being more restrictive is that we don't feel that there's sufficient evidence of the effectiveness of this… of this test, and I mean, does anybody want to elaborate on that, or does anybody feel like we need to rethink through? So, if you, yeah. Any other comments? Okay, so, um, so now we'll vote.

So, your choices are cover, which means basically cover all the time, no cover, which means we don't pay for PET ever, or cover with conditions, and the conditions are specified, basically the same set of rules that we would apply to SPECT, except that PET will be used when SPECT is either not technically feasible or inconclusive.

Josh Morse: 11 cover with conditions.

Craig Blackmore: Alright. It is 20 after 12:00, which should put us on for lunch, and before we go to lunch, I want to check in with Josh. In terms of the key questions, do we have time, should we try to squeeze that into while we eat?

Josh Morse: We're not ahead of schedule.

Craig Blackmore: Alright. We will resume at a quarter of 1:00, and I thank you.

So, the key questions are here. I'd like us just to take a minute and contemplate the key questions and make sure that what we're getting back is going to meet our needs. So, we'll just take a minute and speak up if you have thoughts.

So, I guess as I look at this, I am looking at key questions one and two, and under key question one it says what is the comparative clinical effectiveness, and it goes on. Then, in question two, it sort of defines the impact of salvage or palliative treatment, disease progression, etc., etc., and it seems to me that clinical question two is really just defining

the clinical effectiveness that appears in key question one. So, I'm not sure the way it's presented here is...

Michael Souter: Well, you don't see a difference between the treatment with proton beam therapy versus palliation with proton beam therapy.

Craig Blackmore: Salvage or palliation.

Michael Souter: I mean that's what… that's what question two seems to be, it would seem to me.

Craig Blackmore: Okay, so I get it. So, then I would argue that we need to talk about what clinical effectiveness we care about up here, and we should make that explicit that we're really, it's nice to see the tumor shrink, but what we really want for key question one is survival, disease progression probably less so, and then health-related quality of life and patient outcomes, right?

Michael Souter: Yeah.

Craig Blackmore: Does that make sense, Dan. I don't… we want to make sure that we get at these real patient outcomes rather than simply...

Michael Souter: My main concern in looking at this one is actually the list of tumors that we have to go through there, because we know when we get down to it, we're not going to find one study that covers all of those. Nor are we probably likely to find four or five that covers all of those. We're going to find bits and pieces of small data. That's my guess, based on exactly this, we're going to have probably about 30 or 40 studies, which is a wild guess off the top of my head, but we're going to have lots of little bits of data. So, then our approach in these in the past has been, okay, well let's just talk about each category singly, unless we start making some wild extrapolations and bundling them, and that's when people start getting uncomfortable, and I honestly don't know that we will be able to get through, you know, how many are there? So, if you have eight different disease categories considering the evidence back and forth for each one.

Craig Blackmore: I think one of the concerns, which has been expressed to me, around proton beam is that there is data on some tumors, but it costs a lot of money to build a machine, so people use it for everything. So, you might say in a couple, particularly… again, I have not looked at the data, but anecdotally, there are some pediatric tumors that maybe it has some defined manages, but you have the machine, so let's do it on early stage prostate cancer.

Michael Souter: And I get that, but maybe those should be the ones we should prioritizing first.

Craig Blackmore: So, how do we express that for Dan so that what we get back is useful? Do you know what I mean?

Michael Souter: I suppose my reservations about the scope of the key questions, rather than adapting the key questions, do we honestly think we're going to be able to deal with all of those in sufficient accuracy, especially for limiting it to a half day session. I just don't see us being able to do that properly?

Michelle Simon: Well, how were these chosen? Are these chosen because there is data on them already? Or how did we get this list?

Daniel Ollendorf: So, we looked at a number of systematic reviews that have focused on proton beam to identify the major cancer types. We also admittedly looked at the Procure website, that's the Seattle facility, to see what cancers they list. I guess our thought going into this was that we would document where there's a burden of evidence and where there is not. So, if there's no studies in a particular cancer or only small case series we would note that so you would be able to see where the evidence is and where it's not.

Craig Blackmore: So, I'm not sure we have a way around having to go through the list is the problem.

Michelle Simon: I think it makes sense to have the wider net and then see where the data lies and then decide on that.

Seth Schwartz: I think that's a very valid point. It's going to be hard to get through all this, but the specific questions I have here are two. I think, with the second question, I think we might need to separate salvage and palliation, because I think salvage you're still going for cure, so that's the outcome you're looking at, whereas palliation, the outcomes are going to be completely different. So, I think it would make sense to separate those. The other issue I'm wondering about is tumor stage. So, I mean, there's a very big difference in terms of, like, there's some tumors where you might, based on size it may not, radiation may not be the option. So, it's sort of hard to compare. We've been in that situation before where you're kind of like, well we're trying to compare surgery to radiation, but clinically you would never do radiation for that tumor, because it's for whatever reason, it's only [inaudible] manageable. So, I think it would make sense. I don't know exactly what the situations are, because I'm not familiar with a lot of this, but we end up really wringing our hands when we can't… those are the situations where we can't compare what the data is saying. So, if there's a way to sort that out, you know, to find out clinical situations where is radiation only used for treatment of, you know, stage I tumors or tumors below a certain size or not and kind of parse those out.

Daniel Ollendorf: We do have tumor characteristics listed as one of our subgroups of interest. So, is there differential information by location, volume proliferative status, etc.?

Craig Blackmore: And you may have to let the data guide, you know? If you get to… I'll just make something up, but you know, you get to prostate cancer and there's only two trials and they're in stage I, then here's the stage I data and stage whatever, there's nothing.

Seth Schwartz: But it may be beyond that. I mean, maybe this is an area where we need to get the clinical expert involved in an earlier stage and say hey, you know, you would never use proton beam for this, so we shouldn't lump this. It should really be called out separately, because there may be studies or not studies, but regardless of whether there are studies, it may be, there may be a clinical reason for that. We just don't know, but that's where our clinical expert can weigh in.

Craig Blackmore: So, how do we operationalize that?

Seth Schwartz: I think we need to ask our clinical expert to see if there are circumstances where radiation would not be used because of clinical scenario or not, and then parse that out ahead of time, and I think they could review that and say yes for lung cancer. If you have stage III lung cancer, you would never use proton beam, you would only use surgery. I don't know what those circumstances are, but if we're gonna have the clinical expert… I mean that's why we have them, right?

Craig Blackmore: Yeah. I'm not sure it's going to be that simple, but I don't know.

Seth Schwartz: I don't think it will be easy, but I don't think we should have to do it.

Michael Souter: Is it going to [inaudible]?

Seth Schwartz: Because we're not equipped to handle that.

Josh Morse: It's currently scheduled for [inaudible].

Craig Blackmore: I mean, I think it depends on the data. How much data are you going to encounter, Dan? You started casting the net a little bit.

Daniel Ollendorf: These are not long systematic reviews that have been published previously. Most of the, the work that we had done previously as an organization was focused on prostate cancer, and at the time we did it, there were a couple of RCTs looking only at the use of proton to boost radiation dose so there was a photon component, as well, and everything else was a case series. So, there's not going to be a ton of evidence anywhere.

Craig Blackmore: So, I guess, I don't know if hope is the right word, but it may be pretty quick if there's nothing there.

Richard Phillips: One other thing is that, in 2012, we did separate studies on the intensity modulated radiation therapy and on stereotactic radiation surgery. There's a possibility that what is going to be presented here could be in conflict with our findings and recommendations, and it would seem to me that the investigator should be well aware of those recommendations so that we don't put ourselves in the situation of recommending something that might conflict with our prior recommendations and/or let us rectify it at the same time. Because it seems to me that there is going to be a lot of crossover here.

Craig Blackmore: So, having that available at the time would certainly be helpful.

Richard Phillips: Well, it makes our job immense, too, potentially, and I would like to find a way to make it less so.

Craig Blackmore: I mean, we would not be in a position to revise our previous decisions, because we wouldn't have that literature, but definitely if we can use our previous decisions to inform what we're doing now.

Richard Phillips: Yeah.

Craig Blackmore: So, definitely having that information would be useful. Any other thoughts?

Seth Schwartz: I guess one question I would have is, a lot of times they do concurrent therapy, chemoradiation therapy, and I'm not sure how we separate that out if we're commenting on proton beam alone versus proton beam in combination with chemo if we're not going to have any data on chemo. So, just functionally I'm not sure how that would go.

Craig Blackmore: Well, it's worse, because the question is proton beam versus, you know, some other form of radiation. So, it's not is proton beam valuable in addition to chemo, it's is proton beam valuable instead of external beam or whatever it is. Again, you're dealing

with a technique that's much more expensive. Do you have some evidence of benefit that makes it worth doing, which is, again, why I wouldn't anticipate a huge body of literature. Any other thoughts? We're gonna be stuck with this, so we have to make sure we get what we need.

Richard Phillips: Is this going to be something that is scheduled for half day?

Craig Blackmore: Yes.

Richard Phillips: Gosh, that's gonna be… that's a lot of data. [inaudible] in a half day.

Joann Elmore: Well, it depends on what you find. Did we address Seth's comment about the word salvage in question two, because question one addresses initial treatment. It specifies initial, so you've got it clean. Then, question two was the palliative, sort of end of life kind of stuff, but what about secondary, you know? They've failed the first one. How do you want to address that?

Craig Blackmore: Well, I think, I mean, we're going to try to separate those out.

Joann Elmore: Okay, good.

Craig Blackmore: Right? I think that's, right Dan?

Daniel Ollendorf: Yeah.

Craig Blackmore: And again, it will be dependent on what data there is, but we want to try to…

Joann Elmore: There probably won't be data.

Craig Blackmore: Okay, thank you.

Josh Morse: So, two items on this.

Craig Blackmore: Sorry.

Josh Morse: This is available for public comment for the next two weeks. This went online early this morning, I believe. It's available right now on the Health Technology Assessment websites at our Health Technology Assessment program webpages and at the moment, I don't believe we have another topic scheduled for this day, which is currently scheduled for May. So if, we could reserve that day for one topic if you feel that's, you know, better to do that.

Kevin Walsh: Can we wait and see how much evidence there is?

Josh Morse: We can.

Craig Blackmore: Okay, thank you for that input. We're going to get back onto the regular agenda now. So, the next topic is carotid artery stenting and we are in the scheduled public comment period, so we will proceed with public comments. What have we got, Josh?

Josh Morse: We have three previously-scheduled comments. The first is going to be Dr. Ring who should be on the phone, and we need to get Dr. Ring's slides up.

Craig Blackmore: So, while we do the phone thing here, I just want to ask everybody who addresses the committee if you could please tell us who you are and if you are representing just yourself or if you're representing some other group and whether you have any financial conflicts of interest, please. Okay, so Dr. Ring is it? Dr. Ring are you with us on the phone?

Michael Ring: Yes, I am. Can you hear me okay?

Craig Blackmore: Yes. Please proceed.

Margaret Dennis: He has some slides, and I'm bringing them up.

Michael Ring: And I understand, too, that somebody will be able to advance the slides for me.

Craig Blackmore: Okay.

Michael Ring: And I will let you know when that's appropriate, if that's okay.

Craig Blackmore: If you can just give us one minute for the slides. We're going to pull them up. We'll let you know.

Michael Ring: Sure, and while that's being done, I would like to thank Dr. Blackmore and the committee for allowing us to present today. By way of introduction my name is Michael Ring. I am an interventional cardiologist in Spokane at Sacred Heart Medical Center and the current governor of the Washington chapter of the American College of Cardiology. Also, to let you know, I am a last minute substitution for Dr. Larry Dean who, unfortunately due to medical issues, is not going to be able to join us, and I apologize for not being present in person to do this, but because of the last minute nature of what occurred, I appreciate though the opportunity to do so over the phone. I will be presenting on behalf of both the Society of Cardiovascular Angiography and Intervention, as well as the Washington chapter of the American College of Cardiology. In regards to my conflicts, which were submitted earlier this morning for disclosure, I don't have any industry or commercial conflicts. I, as mentioned, represent the two societies who are supported by member dues.

Craig Blackmore: And we have your slides, so please go ahead.

Michael Ring: Well, thank you. I will go ahead, as I again acknowledge these are the slides of Dr. Dean's, who I am borrowing, so we will move to the second slide and briefly the goals that I hope to cover during this presentation will be to summarize and review the multispecialty guidelines regarding carotid stenting and revascularization, which I will reference shortly. Also, to bring to the committee's attention consideration of an upcoming National Institution of Health study relevant to the topic at hand of carotid stenting and carotid revascularization, as well as to discuss possible upcoming changes in Medicare coverage for carotid artery stenting. Next slide.

The document that I suspect that you are very familiar with was published in 2001, which represents the summary and collective recommendations of multiple societies representing cardiologists, interventional radiologists, as well as vascular surgeons specific to the management of patients with extracranial carotid and vertebral artery disease. Next slide.

The reference for the paper is listed above. So, moving to the next slide, five, regarding classification of recommendations and level of evidence, I know this is a very busy slide, but I think it is important just to understand how, in understanding the recommendations that will be forthcoming. Typical for these types of papers is that the recommendations that are issued are based both on terms of the relative benefit versus risk and then categorized as to the level of evidence supporting it. For example, class I recommendation being the highest level, that there's benefit of a certain procedure or treatment over not doing it, and level A being the highest level of evidence typically including several randomized clinical trials. As an example, level C would be something where there is an almost universal consensus about doing something, but there isn't randomized trials. That's probably not atypical for much of what we do in medicine. Just as a dramatic example would be, you know, performing electrocardioversion for somebody with ventricular fibrillation cardiac arrest. I think we would all agree that that is the right thing to do, but there is not likely to ever be randomized trials to that particular issue. Within class II recommendations, they are broken down further into A and B with A being the stronger one where it is felt that it is reasonable to perform the particular procedure or treatment while class B recommendations would certainly be considered and possibly reasonable, but that there is perhaps more controversy in that recommendation where class III would be not recommended in almost all cases where the treatment is felt to be of no benefit for potential risk in the majority of patients.

Moving on to the next slide for revascularization. So, these are the recommendations specific from that society recommendation for carotid revascularization. I'm not going to address vertebral artery revascularization. So, moving to the next slide about recommendations for selection of patients for carotid revascularization.

The highest level of IA means multiple randomized trials where carotid… for patients at either average or low surgical risk who are symptomatic having experienced nondisabling stroke or TIA within the past six months. The recommendation would be that those patients undergo carotid endarterectomy, if the offending carotid artery stenosis is at least 70%, as documented by noninvasive imaging. The recommendations for between 50 and 70% by angiography would be a class IB recommendation where the bulk of evidence does support it, but there may be some conflicting or controversial data in that regard and assuming, too, that the procedure can be performed with perioperative risk of stroke or death of less than 6%.

Moving to the next slide, regarding carotid artery stenting as an alternative for carotid endarterectomy would be in the similar patients mentioned above who are symptomatic, but, excuse me, let me rephrase that. It would be considered as class I recommendation, coronary artery stenting for patients who are at low risk, average to low risk with a stent procedure in whom the diameter of the carotid artery stenosis is reduced by at least 70% by noninvasive imaging or 50% or more by angiography in whom the anticipated risk of stroke or death is less than 6%.

Next slide would be for patients who are asymptomatic, be considered for carotid revascularization, that the level of evidence would be IC for asymptomatic, in that their treatment should be individualized. What that is basically saying is that asymptomatic patients with high-grade carotid disease represent a very diverse group of patients, both in terms of their clinical characteristics, life expectancy, and anatomic features in that the recommendation is that the approach be individualized.

Moving next to the next slide, which would be slide 10. In regard to patients who are asymptomatic with more than 70% stenosis of the internal carotid artery, it is

considered reasonable for class IIA level of evidence A being the highest, that it would be reasonable to perform carotid endarterectomy in asymptomatic patients who have a greater than 70% stenosis, assuming the risk of death, stroke or MI is low and it would be reasonable to choose carotid endarterectomy over carotid artery stenosis when, in older patients especially, the anatomy appears to be unfavorable for an endovascular approach. That's with carotid artery stenting.

Moving to slide 11, in patients, it would be reasonable at a class IIA with B-level support to choose carotid artery stenting over carotid endarterectomy when the revascularization is indicated, as mentioned above, but in whom patients have a neck anatomy that is unfavorable for vascular surgery, such as having had previous surgery on that side or if the stenosis is either high or low within the neck that makes surgical access difficult or impossible, or if patients, for example, have had radiation to the neck, as examples of where vascular surgery would be much more difficult and stenting would be probably preferable in that case. In patients who are symptomatic and have had a recent TIA or stroke, and there are no contraindications for early revascularization, the level of support for doing the revascularization within two weeks is, although a little bit more controversial, still would be considered a class IIA recommendation with B-level support. So, it has to do with the timing.

Josh Morse: Dr. Ring?

Michael Ring: Yes.

Josh Morse: You have about two minutes to go, please.

Michael Ring: Okay.

Josh Morse: Thank you.

Michael Ring: So, in patients who are, I want to address the asymptomatic patients, so patients who are asymptomatic that it would be considered, but in whom, let me actually move on to the next slides, because I don't have the time, but class III recommendations would obviously be for those patients who are unlikely to benefit from the procedure.

Then, moving on I want to talk about an upcoming, so we're going to move to slide 15, NIH research on treatment of carotid stenosis. There is an upcoming study that is being planned and approved called CREST-2 that will look at optimal medical therapy versus revascularization in asymptomatic patients, which is a very important trial that's been approved by the FDA and should be initiated in the very near future, and it would be important to keep this trial in consideration, as we make our recommendations.

The other thing, moving onto slide 16, is the committee hopefully is aware that Medicare is looking into coverage, expanding coverage for carotid stenting and particularly looking into expanding coverage so that patients can participate in the aforementioned CREST-2 study and that hopefully recommendations from this committee will be in sync with those that will be coming from Medicare.

So, in slide 17, in summary, to summarize that carotid artery stenting in symptomatic patients is supported with class I level support and that it is certainly very… carotid artery stenting is very reasonable over carotid endarterectomy in symptomatic patients who have unfavorable neck anatomy. The approach to asymptomatic patients is less clear, which is going to the next slide why it's important to undertake this, the CREST-2

Study to examine the best medical… the approach of best medical therapy versus revascularization in this group and that it's… and finally, we believe that the people in the State of Washington should have access to this technology based on the current evidence and importantly the opportunity to participate in the study and examine the evidence base by future clinical studies, specifically the CREST-2 as mentioned. Thank you, very much. I appreciate the opportunity to present.

Josh Morse: Thank you, Dr. Ring. Our next scheduled presenter is Dr. Kim. Dr. Kim will have five minutes.

Louis Kim: Thank you for the opportunity to speak. I am the chief of neurosurgery at Harborview Medical Center, and I represent UW Harborview, as well as the Washington State Society of Neurological Surgeons and our neurosurgery parent organizations, the American Association of Neurologic Surgeons and the Congress of Neurological Surgeons. I believe the committee has the key questions in front of them.

Craig Blackmore: Sorry, can you just share whether you have any financial conflicts, please?

Louis Kim: I'm sorry. I do not have any financial conflicts. I believe that the committee has the key questions, and if you could just… I don't know if I can move the slides forward, but maybe we could just go to the first key question number one. Does it work? Alright, thank you.

So, regarding key question number one, and the previous speaker, I think, was an excellent overview and data-driven sort of explanation of why we're pursuing this, but in terms of key question number one, there are no studies comparing extracranial carotid artery stenting versus medical therapy alone. There have been numerous trials that looked at carotid endarterectomy compared to medical therapy in both symptomatic and asymptomatic populations. All these trials regarding endarterectomy historically have demonstrated definitive prevention of strokes with treatment compared to medical therapy. The CREST trial, as you've been hearing about, was the best level of evidence trial that compared endarterectomy and carotid artery stenting head to head in symptomatic patients and has demonstrated rates of both short and long term comparative efficacy that are similar for both procedures in both populations of outcome. So, in terms of patient morbidity, mortality, the rates and the efficacy were similar. There is ample evidence, in particular, for symptomatic patients, which the previous speaker very rightly described for both treatments, both endarterectomy and carotid artery stenting that provide, again, short and long term efficacy. I am happy to pause at any point along the discussion if there are any questions specific to each key question, since it might get kind of complicated at the end if we don't go in turn. Feel free to interrupt me.

Regarding key question number two, I don't want to spend a lot of time. It was working and now it's not. Key question number two regarding SPECT intracranial stenting and intracranial stenosis treatment is a little off the topic, but again, there's not clear evidence that intracranial angioplasty and stenting is better than medical therapy unless one has failed medical treatment. So, I think we can quickly move on to key question number three. Perfect.

And the question is, is there evidence regarding the periprocedural complication rates of endarterectomy and stenting, and the answer is, yes there is. There is a great deal of evidence and studies on both of these techniques. Over the course of time, the complication rates of both procedures has decreased with expertise, with familiarity

with technology improvements, and this is particularly true for carotid artery stenting where distal protection devices and with better training, more rigorous training methodologies and our governing bodies kind of overseeing this, the complication rates have now fallen into the rates that are comparable for endarterectomy. CREST trial demonstrated a lower complication rate for both endarterectomy and stenting in a prospective study in both groups, essentially, compared to historical trials. It shows that everything has improved over time and the complication rates have, in both techniques, have fallen below the minimums that we would expect. Even within the CREST trial alone, we saw an improvement in the morbidity rates in the second half of the study versus the first half, and these are experts that are enrolling in this trial. These are not the general community, and as I alluded to currently in qualified U.S. centers, both procedures, including stenting, will likely meet the AHA criteria of less than 3% and 6% for asymptomatic and symptomatic patients, and that's the stroke rate, of course, that I'm discussing respectively.

With regard to key question number four, the main subpopulation where there is a demonstrated differential efficacy in stenting is age, and it's the opposite of intuition. The older patients actually do worse with stenting, presumably because of the tortuous anatomy and the diseased arteries, as you navigate through with the stenting devices. Numerous studies have demonstrated increased risk of adverse outcome for stenting with increasing age with CREST being our best recent study demonstrating a crossover at about age 70. So, if you're older than 70, you're probably better off actually having the endarterectomy, as opposed to the stent, but there certainly are subpopulations within this group that benefit from stenting over endarterectomy, previously radiated neck in the setting of cancer, for example, patients with previous surgery, where it be a revision surgery, those types of subgroups, which is not an uncommon patient population to be dealing with in our world would certain benefit. Of course, as the previous speaker alluded to, unfavorable anatomy, which is when you have bifurcation, surgically less accessible or inaccessible carotids in the neck in the extracranial space.

So, to key question number five, there is no data comparing the cost effectiveness of stenting versus medical therapy, so we cannot directly comment on that. The best data comparing cost effectiveness of stenting to endarterectomy comes from the CREST trial, which again demonstrates minimal difference in the hospitalization costs and one year cumulative costs in both the asymptomatic and symptomatic patients. The cost effectiveness data from the Sapphire, which looked at stenting in the setting of high-risk patients, suggests that stenting may be superior to endarterectomy. Overall cost effectiveness of stenting to endarterectomy is likely a minor consideration compared to the medical factors addressing our question. So, I don't think there's going to be a huge cost differential between the two groups and techniques.

And the last slide is the conclusion. In light of the recent publication, the CREST trial, as well as the FDA expansion and indication for the AVID vascular carotid artery stenting system, published recommendations, etc., it is reasonable to consider, as an alternative to the gold standard of endarterectomy, for younger, symptomatic patients with standard surgical risk and carotid artery stenting over endarterectomy. Coverage should be expanded to include this population and, although current rates of stroke and death for these two techniques are below the AHA guidelines of 3% for asymptomatic, a randomized trial with modern medical therapy is warranted prior to expansion of coverage for this particular indication, as the previous speaker alluded to. There is an ongoing impetus for a CREST-2 to look at this population. Hopefully, I've made the point about the symptomatic group, particularly the younger patients. In the real world of where we are, having the complementary ability to do endarterectomy or stenting is

vital to providing optimal patient care, and if we lose that ability, we are really going to be handcuffed, forcing our patients into a direction that would be more dangerous, more risky, and potentially more expensive in terms of overall healthcare costs. Thank you for your time. I appreciate it, and I'm happy to answer any questions.

Josh Morse: Thank you, Dr. Kim. Our final scheduled presenter is Dr. Andrews.

Torrance Andrews: Thank you.

Josh Morse: Okay, and you have five minutes and can you please state if you have any conflicts?

Torrance Andrews: I have no financial conflicts. I'm just waiting for slides. It looks like it's working. Alright, so this slide should also point out that I'm currently in private practice at Swedish Medical Center in Interventional Radiology. I'm also the former chief of IR at the University of Washington and the director of their center for endovascular therapy, and I still have privileges over there and go periodically on a volunteer basis just to do some cases with the residents and fellows when I have time.

I'm representing the Society of Interventional Radiology today. It's an organization that prides itself on developing technologies that are faster, better, safer, and less expensive, and we do feel that carotid artery stenting, in appropriately selected patients, meets these criteria. These are the main points that I'm going to cover. Let me start by saying that we were impressed by the final evidence report. It's well written. It's comprehensive. We feel like the points that are raised are unbiased, and we are happy with the document. We feel that it shows that carotid artery stenting is appropriate for selected patients. Obviously, there are differences, as we have already heard, between symptomatic and asymptomatic patients. I'll talk briefly about the CREST data, although we've already heard about a lot of that information. I'll review… well, we've already heard about the multisociety guidelines, as well. So, I'll just mention them briefly, and then I'll finish by indicating our feeling that reimbursement should be tied to accreditation.

Now, I don't know if people noticed in Dr. Ring's slide where he was talking about the multispecialty guidelines, how many specialties there were, but there were 14, 14 specialties that signed on, and that included such disparate representative groups as neurosurgery, neurology, vascular medicine, cardiology, vascular surgery, and interventional radiology. So, thought leaders that come at this problem from vastly different perspectives managed to come together and create a very unified document that I think, the fact that they were able to do that when many of their individual members might not be able to sit in a room together, I think speaks volumes. We know that the document and the recommendations suggest that carotid artery stenting should be offered as an alternative to carotid endarterectomy in appropriately selected patients, and we do feel that it is important that we continue to have both options for the people of Washington.

The outcomes have been very comparable between carotid endarterectomy and stenting, and I'd like to point out that endarterectomy has been around for 60 years. It's been refined through the hands of thousands of surgeons and hundreds and thousands of patients, and it's a very mature technology, whereas cardiac stent… or stenting for carotid disease has only been around 10, maybe 15 years. It is relatively immature. When it started, we didn't have distal protection devices. We didn't have dedicated delivery systems. We didn't have appropriately-shaped stents. So, it's a very immature technique by comparison, and yet, the results are comparable and will, I think, in time

only continue to be better and better, as it is better developed and we are more attune to the appropriate patients to benefit from the therapy.

Let's talk briefly about cost. It's already been covered. As you've heard, there is no great difference between or among the various technologies. Some studies show a benefit for stenting. Some show a benefit for endarterectomy, but the difference among the studies is relatively minimal. So, even though financial considerations are important, we don't feel that they would be a driving factor in this scenario, or in this decision.

We feel that accreditation is important. The existing requirements from CMS are rather vague. They are locally determined. There is not a lot of cross-comparison among sites, and we would favor a more rigorous mechanism for accrediting people who do these procedures. There are very few right now that meet the requirements of the two societies that are listed here, and as a result, we are concerned that people may be doing these procedures without adequate experience and without appropriate background skill sets, and that over time, we may see the quality drop off, unless accreditation is pursued. Just as an example of the problems, it's been shown that a lot of patients are inadequately evaluated for their symptomatology, and as we've heard several times, there is a big difference between symptomatic and asymptomatic patients in terms of their likelihood of gaining benefit from stenting. So, if we don't adequately evaluate their symptomatology beforehand, we are going to pick the wrong patients. Stenoses are commonly and significantly over-estimated, which obviously has a downstream impact on the efficacy of the treatment and the ability… our ability to evaluate the outcomes. We think that accreditation will eliminate or significantly reduce those problems.

Primarily, it is important, though, as I have already said, to make sure that the high quality outcomes that have been published are maintained, as this stenting become more and more commonly employed.

You've already heard about the CREST-2 trial. We think it's important that there be funding for that trial. There are questions that remain specifically regarding asymptomatic patients, and CREST-2 should answer those questions. If we are not able to enroll patients, we will not have the power needed to prove the results. And that's my time, thank you.

Josh Morse: Thank you, Dr. Andrews. So, that concludes our scheduled presenters. Do we have any?

Margaret Dennis: We did not have others.

Josh Morse: Is the phone muted?

Margaret Dennis: Not yet.

Josh Morse: So, we will check the phone. Is there anybody on the phone who would like to make comment to the committee today? Okay, thank you. This concludes the scheduled presentations.

Gary Franklin: Thank you, very much. Is this thing on? Is there a way to get the slides up on here?

Margaret Dennis: There should be.

Gary Franklin: Okay. Thanks very much. I'm Gary Franklin, medical director at the Department of Labor and Industries and co-chair of the Agency Medical Directors Group with Dan Lessler. You guys frequently make really tough decisions, like this morning's decision, I think, was really complicated. The good thing about this afternoon's decision is, there's a lot of convergence, I think, of the evidence report and the CMS policies, and the MDG recommendations. So, it might be slightly less complicated than some of your other decisions.

Stroke is the leading cause of death. I don't know if you saw the JAMA report in the last few weeks on the burden of disease in the U.S. and compared the U.S. to all the other developed countries, but cardiovascular disease is the number one cause of early premature loss of life in the U.S. and across the developed world.

Stroke is the third leading cause of death in Washington State. We had, in 2005, over 3,000 deaths in Washington State, and in 2004 over 26,000 hospitalizations. These hospitalizations cost $600 million. Stroke is also a leading cause of serious long-term disability.

The most common site of plaque formation, of course, is stenosis in the carotid artery near the bifurcation of the internal and external carotid arteries. No one is really talking about doing procedures on the external carotid artery. So, really, this whole conversation is about internal carotid artery in the neck and internal carotid artery intracranially. This report and these recommendations do not include issues around doing any of these procedures on the vertebral artery. So, the vertebral artery was not included in this report, in this evidence review.

The therapeutic options for carotid artery disease include best medical therapy, as you have heard from several people, modern medical therapy includes rigorous and compliant use of statins and antiplatelet agents along with treatment of the underlying disorder, such as hypertension, smoking, and diabetes. Carotid endarterectomy plus medical therapy has become more or less the standard of care to restore vascular patency with certain levels of stenosis of the carotid artery in symptomatic patients. Carotid angioplasty with or without stenting, plus medical therapy, has become an alternative, especially in people who are at high risk for surgically-related morbidity and mortality because of a lower degree of invasiveness. However, the less invasive may not equal safer or as safe.

So, I'm going to start with the extracranial stents, as opposed to the intracranial stents. So, on the extracranial stents, the two main classifications will be symptomatic patients and asymptomatic patients. With symptomatic patients, they, of course, would have neurologic evidence of ipsilateral stroke or a TIA or transient monocular blindness. Much of the evidence that is available is from RCTs in this population, and the target populations here are, depending on degree of stenosis, over 70% or more stenosis or 50-69% stenosis. For asymptomatic patients, less… much less is known about the efficacy of any of these treatments in this population, and the management of this disease is still evolving. The target population for stenting relates to current FDA labeling requiring greater than 70% stenosis and inability to tolerate general anesthesia for endarterectomy and some other important things that you heard about just now.

Intracranial stents, the primary therapeutic approach is medical therapy, and this is really a nascent area and without much data. Surgical options, of course, are limited. The FDA did approve intracranial stents only through the humanitarian device

exemption process. In other words, they did not require the usual kind of study for the intracranial stents. So, they are approved for use only in IDE or humanitarian device exemption process for use in patients with at least 70% of an intracranial vessel experiencing recurrent intracranial stroke secondary to disease that is refractory to medical therapy.

Our initial ranking of this, when we prioritized this topic, was high concern on safety, high concern on efficacy, and medium concern on cost.

The current state agency policies on these are primarily either covered or with prior authorization for the extracranial carotid artery and not covered at Medicaid and L&I for the intracranial carotid artery. The other two agencies do not have a specific policy, except to prior authorize.

So, of interest, the centers for Medicare and Medicaid, NCD 20.7, which was last updated in 2008, it has been updated a number of times, says that for treatment purposes, Medicare covers angioplasty with stenting and embolic protection only for patients with symptomatic carotid artery stenosis and in patients for whom surgical risk is high and in patients who have symptomatic stenosis greater than 70%. The other categories of potential use of stenting, that is symptomatic patients with stenosis between 50 and 70%, asymptomatic patients and intracranial stenosis are only covered with participation in research studies in the Medicare policy. So, they break it, you know, it's broken down fairly clearly. The only thing that's actually covered without being participating in a research project is symptomatic carotid stenosis, at least 70%.

This is not, I'm not really sure why it's not, we're not getting a huge number of these procedures in PEBB or in Medicaid, and the costs are, the amount that PEBB is actually paying, it looks like it's between… it's around $25,000 to $30,000, closer to $30,000. The amount that is charged is more like $42,000. So, the difference there has to do with various payments from different coverages that the patient might have. They might have, in addition to PEBB, they might have Medicare coverage, or they might have two coverages in their family with a high deductible. So, the reason that there's the difference here between the $30,000 and the $42,000 is these different coverages, but the actual charges are closer to, I believe, $42,000.

Endarterectomy, on the other hand, is around $15,000. So, I'm not really sure about the minor cost difference that you just heard about from a couple of the folks. It looks to me like there is a pretty big cost difference in these procedures.

There aren't very many intracranial procedures being done. Essentially, it's just about all extracranial carotid artery procedures, and of course, it's in the older age population. So, these are the actual charged amounts to PEBB, and it's $41,600. So, that's how much the total… all of the payers are paying together, but PEBB is only paying $30,000.

I got this little red circle from Kerilyn. It was very, very nice, thank you. Again, the breakdown in PEBB for these. This was the difference between inpatient and outpatient is pretty substantial, about a $9,000 difference.

So, again, the diagnoses associated with the ones that we pay for are primarily carotid artery, almost no vertebral arteries. There are a few.

So, the evidence in the evidence report on the extracranial stenting in symptomatic patients is pretty much, you heard this already, equivalent effectiveness with moderate

evidence, but with a worse safety profile and it is less cost effective. In asymptomatic patients overall, very weak studies that appear underpowered to detect differences in relatively rare events, like death, with no difference in effectiveness, but a nearly doubled, nearly doubled morbidity in one large, I believe it was an observational, study and more costly procedures.

Intracranial stenting, there was one randomized trial, and other than that, the efficacy data is limited, but in this study, the best medical therapy was superior to stenting with best medical therapy, and there was also superiority on safety in that trial. These are for intracranial stenting.

So, our recommendations are basically to go with the Medicare policy essentially, and that is to cover extracranial carotid artery for symptomatic patients with at least 70% stenosis where there are anatomic contraindications or if the patient is at high surgical risk. So, not… you're not considering them equally. You're still considering CEA is the primary procedure… but you can do a stent if there are these problems, potential problems with carotid endarterectomy, and it would be important to either use it the way Medicare is defining it or some other definition of what high surgical risk or anatomic contraindications are.

Due to the poor adverse event profile and low cost/benefit considerations and potential for poor quality studies, we do recommend the following slight deviation from the Medicare policy, because the Medicare policy says they pay for all of these other three major categories in any kind of a study that is either a postmarketing study or an IDE type of study, and the agency medical directors felt like some of these registries might not be the highest quality. We wouldn't necessarily want to be forced to pay for this if the registry did not look like it was a very passive type of registry where people were being followed but not necessarily wasn't a lot of other control population in there. So, we would actually just ask for a slight difference in that decision on allowing the other three categories for carotid stenting only in FDA-approved category B IDE clinical trials, such as probably the CREST study would meet that criterion.

So, thanks very much. I'm happy to take questions.

Chris Standaert: There's a question on coverage for clinical trials. As I understand it, you don't need us to say that at all. You guys can decide whatever you want to decide in terms of covering for clinical trials based on your authority now.

Gary Franklin: That's true.

Chris Standaert: So, we don't really have to specify what you can or can't cover, unless...

Gary Franklin: The Health Technology bill originally written allows that.

Chris Standaert: Right, so that's a standard sort of thing of all of our policies.

Gary Franklin: Right.

Chris Standaert: If somebody comes to you with a study they want that you decide is valid, you can choose to fund that whether we say so or not.

Gary Franklin: Right. So, if you said, not covered, we could still consider it for those other three categories.

Chris Standaert: Right, at your own discretion.

Gary Franklin: Right.

Chris Standaert: So, you actually don't need our permission.

Gary Franklin: Correct.

Chris Standaert: Okay.

Kevin Walsh: I have a, just a real basic question for the expert.

Craig Blackmore: Yeah, so let me, let's do that. We haven't introduced our clinical expert, Dr. Bersin. Welcome. This is the Health Technology Clinical Committee. Thank you for being willing to be our clinical expert. The way this works is, we have a… we're going to discuss and make a decision based on the evidence, and we have a team here that's gone through the literature and will distill that for us, but none of us are people that do this procedure. So, we need you to help us understand the context, and we will undoubtedly have questions about the technical aspects and the population and what you do in that. So, it's very important that you be here. We will direct questions your way and solicit your input, but if you could please just introduce yourself briefly and tell us if you have conflicts of interest.

Robert Bersin: Sure, thank you. The name is Dr. Robert Bersin. I practice at Swedish Medical Center. There, I am the medical director of endovascular treatment and services, as well as structural heart services for the Swedish Heart and Vascular Program. I do have conflicts. I have disclosed those and submitted those. Principally, the relevant ones, I would say, the principle one is that I do receive remuneration to teach physicians on carotid stenting from the manufacturer, Avid Vascular, who produces carotid stents.

Craig Blackmore: Thank you.

Kevin Walsh: Can you help me understand why it costs twice as much money to put stents in as it does to do an endarterectomy?

Robert Bersin: So, I'm not sure, I can't speak to the financial, where that data comes from, in that there were two prospective trials of cost. I think perhaps what he was showing was charges. There are actual cost data from, prospective data, from both the Sapphire trial and also CREST, and we published from our own institution, Swedish Medical Center, a number of years ago our own cost analysis of surgery versus stenting, and what the prospective multicenter randomized U.S. trials would say who looked prospectively at cost analyses were summarized briefly by Dr. Ring, but I'll reiterate, and that is for high increased risk patients, the cost effectiveness of carotid stenting was proven over endarterectomy because of similar cost but better outcomes. In the CREST trial, the actual costs were within $100 of each other and were not statistically significantly different. Now, costs and charges are very different things, and what is charged, rack rates if you will, the private carriers and what is charged is normally not equivalent to what is received, and we know that. The cost to charge ratios can vary widely, but when you actually track cost, that is, they are very similar overall with the two treatments and then with clinical outcomes being superior in the high-risk patient population, as demonstrated in Sapphire, the cost effectiveness of the stent implant was proved to be superior and very much so.

At our own institution, we published in circulation more than 10 years ago, a direct cost analysis of the two therapies, and they were basically equal.

Craig Blackmore: So, Dr. Franklin, what you gave us was payment data, right? Yeah. Other questions?

Gary Franklin: I would like to just say one more thing if I may that ironically a good friend of mine had a serious TIA this past week and it turns out there's a whole new emerging field here that we're not even talking about today, which is the field of the types of plaques in people's arteries that, so you're not talking about stenosis, you're just talking about plaques that are setting of emboli, and it turns out there are three of the eight types of plaques that have been described are at very high risk for future TIAs and stroke. So, we have… this is only emerging stuff. So, I imagine in a few years we'll be having the same conversation about carotid endarterectomy and stents to treat not stenosis but these other emerge… this other emerging area of increasing knowledge. Thank you.

Craig Blackmore: Other questions for Dr. Franklin?

Carson Odegard: I had one question. You mentioned the difference in cost between inpatient and outpatient procedures, but is not the… both procedures, the carotid endarterectomy and the stenting, are they not both inpatient only procedures according to Medicare?

Gary Franklin: I can't answer that question. I don't know if they're ever done in the outpatient facility.

Carson Odegard: I thought they were on the inpatient only lists.

Gary Franklin: Can you answer that?

Robert Bersin: Yes, so it's been a requirement for reimbursement for the patient to be coded as an inpatient, as far as CMS is concerned. Interestingly, you have the flip-flop with certain private payers. There is at least one private payer who will only reimburse the stent treatment as an outpatient. So, you know, it's very confusing to the practitioner, as to how to categorize the patient, because you have varying positions, as far as the payers are concerned, as to what their status should be.

Craig Blackmore: Thank you. Other questions? Okay, thank you. Let's press on with our vendor report.

Andrea Skelly: So, on behalf of my colleagues at Spectrum Research, I would like to thank those who have contributed to this report and I will apologize in advance. I'm overcoming a bit of a cold. So, I will try not to cough too hard, and I got a cough drop just in case. So, let's see, to advance the slide I think I do that. Good, okay.

So, the scope of the report. Our primary goal was to critically evaluate the research on efficacy, effectiveness, and safety of stenting in the carotid arteries and intracranial arteries, and we focused on the highest quality evidence that is available based on our systematic review of the literature.

With regard to background, I don't want to go into a lot of detail, because we've already had good information related to this, but stroke is the fourth leading cause of death, 87% of stroke is usually ischemic, but that does not necessarily mean it comes from the carotid arteries. The heart is a source of emboli, as are other areas of the body; 20-25% may be attributable to atherosclerotic stenosis of the carotid arteries, which is the focus of this report, and intracranial stenting, intracranial atherosclerotic disease is a bit of a

different animal pathophysiologically, and in terms of the preponderance of burden, it's different among different ethnic groups. Needless to say, stroke is a public health and economic burden that is very high in the United States.

With regard to anatomy, there are variations. The most common anatomical features have the carotid artery, the right side coming off of the innominate artery and the left coming directly off of another part of the aorta. There are a number of variations to this. The bifurcation, as Dr. Franklin pointed out, is the most common source, common area for atherosclerotic plaque. The external carotid feeds the face, the scalp, and the tongue. It's the internal carotid that is the primary interest for preserving vascular flow. It feeds the brain, the eye, and branches to the forehead, and the nose. The carotid artery comes up from the carotid… from the aortic arch area up through the cranium and if we go on to the next slide, the intracranial arteries begin at the base of the skull.

Two paired vertebral arteries come together to join… come together to create the basilar artery and the vertebral basilar artery then gives post… rise to the posterior communicating artery. The internal carotid bifurcates, as well, and the sum and substance is that the Circle of Willis is formed from a variety of these different vessels. It's highly variable, and only 50%... in less than 50% may, there may not be a complete vascularization. There is a lot of tortuosity and collaterals and calcification that can occur, and that induces a lot of variability, as well.

In terms of pathophysiology, in terms of the carotid arteries, cholesterol, plaque, is deposited decreasing the blood flow secondary to narrowing of the vessel. Again, the bifurcation is the most common area for that, and a variety of different mechanisms have been proposed for creating stroke events related to thrombus on the plaque itself, thromboembolism from the atherosclerotic material, rupture of the plaque leading to acute thrombolic occlusion. There are structural aspects, as well, and occlusion is possible, leading to decreased blood flow. Intracranial artery stenosis is a bit different in some respects. There are two primary mechanisms that are not mutually exclusive. Again, there can be thrombus that embolizes distally. There can be occlusion to reduced blood flow to areas that do not have sufficient circulation via collateral flow. The primary arteries involved are the internal carotid artery, middle cerebral artery, vertebral and basilar arteries, and here we're talking about the intracranial portions of the vertebral and basilar arteries, and although the traditional risk factors related to all atherosclerotic disease are operational here, it seems like diabetes and metabolic syndrome seem to be more problematic in patients who have… causing more problems in atherosclerotic disease of the intracranial vessels. I'd like to point out that not all stenoses in either of these areas are potentially symptomatic. You can have asymptomatic stenosis, as well.

With regard to imaging, just very, very briefly, there are four primary ways in which the vessels can be evaluated for degree of stenosis. Each has their pros and cons. Duplex ultrasound is probably the first imaging study that's done for most individuals, and it takes into account both the vascular… visualization of the vascular anatomy and the plaque, as well as the velocity of blood flow through a narrowed area. Studies over the years have correlated the peak systolic or diastolic velocities to angiographic findings and the standards for most labs are that if you have over… greater or equal to 125 cm/sec in terms of velocity, that generally is correlated to an angiographic stenosis of 50%. The sensitivity and specificity, if you're above 70% stenosis is fairly reasonable, but below that, it is not as sensitive or specific. Conventional digital angiography is the standard for evaluating. However, it is generally not considered the first thing that people do. Usually, they will try to do noninvasive aspects first. Magnetic resonance

angiography and computed tomography, angiography also allow for evaluation of stenosis, and again, there are pros and cons to each of them.

With regard to treatment options, you've already heard about these, for the most part. Best medical therapy has evolved significantly since the original trials comparing it to carotid endarterectomy. As you know, pharmacotherapy and lifestyle changes are the focus of this. Carotid endarterectomy involves the excision of the plaque and there are no contemporary trials, like I said, versus best medical therapy.

Carotid stenting, again, the important piece is to make sure that the flow is reestablished in the internal carotid artery. It's less invasive, as an alternative. A catheter is threaded through the femoral artery and then threaded to the carotid beyond the area of narrowing, and either a self-expanding stent or a balloon-mounted stent is then deployed, squishing the plaque to the side basically and the reestablishing blood flow and allowing the blood flow through that scaffold of the stent. Because there is a potential risk of plaque disruption during the procedure, CMS and most devices have available now, all of the devices that are FDA approved, have what's called embolic protection devices. There are a couple of different types of embolic protection devices, and the idea is that those will help catch any plaque that's disrupted and prevent any stroke peri-procedurally.

Looking at different embolic protection devices was beyond the scope of our particular report, as some of the previous speakers have indicated that has resulted in perhaps less… a lower rate of stroke and death secondary to stenting. Provider experience is another issue. There is an appendix to the report that outlines both the CMS criteria and the two organizations that provide accreditation for facilities that do stenting, and there can be… you're welcome to take a look at that.

With regards to intracranial stenting, the treatment options are limited. Aggressive medical therapy is the primary option. Stenting and/or angioplasty has only been tried in a number of small case series for the most part and as Dr. Franklin pointed out, there is a human device exemption approval. Currently, the only stent that's available is the Wingspan. Surgical options are limited and not widely recommended.

With regard to the FDA devices, again, there is an appendix in your report that outlines the devices that we were able to find and the labeling stipulates that there be use of embolic protection devices. In asymptomatic individuals, the labeling for most of them in stenoses of at least 80% for most devices. The Acculink for high-risk patients is 80% and for standard risk patients is greater or equal to 70% by ultrasound or 60% by angiography. For symptomatic individuals, the FDA labeling is for greater than 50% stenosis. Again, the Acculink has, for high-risk stenosis of over 70%, greater or equal to 70% for high-risk patients and for standard-risk patients greater or equal to 70%. Stents are indicated for… in individuals where there's an ability to have the individual tolerate general anesthesia if there's prior damage to the contralateral vocal cords. Previous neck surgery on the ipsilateral side, or restenosis after endarterectomy. Contraindications include unfavorable anatomy, unstable plaque, and inability to tolerate either the nickel titanium or the anticoagulant and antiplatelet therapies, uncorrected bleeding disorders and lesions at the opening of the common carotid artery.

With regards to intracranial stenting, the FDA approval is, again, for humanitarian device exemption, which suggests that only… there will be less than 4,000 individuals per year, in the U.S., that would need this procedure. The Neurolink is no longer available, and

the Wingspan stent was the subject of an FDA panel evaluation in March of 2012 and following that, the following criteria needed to be met for intracranial stenting. The patient had to be between 22 and 80 years old, have had two or more strokes despite aggressive medical management, the most recent occurring greater than seven days prior to the planned treatment, and their recommendation was that 70 to 99% stenosis be there in order to perform stenting and that there be an indication of good recovery from previous strokes based on the modified Rankin score. Unfavorable anatomy, treatment of acute stroke, treatment of transient ischemic attacks, highly-calcified lesions, and inability to tolerate antiplatelet therapy or anticoagulation therapy were contraindications.

The key questions are in your report, and I think we're all familiar with them. Key question one relates to comparison of carotid artery stenting and medical therapy opposed to medical therapy alone, or carotid stenting versus… and medical therapy versus carotid endarterectomy and medical therapy.

Key question two focuses on the intracranial atherosclerotic disease and use of stenting. I would like to make a note that both the efficacy, effectiveness, and safety components are included in that key question, as it was most logical to include them in that area for that purpose.

Key question three has to do with safety, particularly looking at periprocedural events, as well as longer term comparing stenting with alternative treatments and based on the clinical guidelines, which have already been presented to you, the question is in persons with extracranial carotid stenosis are the rates of periprocedural death or stroke less than 3% for asymptomatic patients, less than 6% for symptomatic patients?

Key question four has to do with differential efficacy or safety for special populations, and key question five deals with cost effectiveness.

Patient population for this group, there are two. First are patients with atherosclerotic disease of the external carotid artery. The second is patients with atherosclerotic stenosis of intracranial arteries, and we're already familiar with the interventions and the comparators. Primary focus of this report is on the highest available evidence, so randomized control trials and comparative studies with concurrent controls were the primary focus, and full economic studies for the economic portion.

The primary outcomes for efficacy and effectiveness relate to short-term and longer-term outcomes for stroke, death, and the composite stroke or death. For safety, 30-day periprocedural outcomes of stroke, death, or the composite of stroke or death, myocardial infarction, and then others related to major bleeding and persistent cranial nerve palsy. The ICER was the outcome of interest for the economic studies.

We searched multiple electronic databases. We searched previous Health Technology Assessments and used a systematic approach and did look at the bibliographies of major reports that were available. We started out with 1,043 unique citations and included overall 71. The primary evidence that I'm presenting here is based on the following. There are some key questions for which studies provided data on multiple key questions. For key question one, there were 9 randomized control trials. There were 15 reports from those trials and 27 nonrandomized trials. For key question two on intracranial stenting, only 1 RCT was available, but we have 5 prospective case series. One meta-analysis, we used some of the data from Dr. Benotti's meta-analysis for key

question four, which is on differential effectiveness, and then there were 9 nonrandomized studies and 5 full economic studies were included.

To facilitate our presentation this afternoon, I will be dividing into asymptomatic, symptomatic, and intracranial. As a reminder to the committee and audience, the overall strength of evidence is across all studies so that we can take a look at the overall quality of the evidence, not necessarily in any particular study, but across all studies, a high strength of evidence indicates that we are very confident that the effect size and estimate lies close to the true effect, moderate indicates that we have moderate confidence, and low indicates we have limited confidence that the effect size is close to the true effect, usually because there are differences in quality across studies and potential confounding. And insufficient means that we either have no evidence or we do not have any confidence in the effect size.

I would like to bring to your attention a couple of additional pieces of information. Six of the included randomized control trials of extracranial stenting, and the one RCT of intracranial stenting were terminated early. Several… the EVA, the SPACE, and the Leicester were stopped early secondary to concerns over safety or were terminated because interim futility analysis indicated that they would not likely find what they were looking for. Sapphire study was terminated early due to slow recruitment. Two studies were very small, the BACASS and the Regensburg study were terminated early because two larger trials, the ICSS and SPACE were being initiated. The SAMMPRIS trial, which is the intracranial stenting trial was terminated early due to safety concerns. Embolic protection, as pointed out in many of the public comments, is an important consideration, so we did sensitivity analyses, actually as part of the report, even available for public comment, using studies that used embolic protection and were more recent.

You've already heard about the clinical guidelines, so I don't think it's worth my spending much time on the clinical guidelines unless you would like to. They are also detailed in your report in the section in clinical guidelines, which I believe starts on page 76 to 79. So, I won't, like I say, go through the clinical guideline, only to mention again that most of the guidelines, as mentioned by previous speakers, indicate that for asymptomatic individuals, the accepted periprocedural stroke and death rate is less than 3% in asymptomatic individuals, less than 6% for symptomatic individuals.

In terms of payer policies, these are, again, in the same section as the clinical guidelines. Aetna indicates that they will cover PTA with or without stenting, but there needs to be embolic protection if it's necessary in symptomatic patients with at least 50% stenosis. They consider intracranial stenting not coverable, because it is experimental and investigational. Cigna's requirement is very similar for the extracranial stenting. They do not have a policy on intracranial.

Priority Health has a little bit different criteria for asymptomatic patients. They specify at least 70% stenosis by ultrasound or 60% by angiography and for symptomatic patients, 70% or greater by ultrasound or at least 50% by angiography. They also consider angioplasty with or without stenting to be investigational when applied to the intracranial arteries.

I will now present the evidence related to asymptomatic external carotid stenosis. Again, since the clinical guidelines, I believe, have been covered in a fair amount of detail, I don't know that it's worth spending time… spending a lot of time on these. So, I'm going to go ahead if that's okay.

With regard to key question one, which asks about the efficacy in an asymptomatic patient, looking again at short-term, greater than 30 days, up to 12 months, and the longer term greater than 12 months, no randomized control trials comparing stenting with best medical therapy were available. With regard to coronary artery stenting versus endarterectomy, two studies were available, an older study, we called the Kentucky study. It's by Brooks in 2004. It was a small study of 85 individuals and then you've heard about the CREST study, 1,181 who had asymptomatic carotid stenosis. You can see that with regard to… up to four years, most of the data is coming from the CREST study, and you can see that there are no significant differences between stenting and carotid endarterectomy. You might note that there is a higher risk of the composite, any periprocedural stroke, death, or postprocedural ipsilateral stroke at four years in stenting versus CEA. However, it did not reach statistical significance.

If we take a look then at effectiveness related to asymptomatic individuals, effectiveness data comes from nonrandomized studies. There was one retrospective cohort, which compared medical therapy to carotid stenting. It was considered to be low-level evidence, but it was a large retrospective registry study, and it demonstrated that for stroke, death, and the composite of any stroke or death, stenting was the better procedure to do. With regard to effectiveness in asymptomatic individuals looking at stenting versus endarterectomy, there were three nonrandomized comparative studies, and there were no statistical differences at any timepoint for 1.5 to 4 years. With regard to cognitive function, which was a secondary outcome, none of the small studies really provided information to suggest that one did better than the other, although one small study did find some improvement in working memory after stenting compared with CEA in contrast to processing speed, was better following CEA compared with stenting.

Moving on now to key question three, which has to do with safety, and the focus is on the periprocedural period, 30 days around the procedure. There was one cohort study, again, looking at stenting versus medical therapy and no differences in any of the periprocedural outcomes were noted. Looking at stenting versus endarterectomy, again, we have the same two studies in asymptomatic individuals, and we note, again, that in terms of statistical significance, there were no differences between the two treatment groups. However, for the composite of any stroke or death, there were more stroke or death in the stenting group versus the endarterectomy group, but again, it failed to reach statistical significance. You can see that there is also some indication that for myocardial infarction, there was a higher rate of myocardial infarction following endarterectomy versus stenting. However, it was not statistically significant, and there have been questions raised about the way that myocardial infarction was characterized throughout the CREST study.

Looking at nonrandomized studies, there are mixed results across the nonrandomized studies while no statistical significant differences were found in the cohort studies. That could be due to low sample size in these studies. There was one prospective registry that reported significantly higher risk of any stroke, death, and the composite of stroke or death within 30 days following stenting, but the other registry that was included found no difference when they looked at in-hospital time periods only.

If we now turn to key question four, which asked about, is there differential efficacy or safety, and again, we are still talking about asymptomatic individuals. There was one study looking at stenting versus medical therapy, but we felt that the evidence was insufficient. The retrospective cohort looked at the severity of ipsilateral stenosis as a

possible modifying factor, and there was no evidence for modification. Looking at the comparison of stenting versus endarterectomy, age… there were no RCT data available. There were data from a registry study that were available, but we considered it insufficient evidence. The bottom line is that age did not appear to modify the treatment effect for any of the primary outcomes that we evaluated.

Looking at sex, there is moderate evidence from one randomized control trial that sex did not modify the treatment effect for the primary outcomes of interest. With regard to efficacy, there was no modification by sex for ipsilateral stroke at four years or ipsilateral stroke or death at four years.

If we take a look at the issue of high surgical risk, the Sapphire trial is the only study that has focused on a high surgical risk population. This study did not compare the outcomes in patients that also had standard or average surgical risk. Therefore, from the standpoint of evaluating the differential efficacy and safety among high-risk patients, there is insufficient evidence, because we don't have that other comparator group. However, if we take a look at the Sapphire study in terms of its findings for efficacy and safety outside of the issue of differential effectiveness, we see that at one year ipsilateral stroke or death was much less in the stenting group compared with the endarterectomy group, but none of the other outcomes reached statistical significance for efficacy. With regard to safety, there were no statistical differences between the groups, but it is noted that in terms of periprocedural death, stroke, or MI, which is a composite, that those who received stenting had less risk of that composite compared to those with carotid endarterectomy.

With regard to cost effectiveness in asymptomatic persons, there were three cost utility studies available. Two were based on the Sapphire trial, which again was in the high surgical risk individuals, and the primary data that they presented suggested that at a one-year time horizon, the incremental cost-effectiveness ratios indicate that stenting was plausible, but not verifiably superior. There are, however, a couple of concerns about this particular study. The 95% confidence interval goes everything from -$129,000/QALY to $379,000/QALY, so that's a quite large dispersion around the mean. There was also a study based on the CREST trial that looked at standard surgical risk and in the scenarios evaluated, endarterectomy was preferred given commonly-assumed cost-effectiveness thresholds.

If we now turn our attention to symptomatic individuals. Again, I am not going to go over the clinical guidelines, because those have been very well covered by our public commentors. If we take a look again at stenting versus medical therapy, no randomized trials were found related to symptomatic persons. If we're looking at stenting versus endarterectomy, there were 10 reports from seven RCTS available for these data. Two of the reports reported on short-term outcomes, seven on longer terms. I would like to point out that two of the studies, BACASS and Regensburg, had less than 20 people per arm. So, that needs to be considered when we talk about some of the pooled analyses.

If we take a look at the longer term… the short-term efficacy, at four months there were no differences in treatments in any stroke, which excluded periprocedural stroke and the same was true if you looked at ipsilateral stroke that excluded periprocedural stroke. That was true at four months, and it was also true at later time periods up to 5.4 years.

With regard to deaths, at four months one study provided information for that. With regard to death, at four months one study provided information for that and it appears

that there was a higher risk after stenting of death, up to four months. Among those who received endarterectomy, the risk was less and it favored endarterectomy. If you look, however, then at the longer timeframes, there were no statistical differences whether or not periprocedural events were included. There were no differences across five RCTs and one group that included periprocedural events and no difference again among two RCTs that excluded periprocedural events.

If we take a look now at the data related to any stroke or death, including periprocedural events, one smaller randomized control study found no difference between the two statistically. One larger study found a statistical difference between the two in terms of risk of any stroke or death when including periprocedural events at four to six months favoring endarterectomy in the larger study, although the risks in both are higher following stenting, even if they didn't reach statistical significance. If we look at the composite of any periprocedural stroke or death or postprocedural ipsilateral stroke, again, one smaller study appears to have favored CEA in terms of statistical significance with a higher rate following stenting versus endarterectomy. At two to five years, there were no statistical differences between the treatment groups.

Nonrandomized studies looking at effectiveness, we felt that the evidence was insufficient. There was only one study. There was low evidence and no statistical difference reported in one cohort at 2.8 years for any periprocedural stroke, or death, or postprocedural ipsilateral stroke.

If we now turn our attention to safety in symptomatic individuals looking at the 30-day periprocedural period, we see that with regard to any procedural stroke that across four RCTs in the sensitivity analysis that we did. There was moderate evidence that there was a higher risk of stroke in the stenting group compared with the endarterectomy group. The sensitivity analysis excluded older studies, those that had less than 20 individuals in the study, and those that did not include embolic protection devices. So, the forest plot that you see here represents those four studies that include embolic protection and were more recent studies. And you can see that the overall effect does favor CEA.

If we look at death, again, based on sensitivity analyses, there were, if I draw your attention down to the forest plot down below, based on the three studies in the sensitivity analysis, there were no differences. When we included all studies, there were four, and there were no statistical differences in death based on the sensitivity analysis or the primary analysis.

The composite of any stroke or death, again, I am presenting the sensitivity analysis, the full analyses are in your report. If you take a look, again, at the forest plot, you can see that CEA is favored. There is a higher risk of any stroke or death in stenting versus carotid endarterectomy, primarily driven by the rates of stroke, not the rate of death.

If we take a look at ipsilateral stroke alone, two RCTs provided the primary information. The sensitivity analysis is on the bottom of the slide there, and you can see that once we take out the very small study from Leicester, there is much better precision of the estimate and the endarterectomy is favored over stenting for the outcome of ipsilateral stroke.

Taking a look at fatal, major, or disabling stroke, five RCTs provided information for this outcome, and there were no statistical differences between the treatment groups.

Looking at myocardial infarction across four RCTs, there were no differences statistically in treatment groups for that.

If we take a look at other outcomes related to safety, cranial nerve palsy and injury were very difficult to get good definitions across studies. However, there was a statistical difference looking at coronary artery stenting compared with endarterectomy. The rates of cranial nerve injury were lower for stenting. With regard to bleeding, there were no statistical differences between the two groups, and again, these data are detailed in your report.

Looking at nonrandomized studies, again, there were mixed results across studies, and with regard to two large prospective registry studies, there was low evidence that there was a higher risk of any stroke or death with stenting and neither showed difference in myocardial infarction. On registry that looked at in-hospital events reported significantly higher risk of any stroke or death, of ipsilateral stroke, in stenting, and there were no statistical differences in the cohort studies that were assembled, possibly again due to small sample size.

Looking at differential efficacy and safety, no studies comparing stenting to medical therapy were available. With regard to looking at age, there was moderate evidence that age did not modify treatment effect for the outcome of the ipsilateral stroke at four years based on the SPACE trial, but it did modify the composite of ipsilateral stroke or death at two years in a different study. With regard to age, it did not modify the treatment effect for the outcomes at 120 days in the EVA-S trial, excuse me, in the ICSS trial for the composite of stroke, death, or MI, or for ipsilateral stroke in the EVA trial.

If we take a look at age, however, looking at meta-analysis based on data that were available from the Benotti meta-analysis, Cochran review, we can see that age does appear to modify the risk for periprocedural death or stroke. Individuals who are less than 70 years old, it didn't seem to matter whether you did endarterectomy or carotid stenting from a statistical standpoint, because there was not statistically significant difference between the two groups. However, in patients who were over 70 years old, you can see that the effect estimate and the confidence intervals are very different indicating that CEA would be favored in that particular group.

If we take a look at sex as a modifier, there was no modification for outcomes related to death, stroke, or MI as a composite at 120 days or for stroke or death at four years or ipsilateral stroke at two years. Ipsilateral stroke at four years, the crest did not suggest that there was modification by sex, but one other RCT, the EVA trial did suggest it. If we look at safety and sex in terms of the forest plot that's there, there were no statistical differences in terms of the interaction term. There was no statistical interaction with regard to sex and therefore no modification of effect by sex.

Again, looking at sex, no modification related to periprocedural stroke or periprocedural MI. There was moderate evidence from the CREST trial that sex may modify treatment effect for the composite of any periprocedural death, stroke, or MI. In terms of other factors, no modification by treatment was found. If you look at severity of ipsilateral stenosis, diabetes, smoking status, severity of contralateral stenosis, and there was insufficient evidence, but again, no modification was seen related to hypertension, surgical risk, type of qualifying event, or time to treatment.

With regard to cost effectiveness, four cost utility studies were available for evaluation. Two studies found that there was insufficient evidence to favor one over the other, but

across the four studies, they suggested that cost effectiveness was achieved more with carotid endarterectomy. Subanalysis from the Sapphire trial, again which is in high-risk patients, suggested that stenting was more expensive with negligible gain in quality adjusted life years, and the ICERs were very high for this particular cost effectiveness study.

Moving now on to intracranial studies, intracranial stenosis, there was less said about the clinical guidelines for intracranial artery stenosis. The two primary ones that we found were from the American Heart Association, American Stroke Association. In asymptomatic individuals, there were no recommendations made. They suggested that in patients who had 50 to 99% stenosis of the major intracranial artery, the usefulness of angioplasty with or without stenting is unknown and considered investigational, and the other comment, that was from a different, actually a different guideline. The usefulness of emergent or acute intracranial angioplasty without stenting was not well established and again should be considered in the setting of clinical trials. The other set of guidelines for intracranial stenting suggested that asymptomatic individuals, there was insufficient evidence for recommending endovascular therapy for severity of stenosis and that they should… you should counsel the patient, monitor them, and provide them with optimal medical therapy. For symptomatic individuals, they said that patients with at least 50% stenosis who have failed medical therapy, balloon angioplasty with or without stenting should be considered.

There was only one randomized control trial that was in symptomatic individuals that related to intracranial stenting. There were no studies on differential efficacy or safety and no economic studies. The primary endpoint for the SAMMPRIS study, which is the only randomized control trial, was the composite of stroke or death within 30 days or ischemic stroke in the territory of the qualifying artery beyond 30 days, so it's a very complex composite. The trial was stopped early because of concerns regarding safety around this particular endpoint. You can see that for stenting, and that should be intracranial stenting, not coronary artery stenting, as the header. There was a 20% higher probability of that composite among the intracranial stenting group compared with the medical group, and the number needed to harm was calculated at 13.

If we take a look at the safety data, the 30-day periprocedural aspect, you can see that with regard to any stroke again, there is a much higher risk of stroke in the intracranial stenting group compared with the medical group, and that is driving the composite of any stroke or death. Major bleeding or hemorrhage was also greater in the stenting group compared with the medical therapy group for the 30-day periprocedural outcomes.

In terms of efficacy, again, any stroke was much greater in the stenting group versus the medical group, and you can see that for the other outcomes, with the exception of major hemorrhage, that, again, there was a higher risk of any major hemorrhage with stenting compared with medical therapy.

So, finally, in summary, with regard to stenting versus medical therapy, there were no randomized controlled trials. Again, going back now to our asymptomatic individuals, this is a summary for them. There were no randomized control trials, and in the one registry that we found, stenting was definitely favored. If we look at the comparison of stenting versus endarterectomy, there were two randomized control trials that provided data on asymptomatic individuals. The level of evidence was low for similar risk for stroke, ipsilateral stroke, and vessel patency up to four years. The differences in any periprocedural stroke or death or postprocedural ipsilateral stroke were somewhat

higher in stenting versus endarterectomy, but the difference failed to reach statistical significance. With regard to safety, there was moderate evidence that there was no statistical difference in safety outcomes, 30-day outcomes, based on the CREST trial. The risk of stroke and the composite of death or stroke was 2.5% for stenting, 1.4% for CEA. The difference failed to reach statistical significance, but again I would remind you that part of key question three asked whether or not the rates were below 3% for asymptomatic individuals for the composite of stroke or death.

In terms of differential efficacy or safety, there was insufficient evidence with regard to stenting versus medical therapy, that there was no modification related to ipsilateral stenosis. It was also insufficient for comparison of stenting versus endarterectomy that age, surgical risk did not modify the treatment effect. There was insufficient information on surgical risk, and there was no comparison in the one trial that was available with standard surgical risk patients. There was moderate evidence that sex does not modify the treatment effect in asymptomatic patients. In economic studies, we felt that the overall quality across all studies was low, and in high-risk patients, cost effectiveness of CAS may be plausible but was not considered to be verifiably superior at one but may be cost effective over a lifetime, but there are a number of methodological concerns that we can discuss if you're interested. In standard risk patients, endarterectomy appears to be preferred.

Turning now to symptomatic patients. Again, no studies comparing stenting and medical therapy were found. With regard to efficacy, comparing stenting and endarterectomy at the short-term, in other words 30 days up to one year, there was moderate evidence that at four months there were similar risks of stroke, ipsilateral stroke, and there was similar risk for stroke and ipsilateral stroke at four months when we excluded periprocedural stroke. The risk of death was higher following stenting. At four to six months, there was significantly higher risk with stenting for the composites of any stroke, death, or periprocedural stroke or death, and again, the evidence for this was moderate. Looking at the longer term across five randomized control trials up to 4.5 years, there is moderate evidence that the risk of death was similar between treatment groups whether or no periprocedural death was included. The evidence was low, of no difference of death or stroke including periprocedural stroke or death, those events at that time, and any periprocedural stroke or death, or postprocedural ipsilateral stroke. So, those, for the long-term outcomes, there was no… there was moderate to low evidence.

In symptomatic patients, for safety, there was moderate evidence that the risk of stroke and the composite of any stroke or death were significantly higher in symptomatic persons who received stenting. That was based on our sensitivity analysis across four randomized control trials that were more contemporary and used embolic protection. The risk of any stroke or death was 7.1% across studies for stenting and 4.1% for endarterectomy across studies with a risk difference of 3.1 and number needed to harm of 35. For differential efficacy or safety, there was moderate evidence that age for efficacy that modification by age for the composite of ipsilateral stroke or death at two years and those greater than 68 years old had better outcomes with endarterectomy, but there were no modifications seen for other outcomes. With regard to safety, the risk of periprocedural death or stroke, endarterectomy was favored in patients over 70 years old, while those under 70 years old appeared to have similar results regardless of treatment based on, again, three randomized trials that were more contemporary using embolic protection. For sex, in terms of sex being a modifier, there was moderate evidence that there was no modification by sex.

In terms of surgical risk, it was insufficient, because, again, the one trial on high-surgical risk patients did not have a comparison with average surgical risk patients. There is moderate evidence that there was no modification by severity of ipsilateral stroke and insufficient to low evidence for no modification by a number of the factors related to comorbidities, such as diabetes, type of symptomatic qualifying event, severity of contralateral stenosis, time to treatment, hypertension, or smoking.

Finally, with regard to economic aspects, there were four cost utility studies and endarterectomy tended to be cost effective compared with stenting. The Sapphire trial, which was in high-risk patients, was considered more expensive with negligible improvement in quality adjusted life years.

Intracranial stenting, again, no studies in asymptomatic patients, but there was one RCT in symptomatic individuals, which was terminated early due to a higher rate of their composite of stroke, death, or, in the periprocedural area, or ischemic stroke in the territory of the qualifying artery after the 30-day period. We considered it low evidence. Safety also low evidence. There was a significantly higher probability of stroke, any stroke or death or hemorrhagic events with stenting compared with medical therapy. Again, no studies looking at differential efficacy or effectiveness were found, and no economic studies related to intracranial stenting were found.

So, in summary, there are a number of limitations. The remaining questions, as a number of the presenters previously pointed out, there are no high-quality data comparing stenting with current best medical practices in asymptomatic individuals, and there is limited data from randomized control trials in asymptomatic individuals who are low risk, and trials to date have lacked medical treatment comparator. There is only limited information beyond five years on the benefits and harms of stenting and whether or not these would outweigh any periprocedural event risks. The impact of better medical therapy, enhanced surgical techniques, and improvements in stent technology requires further study. There are a number of studies out there that have looked in case series at different types of embolic protection devices and various things that were beyond the scope of this report, and all of those things require some further study in comparative studies.

The extent to which there is differential efficacy and safety in some special populations, including those at high surgical risk is not clear based on the data available. Overall, studies were underpowered, most likely to detect modification of treatment effect, and there is a need for high-quality full economic studies to further evaluate this question.

Thank you for your attention. I know it was kind of long and complicated.

Craig Blackmore: Thank you. Questions from the committee?

Seth Schwartz: Can I go back to slide 18?

Andrea Skelly: If we can find it, yes. Okay.

Seth Schwartz: So, the EVA, the SPACE, and the Leicester randomized control trials were stopped. Can you… because of concerns over safety or interim futility analysis.

Andrea Skelly: Mm-hmm.

Seth Schwartz: Does that mean that the trials decided that they weren't going to show what you wanted to show, so they stopped them?

Andrea Skelly: I did not...

Seth Schwartz: Is that what that means?

Andrea Skelly: ...investigate the, you know, explicitly why… what their futility analysis may have shown. It may not have even been available, but in a futility analysis during a trial, if it does not show… if it appears that there is not going to be benefit to the treatment, they say that it's not going to be worth continuing the particular trial. So, it's futile to consider...

Seth Schwartz: Is it the lack of benefit evidence?

Andrea Skelly: Yeah, basically.

Chris Standaert: No. They don't reach their target goal in recruitment, because they already have hit the point where even if they hit their target goal, they would never change the outcome.

Andrea Skelly: Exactly.

Chris Standaert: What they found is that the difference is so small that they recruit the next 200 patients they had planned in their study, even if they all went great, there's no realistic probability that would change the outcome of what they already discovered, so they stop spending more money, more time, more inventions, and all that.

Seth Schwartz: The other question I had was on page 239 of the report, and it's the mod synopsis of cost utility analysis. I'm not exactly familiar with what third-party payers decide a life is worth, but it struck me as odd that the disability payment for a major stroke was $10,000 but death was $5,000. Am I just naïve?

Chris Standaert: Yet, it's $40,000 to get a stent.

Andrea Skelly: There are different ways of valuing these things, and unfortunately, I can't speak to their way of doing it other than to say I would have the same question. There are lookup tables that you can evaluate different things on.

Seth Schwartz: Can I ask you a question on the summary slide, slide 60? We were looking at it for symptomatic patients, short-term, the difference between stroke favored CEA but then the long-term difference didn't really show a difference. Were the… for the long-term data, does that include everything, or does that exclude the patients who had early strokes?

Andrea Skelly: On the summary slide?

Seth Schwartz: Yeah.

Andrea Skelly: Let me take a look here and see.

Seth Schwartz: In other words, my question is, are you seeing more strokes early in the stenting group but ultimately it's the same, or are they pulling out those patients who had early strokes?

Andrea Skelly: So, you're talking about, I'm sorry, which slide again? I'm sorry.

Seth Schwartz: I'm looking at your summary slide, slide 60.

Andrea Skelly: Okay, slide 60. Okay, so… and help me again with which one you're looking at.

Seth Schwartz: I'm looking at the whole thing.

Andrea Skelly: Oh, the whole thing.

Seth Schwartz: Yeah, my question is, so this is implying that the stroke risk is higher for stenting in the four-month period after the intervention, but if you look at long-term outcomes, there is no difference. What I want to know is, are they… is the… does the longer-term data include the early strokes, or are those patients pulled out for the longer-term analysis?

Andrea Skelly: Let's actually go back to the slide that has that data. I think it will be clearer than trying to talk, and that was on, in the symptomatic individuals or the asymptomatic?

Seth Schwartz: Symptomatic.

Andrea Skelly: Okay, in the symptomatic individuals. So, if you look at the top set of rows, at four months based on one randomized control trial there were no differences when periprocedural events were excluded, and there were no differences in ipsilateral stroke when periprocedural events were excluded. So, there were no differences between treatments at either four months or at the longer time period for those two particular outcomes in terms of statistical differences. So, that's excluding periprocedural stroke. So, that's long-term, short… shorter-term and longer term where we exclude periprocedural events. Bear in mind that many of these studies did not report… it was not possible to tease out periprocedural events from some of their composite measures.

Craig Blackmore: But, why are we excluding periprocedural events? Is there...

Andrea Skelly: Because the concept behind the longer-term efficacy is that the periprocedural events were considered under safety, and again, some of these studies they reported things this way. I would have to go back to the individual studies to give you a more definitive answer, but the idea for the efficacy was that it would be after the periprocedural period for a longer timeframe.

Craig Blackmore: So, if we go ahead to slide 38, please. So now, this is the same studies. So, this is pooling all deaths, or all strokes, or all whatever it is.

Andrea Skelly: Yes.

Craig Blackmore: Is that?

Andrea Skelly: Yes. So, when periprocedural events are included in that top set of data, in one randomized control trial there was no difference. In one other randomized control trial from four to six months, there was a difference. If you look at the absolute risks, both of them are higher for stenting compared with endarterectomy, but this includes any periprocedural stroke event rate that would have been… or death, that would have been part of the trial, as well as anything up to four to six months. That's why it gets really messy. Does that answer your question? No?

Seth Schwartz: No, I'm still confused by this. I'm still trying to understand how those can be… if you include all things… so I guess what I'm trying to understand is, are we seeing more early strokes in the stenting patients and fewer longer-term strokes? That's what I'm trying to understand, because here it looks like if you follow people out, the… more people may die during the procedure, but, or have strokes during the procedure, but ultimately their numbers are going to be the same. So, that would seem to argue that it is more effective longer term, but that's not what I was hearing on the summary slide, which is that...

Craig Blackmore: I think that what you're seeing here is roughly equivalent rates after the procedure, and you've got an excess number of strokes early on that stay the same. So, the percentages change, but the, you know, you basically, I mean, if we look at this we could say there were excess strokes of however many in the first periprocedural period and then things are pretty even. So the absolute difference is similar, but the percentages are different. The...

Chris Standaert: The slide isn't the same patient population though, is it? Short and long-term?

Seth Schwartz: It looks like it's the same.

Andrea Skelly: I think that the basis...

Chris Standaert: 1,710. Where's the 1,710...

Andrea Skelly: ...for both studies… for both slides is pretty much the same, because we've got, well, okay, for the four-month study there was only one randomized control trial that provided data excluding periprocedural stroke, and then, there were two trials available, one smaller and one larger, when we were able to include periprocedural events. So...

Chris Standaert: But if you look at this one, the 1,710 includes periprocedural events and showed a higher rate in the stenting group. If you go back to the other one, the study of 1,710 excluding periprocedural and with a longer-term follow-up of that same group, the numbers are pretty equivalent. So, if you take out the periprocedural events, they're equivalent.

Andrea Skelly: Mm-hmm.

Chris Standaert: Is what that looks like.

Andrea Skelly: Yeah.

Craig Blackmore: So, I'm struggling with the Sapphire trial. Can you help me understand it? This was done intentionally on high-risk surgical candidates, is that right?

Andrea Skelly: Yes.

Craig Blackmore: And it was terminated early for some…?

Andrea Skelly: Because of slow recruitment. That was the stated reason in the literature.

Craig Blackmore: Okay, and so I, did I, did you give us results, or they didn't publish results, or did I… I mean I might have missed it. There was a lot here.

Andrea Skelly: Oh, yeah. I understand.

Craig Blackmore: Slide 32, thank you. Okay.

Andrea Skelly: The Sapphire study was primarily among asymptomatic individuals and in your report, I would have… I'll have to look up the page, but there is a listing of the comorbidities and aspects of patient population for those individuals compared with the more "standard" surgical risk studies.

Craig Blackmore: So, the… just in a very crude sense… well no, I'm not even going to say that. Never mind.

Andrea Skelly: So, in terms of the Sapphire trial, we put it under special populations, because that's where we thought it fell… it would best fit. Unfortunately, it did not compare versus standard or average surgical risk patients, so the question of differential efficacy cannot be answered. However, the data on the trial itself are presented here, and you can see that among high-risk surgical risk patients, there was a much higher rate of ipsilateral stroke or death at one year among those who received endarterectomy compared with those who received stenting and then at three years, stroke, or ipsilateral stroke or death, although it was not statistically different, you can see the percentages for the stenting group were somewhat higher, not a lot higher, and for the ipsilateral stroke somewhat higher, but not higher, but not statistically significant.

Michelle Simon: So, this study seems to go against most of the other studies, in that it possibly shows a benefit to stenting. I'm curious about where the trial was done, risk of bias, any of that stuff.

Craig Blackmore: Well, I mean, I'm just looking at this and I'm seeing a 10% stroke or death rate in stenting, which is very similar to the other groups, but a much higher risk in the CEA group, which makes sense if you're doing surgery on high-risk surgical patients, right?

Joann Elmore: A lot of comorbidity.

Chris Standaert: So, what, what this looks like is...

Craig Blackmore: It was… then the risk stabilizes after that. The absolute difference at three years is very similar to the absolute difference at one year.

Chris Standaert: It looks like if you take out the… if you look at the stroke numbers in three years, which are the same, and then the first year stroke or death. What that implies is you have a lot more people die following the endarterectomy in this high-risk population within a year. So, you're operating on very high-risk people, and you had a higher mortality rate associated with the short-time after the surgery. Then, it sort of stayed relatively even after that, it looks like, but it looks like that what they found, and they're doing a high-risk surgical population.

Craig Blackmore: Whereas some of these other studies in the lower risk surgical patients, it seems that the stenting has a higher periprocedural morbidity, which would, I think, make sense.

Robert Bersin: If I could volunteer a comment?

Craig Blackmore: Sure.

Robert Bersin: So, what she's showing here is just the asymptomatic cohort of the trial. The trial did include symptomatic and asymptomatic patients, and it was the only randomized trial looking at high surgical risk patients. Historically, it was the first and only one done on high-risk patients here in the United States or anywhere else, and the feeling at the time was to take of course the high-risk surgical population to test the alternate therapy. So, it's the only trial that's been done on high increased surgical risk patients because of the outcomes. The symptomatic cohort was more equivalent, in terms of outcome, smaller number. Typically, that's the case. It just took all comers who were high-risk individuals, but what she's showing here is only the asymptomatic.

Craig Blackmore: Do we have the symptomatic?

Andrea Skelly: Yes, we do.

Robert Bersin: So, I just wanted to clarify that.

Andrea Skelly: Yes, and I did not put it on the slide, and I probably should have. On page 233 of your report, there's a description of the Sapphire trial among symptomatic individuals. There were only 96 individuals that were symptomatic, and it… the results suggested that these patients had similar risk of stroke through three years, that the composite outcome of ipsilateral stroke or death through three years, and ipsilateral stroke or death through one year, regardless of the treatment received. So, basically, the results were similar. Safety data from the same trial, we found that these patients had similar risks for the composite outcome of periprocedural death, stroke, or MI regardless of the treatment received, and that's what we have for the Sapphire trial. We also do have the data abstracted in the appendices, if there are specific data that you're interested in.

Chris Standaert: And there is no nonintervened upon arm in this study, I assume. You have high-risk surgical patients, and they didn't stratify one group of them, just a medical therapy.

Andrea Skelly: No.

Craig Blackmore: Other questions for Dr. Skelly?

Michael Souter: You said there was...

Richard Phillips: Question regarding the intracranial stenting. Did the cases that you discussed only include anterior circulation? In other words, you did not, you excluded all vertebral artery, correct?

Andrea Skelly: Anything that was extracranial. Actually, the only, there was only one study that was on intracranial, and we included all data from that study, but if it was an extracranial vertebral or extracranial, it was not included. That was not part of the scope, extracranial, vertebral… or was not part of the scope.

Michael Souter: I just have a question about restenosis and the… from what I'm reading here, there had been no difference in the restenosis rates between stenting and endarterectomy groups, is that correct?

Andrea Skelly: That is correct.

Michael Souter: How far out was the, let's just say, you know, the majority of the patient population? You know, it would seem that there's some, you know, evidence out as long as five, over

five years, but I'm trying to get a sense of, you know, where the majority of the population, you know, how long were they assessed out towards?

Andrea Skelly: On page 144/145 of the report, it talks about restenosis in symptomatic individuals and some reports went for two years. The longest was 5.4 years.

Michael Souter: I'm just trying to get a sense of the ends.

Andrea Skelly: Yeah, page 145, the largest study was the SPACE study, and it had 1,196 patients. The smallest study was BACASS, which only had 20 patients.

Michael Souter: Okay.

Andrea Skelly: There was a study that did not meet the inclusion criteria from the CREST trial, which included both symptomatic and asymptomatic individuals, and we were not able to segregate the data. That's why it was excluded, and I can call that study up if that would be of help, but basically it showed that there were no differences in restenosis… that restenosis rates were low across both treatment groups.

Chris Standaert: I don't know if you would know the answer, maybe our expert does. Endarterectomy has been around for a very long time. Do we know the long-term restenosis rates in endarterectomy, so a 10/20-year restenosis rates, or do we not know them?

Andrea Skelly: I don't know that.

Chris Standaert: Is that out there somewhere?

Robert Bersin: 10 or 20, no; 5-year has been reported extensively. Basically it goes like this, 5 years about 5%.

Chris Standaert: Five years about 5%?

Robert Bersin: And the best… sort of the best tracked trials were the, as far as recurrence risk with either endarterectomy or stenting, the best one was Sapphire, which did it out prospectively to three years, and it's the same. It's 3% at three years. So, just keep in your mind 1% per year up to five years.

Chris Standaert: Okay, thank you.

Craig Blackmore: Well, it's 5 of 3:00, so I think it's time for us to take a quick break, and then we will resume and go through our deliberations. Five after 3:00 everybody? Thank you.

Alright, I'm going to call the committee back to the table, and we are most, unfortunately, going to have to start before the coffee gets here. When the coffee gets here we can get some.

Alright, so, back on the carotid artery stents, and we can continue with questions from our presenters or if we're ready, we can start to move on to the committee's members discussions. Are there any other questions at this point?

Michael Souter: Yeah, sorry. I just want to follow up on this question of the restenosis, right, again. So, I'm just looking at the table that you referred me to on page 155, and in my

understanding, there is that… we're talking about the longest follow-up. So, these are really the outliers of follow-up that you're listing here, these time periods. Do we have any sense of where the majority of the patients in those groups were followed up to? Was there a minimum period of follow-up, because that's what I'd be more comfortable knowing.

Andrea Skelly: We will have to look that up.

Michael Souter: Okay.

Andrea Skelly: Because I don't, I don't know off the top of my head. I can't tell you.

Craig Blackmore: Any other questions while she's working on that?

Richard Phillips: One other thing about the restenosis, just for clarification, there are a number of surgeons who, when they do carotid endarterectomies, they enlarge the artery with angioplasties. My impression was that, that was not permitted as part of these procedures. I was wondering if you could check into that, just to make sure. In other words, they did not do Dacron patch, or whatever it is, to enlarge them, because of the incidence of restenosis, and there are some surgeons who will do it routinely and some don't. So, that might make, whether it makes a difference or not, I don't know, but it, I mean, sure it affects the restenosis rate.

Craig Blackmore: Alright, any other question? Well, we will give Dr. Skelly some time to work through that.

Chris Standaert: I do have one question for her on the study. So, I asked that question about in the high-risk patient group that there was no medical treatment harm, but they all had surgical risk, but I noticed the SAMMPRIS trial that you mentioned some on page 148 of your document.

Craig Blackmore: That's intracranial.

Chris Standaert: Oh, intracranial, okay. Never mind. Sorry, thank you. That was the one that was killed, okay, gotcha. Never mind.

Craig Blackmore: Well, while we're digging down for some answers, does anybody want to get us started here? We've got three groups, asymptomatic, symptomatic extracranial, and then intracranial in general. So, I think at least initially we should consider them all separately and I guess we could start with the asymptomatics, they're the first ones we got to.

Chris Standaert: We could start with intracranial.

Craig Blackmore: You want to cover intracranial?

Joann Elmore: Let's do the easy one.

Craig Blackmore: Alright, we'll start with intracranial. What do we think about intracranial? Joanne, what do you think about intracranial? Do you want to give us a starting place?

Joann Elmore: Inadequate data. No studies, asymptomatic. The one RCT in symptomatic terminated early. Noncoverage is what I would recommend.

Craig Blackmore: Yeah, it didn't just terminate early. It showed an adverse effect.

Chris Standaert: It's actually beyond… it's actually beyond inadequate data. It's not inadequate data. It's actually very negative data for the intervention.

Michelle Simon: I think if we're looking at a number needed to harm and in the 13s, it's not good.

Chris Standaert: That's not good, no.

Craig Blackmore: Any other thoughts on the intracranial?

Richard Phillips: I had a question. What was the date of the SAMMPRIS study?

Craig Blackmore: The date of the SAMMPRIS?

Richard Phillips: Because they mentioned something about better medical therapy, you know, current medical therapy.

Carson Odegard: On page 149.

Craig Blackmore: Without bothering Dr. Skelly, since we've got her pinned down doing other things, let's see if we can find it.

Chris Standaert: I had it a second ago, obviously.

Richard Phillips: Because it would probably favor medical therapy even more.

Chris Standaert: 2011? It says reference 51, stenting versus aggressive medical therapy, intracranial, arterial stenosis published in 2011.

Richard Phillips: Oh, 2011.

Chris Standaert: New England Journal.

Richard Phillips: Okay, thank you.

Craig Blackmore: So, I'm not hearing a lot of enthusiasm for covering intracranial stenting. Is that fair?

Michelle Simon: Right.

Chris Standaert: You sort of face the very limited database that is largely negative.

Craig Blackmore: Okay. In that case, I think we should proceed with our cards and our tool, and maybe we can work through one of them and then move on to the others. So, let's see, before we do that, let's… is there a national coverage? I don't believe there is for intracranial, is there?

Josh Morse: I believe there is.

Craig Blackmore: There is? Well, let's find that out. Did you… did you find the national coverage decision?

Josh Morse: The complete national coverage decision is in your decision tool beginning on page 4.

Craig Blackmore: Okay, so this is dated November, 2006, and obviously predates the best clinical evidence that we've seen, which was the SAMMPRIS trial, which was published in 2011. That trial… well, we will vote, but that seems to be the best evidence in the eyes of the committee. So, the committee will take our first nonbinding vote, and this is dealing with intracranial stenting, and the first piece of that is effectiveness, and this is going to be compared to medical treatment, and you are to vote more if you believe that the stenting is more effective under some or all circumstances. You are to vote less if you believe it is less effective, and equivalent and unproven are self-explanatory.

Josh Morse: Eight less, three unproven.

Craig Blackmore: So then safety is the next piece.

Josh Morse: Ten less, one unproven.

Craig Blackmore: And then finally, cost effectiveness.

Josh Morse: Ten unproven, one less.

Craig Blackmore: Alright, and then, further discussion? Okay then, we'll move on. Based on the evidence about the technology safety, efficacy, and cost-effectiveness, and your choices are to cover unconditionally, to not cover under any circumstances, or to cover with conditions, and this time, if we vote for with conditions, we will decide on the conditions subsequently.

Josh Morse: Eleven no cover.

Craig Blackmore: And again, we are disagreeing a little bit with the Medicare decision, but that was made years before to what we feel is the strongest evidence that came was the randomized clinical trial, the SAMMPRIS trial, okay?

Josh Morse: Okay, thank you.

Craig Blackmore: Alright, so let's move on, asymptomatic, and have we got any more from Dr. Skelly on our questions, or are you still digging over there?

Andrea Skelly: We're still digging.

Craig Blackmore: Okay. Does somebody want to start us off on asymptomatic?

Michael Souter: I'm concerned with the early termination of trials, I mean, for futility. I do get worried about, okay, sure you don't prove effects. You can see maybe there's not something to warrant a treatment benefit, but we don't get the true chance to assess whether or not there's additional safety concerns when a trial is terminated early, and I think that there's way too many of those for my comfort level.

Craig Blackmore: Okay, other thoughts? Well, I guess I would chime in that I think there is sort of a competing mortality issue here. I don't know if that's the right term, but it seems to me that based on the data, which definitely has some issues, that the postprocedural effectiveness of the two seems pretty similar, but there seems to be the periprocedural complications are higher in the intervention… in the stenting group. That's the way I

would interpret this, but that might be different when we get into the high surgical risk group. In the high surgical risk group, things seem to switch. Stenting is similar, but the high surgical risk has a higher surgical risk, and there is more periprocedural mortality. So, that seems a little different to me, but the question that we can't answer is, should they get medical therapy instead of any procedure in that group, and that we don't have any data. So, I think that's an open question.

Chris Standaert: One thing that struck me is that other than the high-risk surgical group, carotid endarterectomies seem to be very effective and relatively safe, considering the type of intervention that it is in the population in which it is being performed, which leaves a very high bar for a new intervention to prove that it is better, and safer, and cheaper.

Seth Schwartz: It's twice as much money.

Chris Standaert: Yeah, but the endarterectomy itself is actually, I mean, all these numbers are relatively low other than that high-risk pool.

Seth Schwartz: No, I'm just talking about, I'm agreeing… I'm just saying… to underline the score that there's… the new therapy has not proven itself to be better, it's just 100% more.

Chris Standaert: And it's more expensive.

Seth Schwartz: Right.

Joann Elmore: That's what he's saying.

Chris Standaert: Yeah. It hasn't proven itself more effective. It looks more expensive, and it may not be as safe, even. So, it's [inaudible] for something else to move in and edge it out as a more effective treatment, because it's so well done largely, it seems, when… in these studies.

Marie Brown: At least until training, unless there's some training effect, which will take probably five to ten years to see—better training, more controlled.

Craig Blackmore: Yeah, it's hard to get more controlled than a randomized controlled trial.

Marie Brown: I know. I mean, I mean the performer. The surgeon. Sorry.

Michael Souter: I'm also intrigued by an extent by the high-risk surgical group, including those who are at high risk for… or can be done under general anesthesia. I mean, you can… it is perfectly acceptable to perform an carotid endarterectomy under regional anesthesia with the patient awake, and that just seems to have been missed in some of this.

Craig Blackmore: Were they all general in the trial?

Michael Souter: Well, no. It's just with the exclusion factors, you know, being previously listed in some of the trials in the coverage decisions specifically mentioning high-risk because of general anesthesia. It tends to place an emphasis upon going for a stenting procedure instead of, you know, the endarterectomy.

Craig Blackmore: Right, when they need to have the [inaudible].

Chris Standaert: Per our vendor.

Seth Schwartz: Could we ask the clinical expert? How often do you see that procedure done under… endarterectomy, in high-risk surgical patients, under local anes-, under regional anesthesia?

Robert Bersin: So, often the high-risk patients are done under local, or like general so to speak. So, we tend to do that in the people who are at increased risk for anesthesia, but I think the, where that is coming from is that is a… to be included in that trial, like the high-risk trial, these are people who were felt to be at increased risk for anesthesia or surgery in general. So, there was an inclusion criterion, if you will, to be in that trial of people who are high-risk patients. These were very high-risk patients typically, the ones in the Sapphire trial.

Chris Standaert: Question for the vendor on that same issue, then. So, in that trial, do you happen to know in the methodology, did they describe the method of anesthesia used for their high-risk patients? They're high-risk, so did they put them under general or did they do them under regional in the study?

Andrea Skelly: I'll have to look that up.

Chris Standaert: Okay.

Craig Blackmore: Well, is there anybody that wants to defend coverage without conditions in asymptomatic?

Group: No.

Craig Blackmore: Okay. If we had conditions, what would they look like without saying no cover versus conditions, but… what might that look like?

Carson Odegard: I think we'd have to divide into symptomatic and asymptomatic.

Craig Blackmore: Yeah, okay. Starting with the asymptomatic. Just starting with the asymptomatic. Age?

Seth Schwartz: Yeah, less than 70.

Craig Blackmore: Because they seem to do worse in the 70 plus.

Joann Elmore: Right, over 70.

Seth Schwartz: Didn't one of the trials we had 68 as the cutoff?

Craig Blackmore: It was 68. So age and surgical risk would be two, and they unfortunately seem to go in opposite directions, right? Older people did better with CEA and older people are at higher surgical risk, and higher surgical risk did better with CAS.

Carson Odegard: The older people with CEA… oh, I have a question Dr. Bersin.

Robert Bersin: Yes.

Carson Odegard: Okay, so in this older population, somebody mentioned something about...

Michael Souter: Carson, can you use...

Joann Elmore: Could you use your microphone?

Michael Souter: ...your mic? Okay.

Carson Odegard: We're sharing one here, so. In that older population, somebody mentioned that the… that there is a degree of vessels get more tortuous. Is that one of the reasons why they do the stenting versus… or why they can't do the stenting versus the CEA?

Robert Bersin: Yeah, so with age you do get uncoiling and tortuosity of the anatomy, but you also get more generalized atherosclerosis. So, you can have diffuse plaquing throughout the anatomy whether it's straight or tortuous. So, it's clearly recognized that, you know, in the older age groups there is more of both that can weigh in on the risk of doing an intervention. That being said, the age relationship is a linear one where there's no like cutoff, if you will. So, where this age of 70 comes into play is where that linear line crosses the confidence intervals, and it also crosses the confidence intervals on the other side of the coin at around age 55. So, the very young actually do better with stenting, and the older do better with surgery, and that's where they cross the confidence intervals on both sides. So, it's pretty much a straight line.

Chris Standaert: I'm afraid I didn't… I did not see any data saying the very young do well with stenting.

Robert Bersin: Well, if you look at the paper, the lines...

Chris Standaert: Which paper?

Robert Bersin: The CREST, the CREST trial. The age-relationship graph is shown there and it shows a linear relationship as outcomes by the two methods according to age, and where the confidence intervals are and where they cross those confidence intervals, the line of unity and so forth. So, the very young do better with stenting and the more elderly do better with surgery. It's the opposite of what you might think. The point is, there's no threshold. There's no like shelf effect. It's a straight line.

Carson Odegard: Thank you.

Chris Standaert: From what I see, so in the… I'm on slide 30, and this is CAS versus CEA for age, differential efficacy over safety, asymptomatic persons. Tells me no RCT data available and one registry showing insufficient evidence and really no difference by age. So, I'm not sure where the comments about age are coming from for evidence.

Robert Bersin: So, again in the...

Chris Standaert: I'm going back to our evidence vendor for a second. It's her report.

Robert Bersin: Back to her.

Andrea Skelly: Sorry, I, I...

Chris Standaert: And if you [inaudible] boards bring up 68 and 70, where is… am I missing? This slide says there is nothing in the asymptomatic...

Andrea Skelly: Where are you?

Chris Standaert: Slide 30?

Andrea Skelly: What's your question?

Chris Standaert: So, is there an age cutoff somewhere in asymptomatic populations where there is a differential benefit by age? That doesn't seem to be what you told us.

Andrea Skelly: You said slide 30?

Chris Standaert: Yeah.

Robert Bersin: No, I think I was in error, Chris. I think I was speaking about symptomatic versus asymptomatic. So, erase the age.

Craig Blackmore: I mixed those up as well when I said...

Chris Standaert: Because that would be symptomatic.

Seth Schwartz: It was the symptomatic.

Chris Standaert: Yeah, so we're on, so we're on asymptomatic still.

Andrea Skelly: So, slide 30 has to do with asymptomatic individuals, and in asymptomatic individuals, we only had data from one registry study that were parsed out by age, and for safety, age did not influence things for any of the outcomes that were available to look at, but we felt the information was insufficient. For symptomatic individuals, age is an issue. If you look at slide… what is that 50, 49/50? These were data across the various randomized control trials, and those that had… that were less than 70 years old had… there was no difference statistically between the treatment groups, and those that were over 70 years old, there was a statistically significant difference between the groups favoring endarterectomy, but the issue of differential effectiveness suggests that the populations are very different. So, you look at the point estimate. So, the point estimates are different for those that are less than 70 years old versus those that are greater than 70 years old, and the statistical test for interaction was significant. So, that suggests that age does modify, and those individuals who have… who are over 70 years old, endarterectomy is apparently a more… a better procedure based on the outcome of periprocedural death or stroke, and in those that are less than 70, it appears that, there's no statistical difference. Is that what you were getting at, Chris?

Chris Standaert: Yes, and then we had a comment from the expert about that CREST study showing a linear relationship between age suggesting at a very low age, under 55 or so, and the stenting is more beneficial, but we did not see that data brought out that way.

Andrea Skelly: No, partly because we were looking at combining both… segregating symptomatic and asymptomatic individuals. So, I think I know which graph you guys are talking about, and in that paper, I believe that both symptomatic and asymptomatic were included.

Chris Standaert: They were mixed in the… so it wasn't broken out that way.

Robert Bersin: My comments were in the overall context of the trial. Where they… were all combined. They weren't parsed out symptomatic versus asymptomatic.

Andrea Skelly: I do have one answer for the Sapphire study in terms of the methods. They don't give us a whole lot of information regarding whether or not anesthesia was general or not. The one… the main report by Yadav says surgeons performed endarterectomy according to customary technique. That's all they said. Then, the other, the Graham paper, does not appear to elaborate either whether more general anesthetic or more regional anesthetic was used.

Craig Blackmore: Other questions? Alright, so back to the asymptomatic, we talked a little bit about age. We talked a little bit about surgical risks. Are there other considerations around what conditions we would worry about? Alright, I can do...

Seth Schwartz: Can I ask just one question about, you know, a stroke is not a stroke is not a stroke. There's differences and strokes are varied and I'm curious if there's any evidence on differential strokes of area. So, for some of these perioperative strokes, were these people who had mild transient symptoms, or are these people who were left with complete hemiplegia? Is there any data, this is for our vendor, is there any data in the trials about stroke severity in those outcomes?

Andrea Skelly: I'm sorry, were you asking me?

Seth Schwartz: Yes.

Andrea Skelly: My computer keeps dying.

Seth Schwartz: My question is regarding the outcome of stroke in the… for the asymptomatic patients. Is there any evidence on stroke severity? So, we're looking at, you know, an outcome that you have 8 out of 600 people have this outcome versus 15. So, we're looking at really small differences, and I'm just trying to get a sense of whether there's any indication of stroke severity differences in these patients or whether that was even looked at.

Andrea Skelly: With regard to whether or not there was modification by stroke severity?

Seth Schwartz: No. I'm just trying to understand what the outcome means. You know, we're looking at a very small difference in number of strokes. So, I'm trying to figure out if these patients are… how severe these strokes were, and if there's any data on that.

Michael Souter: Was there a Rankin scale or anything else like that for the stroke outcomes?

Chris Standaert: I mean, are the events any different so that the type of stroke or the frequency of different patterns of stroke different after endarterectomy versus stenting?

Andrea Skelly: We did look at that explicitly, but Dr. Bersin has...

Robert Bersin: Yeah, I can address that. If you want me to, I can address that.

Seth Schwartz: Please.

Craig Blackmore: Sure.

Robert Bersin: So, in the CREST trial, which was standard risk patients, that's the one that's best characterized, there was a, as you know, this small… it was a 1.8% I think overall difference in stroke. The difference was entirely accounted for by minor stroke. There

was no difference in major stroke, and they did do an IH and Rankin scale principally. The data was an IH stroke scale, and it goes like this. The minor strokes, there were differences at 30 days because there was a difference in minor stroke. At six months, they get follow-up examinations in strokes scales at 30 days, six months, one year, and at six months, there were seven patients in each group with persisting minor deficits, and the stroke scales were equal between the two. So, although there was a difference overall in stroke, that's a functional thing. The number of patients were, at six months with persisting deficits, were the same and the stroke scales were exactly the same.

Seth Schwartz: Okay, and that's including the periprocedural strokes?

Robert Bersin: Yeah.

Seth Schwartz: Okay.

Robert Bersin: They were all, yeah. The periprocedural one.

Seth Schwartz: Thank you.

Andrea Skelly: On table 10 of the report, they have what you are looking for in terms of the different types of stroke, ipsilateral versus disabling stroke, but it doesn't… it doesn't have the CREST in there for that, if that's what you're looking for. That's only in asymptomatic people, or symptomatic people rather.

Craig Blackmore: So, I'm going to… well, are there are any other questions before we proceed? So, I'm going to try to work this through the way we've been doing it, which is to start off with a sort of a straw vote so we can narrow our target a little bit, and then try to use that to move on. So, can I get just a nod of heads or a show of hands on whether there's support on the committee for a coverage without conditions, so full coverage? Are there people here that would support that?

David McCulloch: I'm going to be a contrarian and say all this, I mean, from everything I've heard, if this costs… if the cost was identical, provided people are using these very carefully thought out clinical guideline criteria, I don't care whether a neurosurgeon uses endarterectomy or a stent. Use your clinical judgment with the patient. They're both about the same, and stenting is getting better. I mean, I don't… I would be totally comfortable saying, these are about equivalent, so as long as those criteria are being used for both I can't find anything to say that definitely we should be advocating for… continue to use endarterectomy as opposed to stenting. I feel as if surgeons will all use good clinical judgment.

Craig Blackmore: Would you...

Kevin Walsh: But you said...

Craig Blackmore: Which of the criteria are you...

David McCulloch: Like, well, the… page 35 for symptomatic is one of them. Basically...

Chris Standaert: Slide 35, what are you talking about?

David McCulloch: Slide 35.

Michelle Simon: That's symptomatic.

David McCulloch: Yeah, it's symptomatic.

Craig Blackmore: You're ahead of the...

David McCulloch: You're, you're using those, I think that Class I, II, IIB-C, all that stuff. They seem about the same to me.

Kevin Walsh: I tend to feel it's like...

David McCulloch: I'm not convinced that...

Kevin Walsh: ...but there is...

David McCulloch: ...cost.

Kevin Walsh: But there is evidence about cost.

David McCulloch: Well, there's… there's evidence that what's being charged is higher, [inaudible] actually costs to do, and in that case let's make the decision based on [inaudible].

Kevin Walsh: I would posit that the charge is reality.

Craig Blackmore: The agency data is not charge, it's payment. It's how much the… how much the state is paying the institutions to do this.

Kevin Walsh: And it's twice as much. So, I mean, I agree with you, but I… but… but the answer to your first sentence is, if the costs were the same and the answer is they're not the same. They're vastly different. So, if you, if we go, if we march through our logic tree, if efficacy and effectiveness are thought to be equal, and safety is thought to be equal, then it comes to cost; 90% of the time we don't have enough information to make that call, but personally, I feel like this is pretty clear.

Chris Standaert: Guidelines are tricky too, 'cuz they don't necessarily tell you what to do. They're not an AUC, which is sort of different, and they're not a… they're not an HTA. They're a different sort of beast, and they sort of look at the evidence and say rank it based on sort of the quality of evidence and the strength by which you can make a statement, and then what they're really saying is the Class I recommendations, or the patients with lower average risks should undergo CEA and that with a lesser degree of strength, you can say CAS is an alternative to it, but the primary recommendation is endarterectomy, and then there's the lower class recommendations with lower levels of evidence are that in circumstances where you really have a bad setting for an endarterectomy, unfavorable anatomy of prior neck surgery, you have a prior cranial nerve injury or for some reason where you really don't want to go into the neck again, endarterectomy, the stent may be reasonable to choose over the endarterectomy.

Craig Blackmore: Anybody else want to chime in?

Michelle Simon: Well, I feel like we don't have two equivalent procedures here. I think there is some suggestion that there is at least perioperatively a higher degree of stroke risk in these patients, so I don't think safety is necessarily equivalent in the two procedures. I think the cost is quite a bit higher, and if we think about what we're doing with our state

dollars, if we put a portion of that towards dealing with diet and the lifestyle up ahead of this problem, that might be a better use of the funds. Of course, that's not our charge. I understand that, but this is dealing with the symptom in the end.

Craig Blackmore: Thoughts from this side of the table?

Andrea Skelly: Did you want some information? I think we finally have some information on a couple of your questions.

Craig Blackmore: Sure. Please.

Andrea Skelly: The first question addressing the question about major stroke versus minor stroke in the CREST, we've got the study up. The majority of the strokes were minor strokes, less than 20% or about 20% were major strokes based on… for both asymptomatic and symptomatic individuals. That's what you were asking. I think Dr. Bersin already beat me to the punch on that. With regard to follow-up, follow-up and restenosis, there isn't a lot of good information from the studies. The one study, the SPACE study, they just basically say that they monitored patients at certain intervals and that they had an 89% follow-up rate at two years, but they don't really tell us at what point they measured the restenosis, and we don't have good data from them regarding what number of individuals there may have been at any given point to do restenosis. The EVA study, again, they just basically said that they had a three… three and a half year length of follow-up. The follow-up ranged, for the mean, was 42 months in one study… in the stenting group. And 43 months in the endarterectomy group, and the ranges were pretty comparable, 31 months to about 48 months. For the BACASS, bear in mind that there were only eight people in one group and nine people in another group, and they… so statistically you're probably not going to find an effect in any event, but basically at one year they had 100% follow-up in the stenting group and 90% in the endarterectomy group and 80% at two years in stenting and 90% in CEAs. I don't know if that really helps you. The Regensburg study, one thing that should be noted is that 32 of the 43 people who had stenting had ultrasound to confirm restenosis. So, not everybody got ultrasound to look at stenosis, and only 29 out of 44 in the endarterectomy group had ultrasound to look at stenosis, and all they give us is the median follow-up of 65 months. So, that doesn't help, you know, a whole lot. And then the last remaining question, was there, was that the only other question? I think that was it.

Craig Blackmore: Any other questions? Okay, so again, I try to narrow things down. I'm hearing that there's some enthusiasm for just covering. Is there enthusiasm for not, for never covering, for no coverage, the other end of the spectrum? You guys aren't making it easier for me, you know? I'm trying to narrow it down here. I'm making it easy.

Joann Elmore: Well, what about patients with abnormal neck anatomy? They've had…

Michael Souter: I would think you'd go to...

Joann Elmore: ...radiation and, you know.

Michael Souter: ...high risk coverage.

Joann Elmore: ...CEA is not available to them.

Michelle Simon: That's in here. We saw some data.

Joann Elmore: We saw no data, but it's...

Andrea Skelly: The… the focus of the report was on atherosclerotic disease. So, studies that looked at stenting in patients with postradiation stenosis, malformations, etc., were not included. They were not part of the scope. However, if some of the patient population characteristics in the Sapphire trial, if you look, there's a page in here, and I will try and find it for you. It tells you what percentage of those patients had some problem or some higher risk thing like stenosis or malformation in there.

Chris Standaert: So, I guess here's a question. Can you… are there circumstances where you would have an asymptomatic patient with a bad artery you want to fix but for some reason you really don't want to operate on it, because you can't access it. The neck anatomy is wrong. They've had prior surgery in that area, but it's not because they have atherosclerosis, though.

Joann Elmore: But you said asymptomatic.

Chris Standaert: We're on asymptomatic.

Joann Elmore: Oh, okay, never mind.

Chris Standaert: So, but in those, you have patients… well they're asymptomatic patients who get endarterectomies in critical stenosis. So, but in those patients who, for whatever reason, you can't operate, or you really don't want to operate because the anatomy is so bad or something else has happened to them. They've had prior cranial nerve paralysis. They had vocal cord paralysis on the other side and you can't risk it on this side, do you… is it okay to stent them if you, if you're...

Craig Blackmore: Is it okay to stent them?

Chris Standaert: ...if you're worried about what you might do to their neck if you do the endarterectomy, because it's very different than the stroke outcome.

Joann Elmore: Right.

Chris Standaert: I agree with what Michelle said about the data, but in that special… in that… in those populations do you allow stenting or not? It is somewhat… given what Michelle said before...

Joann Elmore: Or do we not go into that level of detail and let the state level sort of make the exceptions on these cases?

Craig Blackmore: They don't...

Marie Brown: They have to require prior authorizations.

Craig Blackmore: They don't make exceptions.

Chris Standaert: We have to spell those out, at least to some degree.

Carson Odegard: I mean, some of these guidelines say, okay, you've got a patient like… he's asymptomatic and some of the guidelines are saying that 80% stenosis [inaudible]… but so you've got somebody that anatomically can't be, or physically can't be operated on,

but you still have to include the 80% stenosis factor, if that's something we would even consider.

Craig Blackmore: Yeah, we haven't even talked about...

Carson Odegard: Yeah.

Seth Schwartz: I think the other way of looking at that is that we're, I mean, I think there's a little bit of disagreement, but for the most part, we seem to think that they're… that both CEA and stenting are fairly equal in terms of their efficacy. So, the next things we look at are safety. So, we're basing our safety concerns about this small stroke risk, which is, you know, in the whatever, several percentage points and more incrementally different between the two groups, and as far as major events, probably even less than that, but here you're talking about a group where the safety profile might be very different. So, you have fairly compelling reasons to want to avoid surgery. So, to say, well we're not going to offer it in that situation seems like we're not paying attention to what the data does show us. So, I think in that group, even though there's not, they haven't been specifically called out, the weight of the argument has shifted substantially, as far as safety is concerned.

Chris Standaert: That sort of morphs into a bit to the high-risk surgical patients. I mean, that study of high-risk surgical asymptomatic patients, clearly the stenting was safer. I have, you know, you wonder why you're operating in the first place when 20% of the people having a stroke or dying in the first year, but… and that level of detail we don't have, and medical therapy would have been very nice in that study, but it, you know.

Craig Blackmore: So, the no cover… the people who are thinking no cover, are you persuaded by this argument that there might be a higher risk subset in which coverage would be appropriate, or does that not resonate, and I'm…?

Kevin Walsh: If we… if we limited coverage to that subset?

Craig Blackmore: I'm trying...

Kevin Walsh: That's the obverse, that's the, I mean, I'm just hypothesizing.

Craig Blackmore: Yeah.

Kevin Walsh: So, the obverse would be to cover only those people.

Chris Standaert: Right.

Craig Blackmore: So, can I, can I bring...

Kevin Walsh: In asymptomatic patients.

Marie Brown: So, that would be cover with conditions.

Craig Blackmore: Can I bring us to a choice between cover everyone or cover with...

Kevin Walsh: Conditions.

Craig Blackmore: ...people who are at high risk. Yes, some, some conditions formulated around it might not be a good idea to do the CEA on them, and I want to see if that's going to get us to a comfortable place. Okay, so what's that look like? High surgical risk?

Chris Standaert: That's a little tricky, because part of our… our study didn't actually look at CEA. So we don't really know what the indications for CEA are defined as, or, we can't define them well. So, we're left with a person in whom carotid endarterectomy is felt to be medically appropriate, but the patient...

Craig Blackmore: [inaudible]

Chris Standaert: ...is, yeah.

Craig Blackmore: Yeah.

Chris Standaert: But the patient is at high risk for complications of surgery either due to access or medical comorbidities.

Craig Blackmore: Yep.

Chris Standaert: Something like that.

Craig Blackmore: And is that sufficient? Do we need more granularity? Can we provide more granularity? I mean, I'm not sure we can, because, maybe… can you… can you give us the inclusion criteria on the Sapphire trial? What do they mean by high surgical risk?

Andrea Skelly: I'll have to, have to...

Craig Blackmore: And I… I guess the other thing we can look at some of the guidelines and see how they define surgical risk.

Andrea Skelly: On page 120 of the report, there is a table outlining the percentage of individuals with different risk categories of things, and in the meantime, Erica has the inclusion/exclusion criteria for the Sapphire trial. Inclusion criteria, over 18 years old, unilateral or bilateral atherosclerotic or restenotic lesions in native arteries, symptoms plus stenosis of more than 50% luminal diameter, no symptoms plus stenosis of more than 80% luminal diameter. Criteria for high risk, at least one factor was required, clinically significant cardiac disease, which they have, including congestive heart failure, abnormal stress test, or need for open heart surgery. Others included severe pulmonary disease, contralateral carotid occlusion, contralateral laryngeal nerve palsy, previous radical neck surgery, or radiation therapy to the neck, recurrent stenosis after endarterectomy and age over 80 years. Those were the inclusion criteria. Do you want the exclusions?

Craig Blackmore: Sure.

Andrea Skelly: Okey-dokey. Ischemic stroke within previous 48 hours, presence of intraluminal thrombus, total occlusions of the target vessel, vascular disease precluding use of catheter base techniques, intracranial aneurysm of more than 9 mm in diameter, need for more than two stents, history of bleeding disorder, percutaneous or surgical intervention planned within the next 30 days, life expectancy less than one year, and ostial lesions of common carotid artery or brachiocephalic artery, and that's the list.

Again, on page 120, there's sort of a comparison of the percentage of patients with comorbidities and other things from the Sapphire trial compared to other trials.

Craig Blackmore: So, if we ask our agency directors, if we created a condition that said something along the lines of high surgical risk or high risk of complications from open surgery, would that be operationalizable without us being granular about what constitutes high surgical risk?

Gary Franklin: We'd have to, you know, implement those specifics in our utilization review program. It wouldn't be easy, but it could be done.

Craig Blackmore: In fact, I see that in the agency recommendations. Surgical risk of CEA is high.

Gary Franklin: For which one?

Chris Standaert: We're just following their recommendations.

Josh Morse: On page five of...

Gary Franklin: Are you talking about symptomatic patients?

Josh Morse: ...the decision document you'll see the current Medicare for high-risk asymptomatic.

Craig Blackmore: Alright, page five, high-risk asymptomatic, yep.

Michael Souter: Yeah, that's what we're talking about.

Josh Morse: It defines risk below that.

Craig Blackmore: This is the national coverage decision?

Josh Morse: Yes.

Craig Blackmore: So, one approach would be to agree, in essence, with the Medicare National Coverage Decision, which is, as we said on page 5 of the tool, the patients who are at high risk for CEA, asymptomatic carotid stenosis greater or equal to 80%, and then I don't know about the rest of this language, and then high risk for CEA defined by these criteria, which includes the trials.

Chris Standaert: What they said for asym-, what they said for asymptomatic was they had to be in a trial, basically.

Craig Blackmore: No, asymptomatic is their goal point, right?

Chris Standaert: Yeah, but in accordance with [inaudible] trials, as a routine costs under the clinical trials policy, or in accordance with the NCD on CS post approval studies. So, they're covering it, that's a cover with, they've got cover… evidence development I think it looks like, but the idea of patients who are at high risk for CEA and have asymptomatic carotid artery stenosis greater than 80% would be sort of that category we're after.

Gary Franklin: Sorry, Craig, I have a question. So, you're talking about asymptomatic now, right?

Craig Blackmore: Yes.

Gary Franklin: So, there aren't a lot of asymptomatics that get carotid endarterectomy and the Medicare coverage decision is that for an asymptomatic, you have to have at least 80% stenosis and it's only in a research paradigm. So, if you make a different decision, then you'd have to say that it's different than Medicare.

Craig Blackmore: Yeah, I mean we can make a decision that agreed with these criteria but didn't have it be in a research protocol but was based on these criteria, which align with the Sapphire, which is the… one of the pieces of data that we have. Or, we could just cover without. I mean, I don't… but for purposes of our discussion, I want us to sort of crystallize what the conditions would look like, so we can make a decision… so we can make a choice. I'm not going to make Margaret write this on the board if I can avoid it, since it's printed in the… page 5 of the document. Are there other thoughts people have about what conditions might look like if we were to use conditions?

Michelle Simon: Is there any concern about what facility does this? There's a lot of talk here in the Medicare about approved facilities for this.

Craig Blackmore: That's a good question. Where is that?

Michelle Simon: Page 6 and 7. The facility has to meet one of the following and then in the four on the top, seven out of the four criteria.

Chris Standaert: Doesn't the state authorize various centers for specific procedures at certain times? Does the state do this?

Gary Franklin: We haven't done that before, but I thought that was a good idea. I mean, you know, we'd have to work on that, but, sort of the accreditation piece?

Chris Standaert: Correct.

Gary Franklin: Yeah.

Chris Standaert: Right. I mean there are...

Gary Franklin: We haven't done that before and there's typically problem saying you can do it and you can't do it.

Chris Standaert: Right. What we're going to have trouble with is who's a legitimate...

Gary Franklin: But you, you make a decision...

Chris Standaert: ...accreditation body?

Gary Franklin; ...and then we have to do it.

Chris Standaert: ...body, I mean, but if we make a decision as to which body is this, I have no idea whose accrediting bodies, which ones are valid and which ones aren't and which ones… I don't know how to do that.

Craig Blackmore: I mean, that's not, that's established. There's… there's… it's, Dr. Skelly's going to.

Andrea Skelly: There is… there is information in the appendices on CMS requirements for facility accreditation. It's required for reimbursement. There are also two tables, and it's in Appendix I, page 152, that describes the two accreditation processes that are available, if that gives you any assistance.

Chris Standaert: Where is that?

Andrea Skelly: It's in the appendices. It's Appendix I, and Appendix I is sort of the catchall FDA approved stents and accreditation, but it starts out with accreditation. There is intersocietal commission accreditation, and then there's also the accreditation for cardiovascular excellence, which is an ACC associated group, and then following that page are all the requirements for the CMS and the list of the facilities in Washington State on the following pages that meet the criteria.

Craig Blackmore: So, I mean, I guess one approach is to say that it needs to be at an accredited facility that's, as determined by the state, so that we don't have to put ourselves in the position of deciding whether or not the American College of Cardiology is a reasonable body, but we would then give the state the opportunity to look at these various accrediting groups, and then they wouldn't have to be the ones who say yes to that hospital or no to that hospital or whatever? Does that make sense from your standpoint, Gary?

Gary Franklin: Well, if there's a body that's doing this and everybody is using that body, then that's the body we would use.

Craig Blackmore: Right.

Gary Franklin: And when they… the one they spoke about is probably the one that people should be using.

Craig Blackmore: Yeah, but then we don't have to be, you know, we haven't seen the standards of these accrediting body. We don't want to be the ones who are right now making a judgment, but it's probably pretty obvious. Okay.

Gary Franklin: So, Craig, one more. Did you say there was an 80%, did you say anything about the degree of stenosis for the asymptomatics?

Craig Blackmore: Well, so, we're… if we're modeling after the national coverage decision, then it's an 80%... greater than or equal to 80%. That's what is in the national coverage decision.

Michelle Simon: And this is from 2005, this coverage decision?

Craig Blackmore: Uh, yes. So, we've conflicted with this already, because the more recent evidence on the intracranial, we thought, was different, but, you know, we can… we can agree or disagree. We just have to be explicit.

Josh Morse: Well this, just for the record, the last review date on this is December, 2009.

Craig Blackmore: Okay. Thank you.

Josh Morse: [inaudible] that says that.

Craig Blackmore: Okay, still before the SAMMPRIS trial. Okay, so, I'm hearing coverage consideration would be from the Medicare national coverage decision, third bullet point on page five

with the exception of the… it has to be in a research trial, high risk as defined by the national coverage decision, and we would want an accredited facility, as recognized by the state and in that I would direct them to consider the two organizations defined by the vendor, which are the ACC and the intersocietal commission for the accreditation of carotid stenting facilities, and then they would be in a position to make a decision about that. Any other thoughts on what coverage with conditions would look like? Are we ready to move to our straw vote or our brown cards?

Josh Morse: So, before, let me go back through these.

Craig Blackmore: Yep.

Josh Morse: So, the one difference is there will not be requirement for a research trial?

Craig Blackmore: Right. I think it is the belief, well, if the committee votes this way, it's because they believe that current evidence is sufficient that it doesn't have to be done in the context of a research trial. Now, I don't know if the committee is going to vote this way.

Josh Morse: No, I just want to make sure of that.

Chris Standaert: So, are we going to vote on asymptomatic and then we're going to vote on symptomatic separately, or are we...

Craig Blackmore: Yes.

Chris Standaert: ...just going to do them as one thing.

Craig Blackmore: No, we're going to vote on asymptomatic.

Chris Standaert: Okay.

Craig Blackmore: It may be the same, but that's how we start, so.

Michelle Simon: Can I hear it one more time? I'm sorry. Can I hear it one more time?

Craig Blackmore: Yep. So, the conditions would be, patients who are at high risk for CEA and have asymptomatic carotid artery stenosis greater than or equal to 80% and high-risk for CEA is defined as having significant comorbidities and/or anatomic risk factors, i.e. recurrent stenosis and/or previous radical neck dissection and would be poor candidates for CEA. Significant comorbid conditions include but are not limited to...

Michelle Simon: [inaudible]

Craig Blackmore: ...you got those, so that's the, and I mean, is there anything else you would add, or? Okay, so the brown cards? Is there sufficient evidence under some or all situations that the technology is effective and the comparator in this case is with CEA by default, because we really don't have information on medical management? So, is it under some or all conditions, more or less equivalent, or unproven effectiveness?

Josh Morse: Nine equivalent, two unproven.

Craig Blackmore: Okay, next is safety, and again, you should specify more if you believe there is some condition under which it is more effective, and you should specify less if it's less under all conditions.

Josh Morse: Two unproven, nine more.

Craig Blackmore: And then cost effective.

Josh Morse: Ten unproven, one less.

Craig Blackmore: Further discussion? Okay, we will proceed to the vote and, so, specifying again, this is asymptomatic with detailed conditions and your choices are we're never paying for stents, we're paying for stents under all conditions, or we're paying for stents under the conditions we've specified.

Josh Morse: Eleven cover with conditions.

Craig Blackmore: And again, we are similar to the coverage decision, just that we feel that current existing evidence is sufficient that a trial doesn't need to be done just in the context of a trial. Okay, symptomatic. Who wants to start me off on symptomatic? Nobody wants to start me off on symptomatic?

Chris Standaert: Well, oddly enough the benefit that stenting seemed to show in the high-risk population in asymptomatic does not hold in symptomatics, and that was its one particular advantage that actually came out in the literature review. So, it's left with… it seems still costly, perhaps less safe, and you know, at best equivalent in terms of long-term efficacy.

Marie Brown: Except for age. Isn't that where age comes in?

Craig Blackmore: So, this is where we have the data on age, right?

Chris Standaert: Well, what we had was at 70, it becomes… CEA becomes clearly more beneficial and they are relatively equivalent at a younger age.

Michelle Simon: Yeah, so age points to CEA.

Chris Standaert: So, over 70, CEA is favored. Under 70, they seem equivalent in this population in symptomatic patients. That's slide?

David McCulloch: 49 on page 25.

Chris Standaert: Yeah, 49, and we have sort of pooled analysis after pooled analysis all showing bars on the CEA side.

Richard Phillips: That's for death and ipsilateral stroke.

Marie Brown: So, is that covered? So is that do not cover for stenting?

Chris Standaert: Or don't cover it over 70?

Craig Blackmore: I'm asking you guys. You tell me.

Kevin Walsh: I would propose that it… we cover it under the same anatomic high-risk conditions that we voted for asymptomatic up to age 70. Well, I guess that… that's not true, because you still want to offer the CEA.

Chris Standaert: You still may need to do it in someone over 70 who has no other choice.

Kevin Walsh: You're, you're correct.

Craig Blackmore: And then there's the additional issue of the trials on symptomatic patients using a lower threshold for stenosis. So, we use 80%, because that's what Medicare coverage decision and that's where the trial data was, whereas for the symptomatic patients...

Michael Souter: 70%.

Craig Blackmore: 70, and Medicare even talks about, well, 50 to 70 under experimental exemption, but they use 70.

Chris Standaert: In our trials, what was the cutoff? Are they using 70 typically or did they, did any of these studies use 50% as a cutoff?

Andrea Skelly: We'd have to look it up, but many of them were between 50 and 99%. We can look up the percent of stenosis.

Chris Standaert: So, a pretty broad range?

Craig Blackmore: And this is very inexact science. I mean, I measure a lot of these, and it's very inexact.

Kevin Walsh: Right. This is operator dependent and how much coffee.

Craig Blackmore: Do you have a comment, Dr. Bersin?

Robert Bersin: I have a comment, yes. So, the trials were based largely on surgical outcomes, you know, in the literature, and when it comes to symptomatic patients, there was a large scale, this was years ago, meta-analysis of surgical outcomes that clearly demonstrated statistical benefit of an operation over medical therapy when, in a symptomatic individual, when stenosis severity exceeded 50%. Under 50%, there's harm. Over 50%, there's benefit. So, on...

Craig Blackmore: Are you talking about the [inaudible]?

Robert Bersin: Well, this was actually about 30 trials, you know, all of them put together.

Craig Blackmore: Okay.

Robert Bersin: And so, the recommendation going forward has always been to intervene or operate on a symptomatic lesion that's more than 50. Now, when it comes to asymptomatic, there's two criteria. The 80% that you're reading in the Medicare is for the high-risk individual, and yet, for the standard-risk individual, you saw when she made her presentation, you saw 60% in there, and all these studies that were done on standard-risk patients used a minimum bar of 60%.

Craig Blackmore: Yeah, but we're not covering standard-risk patients.

Robert Bersin: No, but for the high-risk, 80, and you can see how you adjust your threshold to treat based on what's the risk of the treatment.

Craig Blackmore: Yeah, that makes sense. Okay, so I'm sorry. The proposal was to use the same criteria at some lower threshold and then what about the age 70? That's a challenge, right?

Chris Standaert: I don't think it's really a challenge, because there's no argument for doing CEA routinely over age 70. Certainly, doing stenting over 70 certainly, but you have the same dilemma that you're going to have some patients over 70 who have had prior neck interventions and can't… you don't want to go operate on them. Their operative risk is too high. So, it's a same category of people, and I think all the age thing does is really make it clear that there's no benefit to stenting routinely over a certain age. It's clearly just in circumstances where the surgery is going to be untenable, I would imagine.

Craig Blackmore: Okay, so that… so I'm hearing high-risk only, which encompasses that age-risk issue. Is there a feeling towards broader coverage? I've heard that before, coverage of just everybody if they're symptomatic at the discretion of the team?

Chris Standaert: No. Even, you know, this one, even in the higher-risk, the people who can't have surgery because of an anatomic problem with their neck are in one category, and then the medically high-risk people are another, and in this group, the medically high-risk people didn't do any better with the stenting, whereas in the asymptomatic, they did. We lumped them together in the asymptomatics, but in this group… they're two different categories, people who anatomically can't have neck surgery, and then there are people who medically are at high risk for a surgery of any sort, or this sort of surgery, but they didn't really have any benefit with the stenting, so…

Chris Standaert: There's so many consistencies in the data.

Kevin Walsh: So, you want to modify the conditions to make it surgical exceptions, not medical, to take away the medical.

Chris Standaert: I'm throwing out whether we want to do that or not.

Michelle Simon: That's a good question.

Craig Blackmore: Richard, were you going to say something?

Richard Phillips: Just the… I was going to add, perhaps, a contraindication to carotid endarterectomy, as a condition.

Craig Blackmore: Contraindication or high risk or surgical risk?

Richard Phillips: If it's the same thing, that's fine.

Craig Blackmore: Yeah.

Michelle Simon: Yeah, beyond that, there isn't any compelling evidence that this is a better choice for efficacy, safety, or cost.

Craig Blackmore: And I'm assuming there's nobody in the no coverage camp, since we already decide we were going to do some coverage under asymptomatic. So again, I guess, I think we're down to unrestricted coverage or coverage based on limitations that we define, and

let's start with… we need a level of stenosis, 50% has been mentioned, 70% has been mentioned. The national coverage decision lists 70%, but it has a research exemption for 50 to 70%. I don't have a compelling reason to pick one or the other.

Michael Souter: Well, research exemptions don't apply to us anyway.

Craig Blackmore: Right, it's just that it's been mentioned, and I don't...

Seth Schwartz: I'm trying to, I mean, I think we're, we're talking about this as an alternative. So a patient is going to be, the decision is made and they want to fix this, we're saying surgery should be preferred but for whatever reason you can't operate on them, so, I would propose that you'd use the criteria for whatever the… if we're deciding on surgery, we should at least base it on these trials, which is 50%. It doesn't make sense to me to try to come up with something beyond that.

Craig Blackmore: Particularly given how hard these are to define.

Seth Schwartz: And who knows where the entrance criteria from the studies that we're looking at, so…

Craig Blackmore: So, we're...

Michelle Simon: Was it 50, or was, are they all 50?

Andrea Skelly: They varied. Looking at… looking at our data abstraction, 50 was a common inclusion criteria. Some of them used 70 as a common criteria. So, it ranged from 50 to 99%.

Craig Blackmore: Given that they're symptomatic, I'm willing to err more on the side of...

Michael Souter: Let's hope they tell us what the coverage decision states, isn't it, 50%?

Craig Blackmore: No, the coverage decision says 70, 50 to...

Michael Souter: I'm looking at page 5 here.

Craig Blackmore: Yeah, 50 to 70 is under the research exemption. So, we would make a slight difference from there.

Michelle Simon: I would be inclined to be more broad with it, if I knew that this was really an effective thing. I mean, I don't think it is, and I think it's a much higher cost, and there's more chance of perioperative stroke. There's just… I'm not sure why we're compelled to broaden it beyond what the data shows.

Seth Schwartz: Because, well… I think that's reasonable, except for we're only talking about the patients in whom you're not going to be able to op-, or it would be unsafe to operate in. So, I think we're looking at equivalent or at least close to equivalent efficacy. Cost becomes less of a concern, because we are dealing with the risk, and the risk shifts, so...

Michael Souter: But we already heard from our clinical expert that you balance that risk shift according with their background risk anyway. So, in someone who is a higher risk, you would actually want, you know, a kind of greater indication of pressing disease in order to actually push you towards a treatment decision anyway.

Craig Blackmore: Well, but, I mean, they're symptomatic, you know, so…?

Michael Souter: Yeah, but they're symptomatic, and symptomatic, are we talking about...

Chris Standaert: Yeah, they had TIAs, they had a stroke, they're… I mean, what does symptomatic mean?

Craig Blackmore: That the… I don't think the… well, I'll leave that.

Seth Schwartz: I guess I'm just presuming that this is a patient in whom… we're trusting the clinical judgment of the clinicians that it's time to intervene based on the way we're talking. We're not saying do it in everybody. We're saying if you're going to decide to intervene, and you can't operate, then it seems to me a little bit of micromanaging to say, okay, we… because for us to try and assess the risk, I mean, if they say that, the clinicians can assess the risk and decide, but…

Michael Souter: All they come up for a present indication to do a surgical treatment over medical treatment was a 70% stenosis.

Craig Blackmore: In symptomatic?

Michael Souter: In symptomatic patients.

Seth Schwartz: Well, there was the guideline. Let's look at that guideline. What page is that on?

Michael Souter: Can we ask the clinical expert again?

Craig Blackmore: Ask him.

Michael Souter: Yeah. Can we ask you, the current decisions to treat surgery versus medical treatment in symptomatic patients, what's the degree of stenosis on this?

Robert Bersin: In symptomatic versus medical is still a 50% criterion.

Michael Souter: 50%?

Robert Bersin: Yeah.

Michael Souter: Okay, well, then.

Robert Bersin: So, so we still, you know, regardless of how you treat them, somebody is actively having TIAs, and if it's 50% or greater, we fix them.

Michael Souter: Okay.

Robert Bersin: Because the evidence is clear on that.

Michael Souter: Then, that's fine.

Craig Blackmore: Then I, I would go with the 50.

Michael Souter: Go with the 50, okay.

Michelle Simon: So, where does that differ from the CMS guidelines on this?

Craig Blackmore: That's the point.

Seth Schwartz: Looking at that guideline, there is a difference between how you assess it, you know? Where they using noninvasive or invasive methods. So, I don't, I mean, I don't know whether we want to try to tease that out.

Craig Blackmore: I don't want to try to tease that out personally, unless you can show me data on the differences, I don't want to touch it.

Michael Souter: We didn't look at that.

Craig Blackmore: Okay, so what I'm hearing, so far, is the same as we had for asymptomatic with a lower threshold of 50% for the degree of stenosis and not touching the age issue, and keeping the accredited piece. Are there other concerns, other things we need?

Michael Souter: Do you want to define symptomatic? I mean, there's a definition given in the national coverage decision that we could stick to.

Craig Blackmore: There is a definition at the bottom of page 5.

Michael Souter: Yeah.

Craig Blackmore: Which, again, I think we could certainly do that and it would be consistent with the national coverage decision. So, that might be useful. It also says patients who have had a disabling stroke shall be excluded from coverage, and those patients were excluded from the trials, so we would have no reason to disagree with this.

Michael Souter: I have one other thought, that just the… we've just talked about the stent and we haven't actually said anything about stenting, you know, mandating embolic protection. I just noted that the coverage decisions include… say something about embolic protection. Do we want to include that given the kind of complications that you see without it? I mean, I think they can...

Craig Blackmore: Yeah, we certainly can. I mean, does anybody do stents without embolic protection at an accredited center?

Robert Bersin: No. The… almost never, and we all… we always intend to. There can be rare circumstances where you're trying and it just isn't feasible. It won't go, and then you're stuck potentially, but it's almost never.

Craig Blackmore: Yeah.

Robert Bersin: And Medicare originally, CMS originally reimbursed the procedure either way but then moved to reimburse only with embolic protection. So, I would personally support that position, that it should be reimbursable with embolic protection. We know that the stroke rate without is about 25%, or at least in the trials that were mentioned here, the European ones.

Chris Standaert: I'd like to add that clause. Maybe just at the bottom, you know? Reimbursable only with embolic protection.

Craig Blackmore: So, uh, sentence on the top of page 5, concurrent with placement of an FDA approved carotid stent with embolic protection. Other thoughts?

Chris Standaert: We should add… is it too… can we add that to our global decision since we've already voted on coverage for symptomatic, or asymptomatic?

Craig Blackmore: We can add that. We can charge staff to add it. Okay, brown cards. I think Josh has got it. You got it, Josh?

Josh Morse: I have it, yeah. We have it from Medicare.

Craig Blackmore: We're cutting and pasting out of, yeah, okay. Okay, is there sufficient evidence under some or all situations that the technology is effective, safe, and cost effective? So, if you think it is effective under some definable circumstance, you would vote more.

Josh Morse: Ten equivalent, one unproven.

Craig Blackmore: Next is safe. So, if you felt it was safer under some definable situation, you would vote more.

Josh Morse: Six less, four more, and one unproven, which gives us 11.

Craig Blackmore: Cost effective?

Josh Morse: Unproven I got two, less… four less, seven unproven.

Craig Blackmore: Alright, further discussion? So, we proceed to the pink cards. So, your choices are that in symptomatic patients, we will cover without conditions, we will never cover, or we will cover with conditions, and the conditions we've predefined, and I don't need to read them again, do I? Do I need to read them again? Okay. So, let's vote.

Josh Morse: Eleven cover with conditions.

Craig Blackmore: Alright, so to look back at the Medicare decision, we identified a few differences. Again, we felt the 50% threshold was more reasonable based on current practice and based on data that has come to light, since the last review, and otherwise, we added the piece about accreditation because that… we know there is a lot of variability, potential variability, and otherwise we are pretty much concurrent.

Josh Morse: Yes, but can you make mention of your review of the guidelines?

Craig Blackmore: And we have reviewed other guidelines from the various societies, and they were shared with us by our comments, and we don't agree with all of them, but... Okay, thank you committee, we finished early.