Washington State Health Care Authority
Health Technology Assessment

For copies of the official audio taped record of this meeting, please make request at: SHTAP@hca.wa.gov.

Health Technology Clinical Committee Public Meeting
January 16, 2015

Craig Blackmore: Good morning, everyone. I want to call the meeting to order. We have a quorum. This is the Health Technology Clinical Committee. Josh, do you want to start us off with the program, please?

Josh Morse: Sure. For those of you who don't know me, I'm Josh Morse. I'm the program director for the Health Technology Assessment program. I'll give a brief overview of today and of our program and a quick presentation here. So, today's topics, we have two topics today, functional neuroimaging for primary dementia, or degenerative dementia, or mild cognitive impairment, and in the afternoon appropriate imaging for breast cancer screening in special populations. The next meeting of the Clinical Committee is March 15th, and there's one topic on that day. It is testosterone testing.

So, a little bit of background on the program. The Health Technology Assessment program is located at the Health Care Authority in Olympia. This program was created by legislation in 2006 and is designed to use an evidence report, and this panel of clinicians to make coverage determinations for medical procedures and tests based on the evidence of their safety, efficacy, or effectiveness and cost effectiveness. Multiple state agencies participate to identify topics and implement the policy decisions that come from this process. They include the Health Care Authority that manages the Uniform Medical Plan and the state Medicaid plans, the Department of Labor and Industries, and the Department of Corrections. The agencies implement the determinations from this committee within their existing statutory and legal frameworks.

So, the purpose of the program is to pay for what works. We work to ensure that the medical treatments and devices and services paid for with state healthcare dollars are safe and proven to work. We provide a resource for the state agencies that are purchasing healthcare, and we develop scientific evidence-based reports on the medical devices, procedures, or tests that are identified for review, and we provide staff support to this independent clinical committee that determine which of those medical devices, procedures, or tests should be covered and under what conditions.

Our overall objective is better health for the citizens of Washington by using health technologies that are proven to work. We strive for transparency and to minimize bias, to be consistent in our processes, and to be aware of any new evidence that becomes available on the technologies we review in order to re-review those technologies.

A very high level view of the process, the Health Care Authority's director selects technologies for review based on nominations from the public or from the state agencies. We then develop the evidence reports working with contracted vendors. Once those reports have been through public comment processes, we bring them to this committee and open public meetings for draft determinations. At a follow-up meeting, the committee will consider any comments that have been received and make a final determination. At that point, the agencies are then charged with implementing the determinations in their programs.

So, the primary questions that we work from are, is it safe, is it effective, and does it provide value, and these inform the evidence reviews. Again, we value transparency. We publish all topics, the criteria developed to identify topics, the draft reports and the final reports, and we conduct open public meetings. We strive to seek the best available evidence. We use a formal systematic process for the review of the selected technologies and again, we have an independent committee here that makes the determinations for the state programs.

The clinical committee decisions must give greatest weight to the most valid and reliable evidence. The charge is to consider the objective factors in the evidence for consideration, including the source of the evidence, the characteristics of the studies and trials on which the evidence is based, and the consistency of the outcomes. Additional factors might include the recency of the information, how relevant it is to the questions being asked in the populations in Washington, and biased that may be apparent in the evidence. Topics that we're reviewing in this cycle this year, 2015, include the two for today followed by testosterone testing in March. There are two topics scheduled for May, imaging for rhinosinusitis and bariatric surgery for overweight and obese. The next meeting following the May 2015 is scheduled for November 15 and includes tympanostomy tubes. That is one topic and we are about to kick off the re-review for lumbar fusion for November 15.

There are multiple ways for people to participate with our program, including visiting our website where we put all deliverables from the program and announcements. Joining our stakeholder distribution list is the way to stay best apprised of what's going on and the most recent publications. Anyone may comment on proposed topics, key questions, draft, and final reports and draft decisions. Anyone may attend the public meetings of this committee or present comments to the clinical committee at these meetings and nominate topics for review.

Some meeting reminders. This meeting is being recorded. We ask that you please use a microphone and state your name. A transcript of the proceedings of these meetings is made available following the meeting on our websites. When participating in discussions, please state your name and use the microphone, as I said, and to provide comment during today's meeting if you are interested in signing up, there is a clipboard posted outside of the room and we do have conflict of interest disclosure forms, and there's some contact information.

One additional piece of information for the committee today, Margaret Dennis is moving on from the Health Care Authority. Today is her last day for those of you who did not know. So, thanks for being here today, Margaret.

Margaret Dennis: Thank you.

Craig Blackmore: Thank you, Josh. This is Craig Blackmore. The next item on the agenda is to finalize our previous meeting's business. That has two components. First is approval of the minutes and second is approval of the draft findings and decisions document from the previous meeting. So, first starting with the minutes, are there any corrections or concerns about the minutes, or else I will entertain a motion to approve.

Marie Brown: So move.

Craig Blackmore: Thank you, and second.

Keven Walsh: Second.

Craig Blackmore: Alright, all in favor of approval of the previous meeting's minutes just raise your hand.

Josh Morse: Eight approve.

Craig Blackmore: Abstain? Alright, next up is the findings and decisions on screening and monitoring tests for osteopenia or osteoporosis. The draft findings and decisions document has been distributed to the committee members and it's in your handout and I will entertain any… oh and we had open public comment period and comments were received and have also been distributed to the committee. Any discussion or I would entertain a motion to approve.

Carson Odegard: Move to approve.

Kevin Walsh: Second.

Craig Blackmore: I guess before we go there, I think there is one area of question about… and thank you for feedback we got on this. In the limitations of coverage we specified long-term glucocorticoids and a 5 mg daily prednisolone dose, and

there was some question whether that was intended to be prednisone or prednisolone. Comments on that?

Kevin Walsh: It's probably prednisone.

Craig Blackmore: Yeah, I think so. So, I'm going to ask the staff to change that from prednisolone to prednisone.

Chris Standaert: Do we have a reason for picking 5 mg? I mean somebody is 4 [inaudible] did that come from somewhere because our original thing said to incorporate some definition. But I haven't seen it, but I mean is there a reason for 5? I mean people on 4 they are also at risk.

David McCulloch: [inaudible]

Craig Blackmore: Yeah.

David McCulloch: The risks of milligram per kilogram.

Chris Standaert: Yeah.

Craig Blackmore: I mean, we could… I… I don't…

Chris Standaert: I mean, we could… I don't… I don't know where the 5 came from. If there's evidence for it, I'm fine. Otherwise, we should just put the… close the three months issue.

Craig Blackmore: Glucocorticoids not otherwise specified.

Chris Standaert: Yeah for more than three months and just leave it there so we don't have to worry about 5 or 4 or 6 [inaudible].

Craig Blackmore: And we, we did not have a discussion of what…

David McCulloch: No.

Craig Blackmore: …specific dose. We were just considering it [inaudible]. OK. So, long-term glucocorticoids, do we want to keep the three months or just leave it at long-term glucocorticoids?

David McCulloch: I think most… most guidelines do say three months but [inaudible]. So, you know, significantly glucocorticoids for three months or more then it's not unreasonable. I think that's consistent.

Craig Blackmore: OK.

Josh Morse: So, I believe in the preparation of this, you asked us to incorporate the information from FRAX, and the 5 mg comes directly from their definition of glucocorticoid use. That's where we arrived at that.

Craig Blackmore: Well, I… it sounds like the committee is most comfortable with just long-term glucocorticoids, i.e. current or past exposure to glucocorticoids for more than three months, and… and the statement. Does that resonate with the group?

Group: Yes.

Craig Blackmore: OK, any other concerns, any other discussion?

Marie Brown: Just the issue that was brought up in the letters about monitoring repeat testing after therapy not… in people with fractures.

Craig Blackmore: And so, what are your thoughts on that? Or what are anybody's thoughts on that? Richard?

Richard Phillips: I think Dr. Shuhart's letter is basically saying that it's the kind of test that you use… we… we almost need this test in order to adequately follow patients. To me, it's a little bit along the same lines as if you had… like people with coronary disease get stress testing and that sort of thing. It's whatever test you have to monitor may be essential. I mean, I think he had a valid point. That was my… what I was getting at, and even though there's a… a lack of evidence, it's in… inconclusive. It was clearly not our evidence that said that we should not do it. I also tried to wade through the… the report from the society. I think it was, I can't remember, yeah… from the… the American Association of Pulmonary Endocrinologists and… and I think they made some valid points, too. I'm not sure if that warrants us changing our… our… or reconsidering our decision, but I do think the issue of monitoring is maybe worth spending some time talking about it, because I think… I… I think he… he makes some very valid points about that for doctors who are, you know, if you're going to give a treatment, I think you have to be able to have some endpoints, and you have to be able to say yes, we are going to do this and we're going to use this as our endpoint. If you don't have that, then why have the treatment?

David McCulloch: Well, Richard, I… I am sorry. I would argue just the opposite. First, the American Academy of Clinical Endocrinologists is about the least evidence-based organization I know, and I'm an endocrinologist. The idea that you need to pick a surrogate marker and then track everything towards that I just think is… it suits endocrinology. It suits specialists. It makes us all feel better. I mean, an argument could be made that, take another field, management of coronary artery disease. If you identify somebody has having high risk based on total cholesterol over HDL rate that are high risk, start them on a statin. Traditionally, when… when we recheck the lipids every three months, every six months, every… every year the evidence actually says that's probably a complete waste of time. It's great for bringing people in and billing and doing all this medical stuff, but once you've started somebody on a statin, you've probably done, you

know, you've identified whether they need a high, low, or medium dose and then that's the treatment, and the whole issue here is yeah, you… you can follow up until the cows come home, changes in the DEXA scan and this and that, but until there's evidence that… that doing that is going to significantly change your treatment in ways that reduce future [inaudible] outcomes like fractures and we didn't see any of that and yes you're right. We didn't see any evidence that it… that it didn't help but, I mean, we… we have to make a, to me, the… we saw no evidence to say repeated follow-up monitoring after you've started treatment is actually going to change your treatment or change outcome. So, I would think… I would just conservatively it would be not unreasonable to leave our decision here the way it was and then revisit it if new evidence arises that says actually it's worthwhile doing a repeat DEXA at one year, three years, five years because in 60% of patients it makes you change your treatment, etc. So, I would argue for a conservative, reasonable approach from last time. I didn't see anything that Dr. Shuhart said that would make me say we should change that.

Kevin Walsh: I'd like to share a study that was in JAMA in 2013 that looked at women on medication and on bisphosphonates for osteoporosis. What they showed was that most of the time people did retesting because they went back and looked at the chart notes actually of 200 people and the repeat tests, the rationale for the repeat test was that they were due, and what they found was, of the people that had repeat tests 84% resulted in no treatment change and among the scans that were abnormal of the people that were tested, 76 had no treatment change. So, the notion… I understand the rationale, but I think that the reality is much less impressive than that, and I don't think that this… I don't think that the tests, either in the evidence of Gourlay that we looked at or this study reinforces the notion that it really doesn't change management that much. It's not a tool that… that does what we would like it to do.

Craig Blackmore: So, before we get too far up field, thank you. We… the process here is… we go through… we evaluate the evidence, we have our public comments. We have an evidence vendor who helps us to collate and understand the evidence. We have a clinical expert, and we go through this lengthy process to come to a decision, and we're now at kind of a quality check on that before we finalize it, and there's two components to the quality check, and the first is, does what's written on the document actually reflect our intent, and I think we've had some discussion around that and made some little tweaks, and then the second component to that is, is there evidence that we've overlooked or is there some piece of this that was not brought to us in the past meeting that might cause us to make an incorrect decision and… and the public comment period is helpful to inform that and a lot of information was provided to us by our commenters and our job is to figure out if… if there's information here that we didn't have before that we might have overlooked, and then we have choices. We can approve what we decided last time or we can sort of send it back for further, you know, for another meeting to… to repeat the process around this part of the decision or to not approve that portion of the decision, but we're not here now equipped to try to go through the… the evidence because we don't have those resources.

So, we could push this back to sort of starting over on a piece of our decision or we could conclude that we had the information when we made the decision and we can approve the decision. So, that's up to us to decide now.

Kevin Walsh: So, we made a proposal to vote.

Craig Blackmore: So, there's a proposal to vote, and then I just want to make sure that there's no, you know, everybody's had a chance if they have concern about whether or not we had the information. So, we had a proposal to vote and we had a second.

Richard Phillips: Mm-hmm.

Craig Blackmore: I believe you second and so favor… in favor of approving the draft coverage decision with the small amendment we discussed, please could I have a show of hands?

Josh Morse: Eight approve, one abstention and…

Richard Phillips: What we discussed, please could I have a show of hands?

Josh Morse: Eight approve, one abstention and…

Richard Phillips: Yeah, I, I have a different point of view.

Craig Blackmore: So, you're not approve is… is your vote or you approve?

Richard Phillips: No, I do not approve.

Craig Blackmore: Not approve, OK, thank you.

Josh Morse: One disapprove, OK.

Craig Blackmore: Alright, next item on the agenda, we move to the new topic, which is functional neuroimaging for primary degenerative dementia or mild cognitive impairment. We'll start with Gary Franklin, Washington State Agency Utilization and Outcomes.

Gary Franklin: Does the presentation come up on this computer?

Woman: [inaudible]

Josh Morse: Would you like a paper copy?

Gary Franklin: I have a paper. OK, we're talking about neuroimaging for dementia and only functional neuroimaging, not structural neuroimaging. So, we're not talking about regular MRIs or regular CT scans. These are tests that give you wonderful pictures of metabolic patterns or blood flow patterns in the brain and the question is really are they useful in diagnosing… either diagnosing or differential

diagnosis of dementia, the various kinds of dementia, and are they useful for, in people with mild cognitive impairment, in predicting whether you were going to go on to develop dementia or not.

The agency medical directors group, from looking at the evidence, with concerns felt that the… our concerns were medium across the board for safety, efficacy, and cost.

Background, I think we don't need to spend much time on this. Alzheimer's is the most common type of dementia accounting for 60-80% of cases. Dementia with Lewy body and frontotemporal dementia are much less common but two other major types of dementia. Mild cognitive impairment is also very common, 10-20% of people over the age of 65 have MCI. About 12% of MCI patients develop Alzheimer's each year. So, these tests have, you know, potential huge use in terms of the amount of testing that could be done in these patients because everything is so prevalent.

Dementia prevalence, of course, increases dramatically with age and it's… here this slide shows the differences and accumulative prevalence with age for men and women.

There are three main kinds of functional neuroimaging, which are the topic, topics assessed in the vendor's report. Positron emission tomography, especially with FDG-PET, single photon emission and computer tomography or SPECT, and functional magnetic resonance imaging. Most of the evidence is in the first two. There's not much evidence, at all, as you saw in the report on FMRI.

I'm not going to repeat the questions, but again, the main issues are diagnostic accuracy and prediction, predictive capacity for people with mild cognitive impairment. The state agency policy is a little bit all over the place. UMP does prior authorization. DOC does prior authorization but Medicaid and L&I don't cover FMRI. There is some coverage of SPECT and prior authorization for PET.

Not many of these things are being done. I think it's mostly an issue of potential for him, and it might be done, as opposed to how many are actually done. So you can see here, this is a Public Employees Benefits Uniform Medical Plan. There were 91 tests, 80 were PET and 11 were SPECT over a four-year period. So, you know, these things are not being ordered a lot, and Medicaid same thing, about 43.

These things are a lot more expensive than MRI scans. MRI scans, you know, Craig, maybe you can correct me here but I think, you know, kind of around $1200 or so. These things are more, like, between $2000 and $3000.

Just some data that we had breaking stuff down by males and females, PEBB and Medicaid. Not a lot of insight, I don't think, from this data, except not many are being done.

So, on the diagnostic accuracy piece, I think you'll hear that FDG-PET, which is the most common type of PET, may not be superior to clinical diagnosis based on the limited evidence. In other words, if you compare the accuracy of just clinical diagnose… clinical criteria versus clinical criteria plus PET, it's not a lot different if you add PET than just doing the clinical criteria, NIH criteria.

The same thing for SPECT. SPECT may not be superior to clinical diagnosis alone, and that's comparing Alzheimer's disease versus frontotemporal dementia, and the same thing for AD versus dementia with Lewy body. I'm just going to zip right through these things here, and then there's almost no data on other kinds of SPECT or FMRI. I do want to point out that there is a rapidly emerging… and we still can't quite figure out why we didn't include this in this report, specific PET testing for amyloid and tau protein, you know, specific markers for those kinds of things and there's a lot of interest in those things. I think that one thing to keep in mind here is, you know, are we really… are we really talking here about a kind of older technology that really hasn't caught on and maybe we need to see much better data on newer things that are coming out, and I know a close friend of mine was just diagnosed with early Alzheimer's. It was based on an amyloid PET, and he was put in a clinical trial in San Francisco based on case definition and amyloid PET.

I think one of the main issues that will come out today is the data is possibly a little bit better, as to whether patient progression can be… you can help determine whether somebody might convert to dementia. There have been a number of studies and the report concludes that there is moderate evidence that a PET might be useful to predict conversion to Alzheimer's disease, but in my own read of these studies, I just pulled out the two highest level studies that were cited in the report, the Level One Study by Zerega and, actually two Level One studies that were cited in the report, and the thing about this is, these were extremely narrow populations that were studied who were pretty much close to being demented at the time this thing was… at the time these tests were done at baseline. The mini mental state exam on average at baseline was 25. If you've got a 24 on a scale of 1-30, you're pretty bad, you know? People that have an MMSE of 24 are left out of all manner of, you know, surveys and stuff because, you know, they have pretty bad memory loss. So, to me, this is not a… this was not… these were not studies done in a broad population of people that walk into the office with, you know, MCI of all varieties. It was a very… these were very narrow populations, and I don't know what you can make of studies reporting to show reasonable accuracy or predict… or reasonable prediction when you're already, I think, pretty close to being demented and also in the [inaudible] Study 25% had abnormal baseline FDG and the… abnormal PET and they did not progress to dementia. So, you know, you got this problem of, you know, giving somebody a lot of concern and worry when, in fact, it doesn't really happen.

Harms of these tests are related primarily to a, you know, a moderate amount of radiation. I'm not an expert in this area and cannot really comment any more than that. People in the room know a lot more about this than I do.

Cost effectiveness, insufficient evidence. These were all simulated cohort studies. I think this evidence is really extremely weak. Almost no one is paying for this… these tests. Almost none of the private payers, CIGNA has limited coverage.

The Oregon Health Evidence Review Commission didn't feel like these were really worth covering, either for diagnosis or for prediction of progression.

So, the Medicare policy is very interesting, I think, and this just summarizes kind of the… what's happened with the Medicare policy over the decade. In April of 2003, they determined that this was, the FDG-PET should be noncovered. In April of 2009, they made a slightly more permissive decision in saying in very limited circumstances when somebody meets the clinical case definition of having both Alzheimer's and frontotemporal dementia, you have to meet the case definition of having both. That's when you can get an FDG-PET or they will pay for it in a CMS-approved practical clinical trial. So, you know, a very, very limited… so over a period of, you know, half a decade Medicare didn't really move much off of its noncoverage. It has very, very limited coverage. On the other hand in 2013, they determined that one of the beta amyloid PET scans should be covered with evidence development. So… and this is very early in the evolution of these tests. So, it seems to me that Medicare sees a lot more promise in these sort of newer tests than they do in the older tests. That's just my impression.

I think one of the main things here is that, of course, since there's no strong treatments for any of these diseases right now, there's no, of course, no evidence that doing these tests leads to any difference in treatment.

So, we're basically recommending from the evidence, which is weak, that these tests either be not covered at all or go with the Medicare extremely limited coverage policy for the FDG… for the patients with both AD and frontotemporal dementia and then we wouldn't recommend coverage for SPECT or FMRI for either diagnostic or risk factor progression. So, this is not, in my view, all that complicated of a subject. Great pictures. Not many people ordering them, and they don't seem to work very well, so, any questions?

Kevin Walsh: If there's not high utilization, I'm not clear why we're doing this?

Gary Franklin: Well, as you know, people buy machines and do tests. We… you know, SPECT scanning was much more common 10 years ago. People bought machines. They fell out of favor after a while. So, with the population, you know, people with mild cognitive impairment are anxious. They want to know stuff and, you know, it's not that hard to think of this thing on, you know, I don't think this… these technologies… that's going to happen to, really, at this point because of

these other emerging technologies, which look more promising, honestly. We were just worried about the diffusion of it given the size of the population with these problems.

David McCulloch: Yeah, Gary, is there a certain group pushing this that would make you suspect to future usage because there's…?

Gary Franklin: No, it was just our brilliant idea. Go ahead, Richard.

Richard Phillips: Another thing is, is it fair to assume that we are not considering amyloid in this based on this?

Gary Franklin: We're not. It's not part of the scope of this.

Richard Phillips: OK.

Gary Franklin: And you can ask why was that and I… actually we can't figure it out. It should have been part of the scope of this, honestly.

Craig Blackmore: OK, any other questions from the committee for Dr. Franklin? OK, well, we'll move on. The next thing I want to do is, I actually want to introduce our clinical expert, Dr. Silbert, hi. Welcome, thank you for coming. The way this works is that the committee, we're clinicians. We're experts in evidence-based medicine, but we're not necessarily experts in mild cognitive impairment and dementia, and so you are here to help provide some clinical context, and we will have questions for you, no doubt, throughout the course of the morning here. We're not asking for a specific presentation but there's always a lot of content that will… we'll ask of you, and I wonder if I could just have you take one minute and sort of tell us who you are and also if you have any conflicts of interest that might be relevant to the discussion.

Lisa Silbert: So, my name is Lisa Silbert, and I'm an associate professor in the Department of Neurology at Oregon Health and Science University, and I specialize in dementia. I have worked in the Oregon Aging Alzheimer's disease Center for 14 years and involved in various research, clinical trials, special interest in imaging, mostly MRI but with amyloid of course. Everyone's interested more in PET. So, and I have no conflicts of interest for this discussion.

Craig Blackmore: Thank you. Thank you for coming. Alright, next is, this is an open public meeting and we have… always have an opportunity for the public to provide comments to the committee and we're a little earlier than what's scheduled, but we'll make sure that we keep the public comments open so that if anybody comes in that window they'll have the opportunity. So, I believe we have three scheduled.

Josh Morse: So, we have one person signed up in advance, but we did receive a message that he may not make it, and we'll see if he's here, David Jang? So, it doesn't appear that Dr. Jang is here.

Male: Is the phone on?

Craig Blackmore: We'll check that. Well, did anybody sign up?

Josh Morse: It looks like two.

Craig Blackmore: OK, so...

Josh Morse: it's not clear, but...

Craig Blackmore: Is there anybody here who would like to address the committee, you are welcome to do so, and if you could come up to the microphone, and if I could have you tell us who you are, who you represent, if anyone, and whether you have any financial conflicts or if anybody has provided funding for you to come, anything of that nature.

Bruce Smith: Sure, and I did sign one of the clipboards, but maybe, are you?

Josh Morse: Yes.

Bruce Smith: OK very good.

Josh Morse: Thank you.

Bruce Smith: Hi, I'm Dr. Bruce Smith. I'm the executive medical director for Regence Blue Shield, which is the third party administrator for the UMP and PEBB program, so at least the majority of them. So, and I'm here representing Regence who, because we will be implementing recommendations that come to this committee. I also speak as a practicing geriatrician for 25 years with a long history of taking care of dementia patients and learning about it and teaching about it and I just wanted to support Dr. Franklin's recommendations that there's relatively little, from my clinical background, separate from my administrative work currently with Regence, but there's relatively little utility in functional neuroimaging for mild cognitive impairment, in particular, and the challenge there is defining mild cognitive impairment, as well. As Dr. Franklin mentioned, one of the studies there looked at patients who are fairly well along in the loss of cognitive function with an MMSE of 25. The mini mental status exam, that is copyrighted by Dr. Folstein we need to point out is a very gross measure of… of cognitive function but at 25 it's measurable that something's going on. The true definition of mild cognitive impairment is somebody who thinks things aren't quite going right but all of their studies are normal or at least within the bounds of normal. So, the challenge… so I've explained it to somebody on the soccer game sidelines, mild cognitive impairment is when you forget where you put your car keys. Dementia is when you forget what they're for, and the trouble is deciding that there's going to be some sort of an imaging study that will be appropriate or eligible for people with mild cognitive impairment, essentially says we're going to allow it for everybody, because

there's no way to determine mild cognitive impairment other than somebody thinks I'm a little more forgetful than I used to be, but when we do all of the screening studies, they all show up normal. So, if we approve studies for mild cognitive impairment, we're effectively approving studies for anybody who wants one. So, that's one concern. The other reality is that these tests just don't help us in our management of somebody who's even a little bit forgetful. Yes, over time certainly many of those folks who are a little forgetful this year become more forgetful enough that we officially diagnose them as dementia later, but as you all know, there's not much we can do in the meantime to change that trajectory one way or the other. So, I rise in support of the… Dr. Franklin's recommendation that this… this technology doesn't seem to have much utility and much value, so thanks.

Craig Blackmore: Thank you.

Josh Morse: So, Dr. Silbert is listed. Did you wish to comment?

Lisa Silbert: Well, I'll say… I agree with a lot of what was just said, although I'd just like to clarify that MCI is definable, and you do have to have objective cognitive impairment to meet criteria for MCI. So, there is such a thing as worried well versus MCI and people with MCI are at increased risk for getting Alzheimer's disease. So, it is a distinct population that can be systematically diagnosed. I do agree, though, at this time point, we don't have treatment for MCI. So, to diagnose someone with pre-Alzheimer's disease who has, we have no treatment for, I think, is not very productive. So, in the endpoint, I agree, but it wouldn't necessarily be something everyone would be included for if it were to pass.

Josh Morse: Thank you.

Lisa Silbert: And actually I'm… I'll make one more comment just about the recommendation. I very much agree that it's not useful… they… for the majority of the population and, but I… I just wanted to add that this can be very useful in specific circumstances. So, I don't know if you want to go into that particularly, but it was discussed that Alzheimer's versus frontotemporal dementia is a… the CMS-approved use of it, but in atypical cases it is also extremely helpful for us to get these studies, and we don't get them very often but when we have a very atypical case, a younger onset rapid progression unclear diagnosis, these tests can be very helpful.

Josh Morse: Thank you. We have one other person listed, Nadia Salama with Group Health. Did you wish to comment? No, OK, thank you. So, we should check the phones?

Good morning, this is the Health Technology Clinical Committee meeting. We have open public comment right now on neuroimaging for dementia. Is there anybody on the call who would like to make a comment?

OK, we're hearing no comments now. We are a little early for the comment period so we will check back in a little while but thank you.

Craig Blackmore: OK. Next on the agenda is our evidence report.

Robin Hashimoto: Good morning. I am Robin Hashimoto. I'm from Spectrum Research. So, I'm going to start with just an overview of the Health Technology Assessment objectives, and then I'm going to talk a little bit about dementia, but we'll try to go through that pretty quickly. So, this Health Technology Assessment asks about the diagnostic ability of functional neuroimaging in patients with primary neurodegenerative dementia or mild cognitive impairment. So, we placed the focus of the report on how functional neuroimaging impacts patient health outcomes and disease progression, the harms associated with it, including those of a wrong diagnosis, as well as the cost effectiveness. We also looked at the… placed less focus on the evidence regarding diagnostic accuracy and reliability of functional neuroimaging and how it impacts different populations, as well as how it affects treatment decisions and clinical management.

OK, so dementia is a condition in which a patient's mental abilities have declined to the point that their ability to function on a daily basis has been impacted, and although it most commonly effects the elderly, it's prevalence increases with age. Of course, it's not a normal part of the aging process. It can range in severity. It tends to progress from a milder to a more severe form, and symptoms vary with a specific etiology but can include impaired reasoning, judgment, visio-spatial abilities, language capabilities, and ability to handle the complex tasks and behavioral personality changes.

So, because the causes of dementia vary and treatments vary with etiology and early and accurate diagnosis is important, this will allow a patient to receive the property medication and therapy, and it can really also be helpful in terms of providing the patient, family, and caregiver information regarding disease progression and how to plan. So, in an ideal situation, patients will get diagnosed following a comprehensive workup, and this would consist of history, neurological exam, detailed cognitive testing, as well as structural neuroimaging; however, most patients that just present to their primary care physicians for evaluation aren't likely to undergo this level of testing.

This comprehensive workup will allow a physician to rule out potentially reversible causes of dementia, such as tumor or hydrocephalus and neurodegenerative dementia can occur as a result of primary or secondary processes, and this report is focused on primary neurodegenerative dementia, Alzheimer's disease, which is the most prevalent, as well as frontotemporal dementia and dementia with Lewy bodies.

OK, so this slide just gives an overview of the symptoms, pathology, diagnostic criteria, and some treatment options for the three… these three main types of dementia. Symptoms vary between the different etiologies, but there are overlapping or common symptoms between them, and depending on patient

presentation, it can make them difficult to differentiate, especially if the patient presentation is atypical.

All three of these diseases are associated with abnormal protein deposits and these affect the overall pathology of the brain. Alzheimer's disease patients tend to have early neuronal loss in the hippocampal and mesiotemporal lobe. Frontotemporal dementia, on the other hand, is typically associated with atrophy and neuronal loss in the frontal and temporal lobes, and then Lewy body dementia tends to be more varied.

So, as I'm sure you're aware, each disease has a specific set of well-accepted clinical diagnostic criteria, and those are listed here, and then finally each disease has specific treatment options, and there's no cure for any of these diseases at this time, but patients can receive medicine to help with their symptoms. Alzheimer's and Lewy body dementia patients can benefit from cholinesterase inhibitors to help with cognitive decline, but these medications are not indicated for FTD, as they can make patients worse.

OK, so the scope of the Health Technology Assessment also covers mild cognitive impairment, and this affects a person's memory and/or cognition. It does differ from dementia in that the person maintains their functional independence. It affects 10 to 20% of people over the age of 65, and it is associated with an increased risk of developing Alzheimer's disease or other dementia, and this is because, it's basically, it can be an early form of these diseases, but not all people with MCI get worse. Some don't progress. Some end up getting better.

OK, so functional neuroimaging can be used to help confirm a diagnosis of a specific type of dementia, particularly in cases where the diagnosis isn't clear or the patient presentation is atypical. It's an add-on diagnostic test. So, it's done in addition to the initial comprehensive diagnostic workup and structural neuroimaging, and the main imaging modality of interest for this Health Technology Assessment are listed here, and I've also listed the recommendations from the European Federation of the Neurological Sciences, and they were the ones that provided the most thorough functional neuroimaging specific guidelines that we were able to find. So, both PET and SPECT involve the injection of radiolabeled ligands. FDG-PET allows for the imaging of glucose metabolism. So, Alzheimer's disease and frontotemporal dementia have distinct metabolic patterns. In Alzheimer's disease hypometabolism is seen in the temporoparietal cortices and then in frontotemporal dementia, the hypometabolism is seen in the frontotemporal lobe. As you've heard, CMS does have a national coverage decision, and this allows coverage for FDG-PET scans in order to differentiate between FTD and AD when the diagnosis isn't clear and other specific conditions have been met.

For patients with mild cognitive impairment, hypometabolism in the Alzheimer's pattern may be predictive of conversion to Alzheimer's disease, and FDG-PET

isn't recommended to differentiate between Alzheimer's disease and Lewy body dementia.

HMPAO-SPECT shows cerebral blood flow and because blood flow is tightly coupled with metabolism, glucose metabolism, patterns of hypoperfusion are similar to patterns of hypometabolism that you see with FDG-PET in differentiating the dementia types, but it does have a lower spatial resolution than PET.

CIT-SPECT is also known as fat scan and imagines the dopamine transporter. It can help distinguish Lewy body dementia from Alzheimer's disease, as Lewy body dementia often results in denervation of dopaminergic nigrostriatal neurons.

The last modality of interest was functional MRI, and this provides real-time imaging of cerebral blood flow, either during rest or during a task. It does not use radiation, and some research has suggested that it can be used to distinguish patients with Alzheimer's disease or mild cognitive impairment from healthy controls and the EFNS Guidelines viewed this as a tool still under development.

OK, so the biggest potential harm with functional neuroimaging is really radiation exposure. The effective radiation doses for the different types of neuroimaging are listed here, and I've also listed the doses for head and chest CT for comparison. Other reported harms are also listed here, and they tend to be minor. The FDA has estimated an effective dose of 10 mSV increases the risk of death from cancer by 1 in 2000, and they have stated that an imaging procedure should be considered when it's medically necessary and is believed to do more good than harm.

This is the analytic framework used and briefly it shows that patients with symptoms of dementia, or mild cognitive impairment, undergo an initial comprehensive workup followed by the add-on test, which is functional neuroimaging. So, first we have context questions, as well as one key question that asked how functional neuroimaging performs in terms of diagnostic accuracy and reliability. Once patients are diagnosed, treatment decisions are made or changed, and how these are impacted by functional neuroimaging compared to the comprehensive workup alone are addressed in key question three.

The meat of the report is really in key question two, and this asks how functional neuroimaging impacts patient health outcomes and disease progression. Harms of functional neuroimaging, including harms of misdiagnosis or of a false positive diagnosis are addressed in key question four. Key question five asks about whether functional neuroimaging performs differently in different populations and cost effectiveness is addressed in key question six.

So, for inclusion, we required that studies use functional neuroimaging to make a diagnosis. This ended up being an important distinction and again, the primary outcomes of interest were those that were directly related to patient health outcomes and to disease progression. Diagnostic accuracy and reliability were considered to be intermediate outcomes.

OK, this is an overview of the literature search and as you can see, a total of 34 studies met our inclusion criteria and were included in this report, and I do have printouts of all the studies available today.

So, I'm going to present the results in terms of the overall quality of evidence, and I'm going to focus on the highest quality evidence available for the primary outcomes of interest, and the way in which we do this is based on our application of grade and ARCS recommendations. The four levels of evidence are shown here, and I wanted to point out that grade was developed for systematic reviews of therapy. We did adapt it to the diagnostic systematic review based on recommendations from ARCS method… methods guide for systematic review of medical tests. The way at which we arrived at the overall strength of evidence, first we start by grading the class or quality of evidence for each individual study, and this largely gets at the risk of bias for those studies, and then we move on to the overall grade of evidence for each primary conclusion. We start with a baseline quality of evidence. If the majority of studies were quality grades one or two, we started a baseline quality of evidence as high, and if there were three or four, we started at low, and then that baseline quality of evidence can then be downgraded due to risk of bias, inconsistency, indirectness, imprecision, and publication bias across that study… across those studies for that particular outcome.

So, after taking all these factors into consideration, we arrived at a final strength of evidence rating. For this report, the most common reason for downgrading the quality of evidence was for risk of bias resulting from methodological flaws in the studies included, as well as further risk of imprecision that results from small sample sizes and details on the reasons for each outcome for downgrading for each outcome are provided in the strength of evidence tables in section five.

OK, so the first context question asked about the inter- and intra-rater diagnostic reliability or reproducibility. So, for inclusion we required that the same method must have been used between each rater or test, and this slide just gives an overview of the evidence base. In total, there were 12 studies that met our inclusion criteria. Seven of these were considered to be at low risk of bias, and as you can see, the bulk of evidence was available for FDG-PET.

When possible, we reported the reliability in terms of the Kappa statistic, and this indicates the percent agreement beyond chance alone. So, for FDG-PET, Alzheimer's disease was… this is up here, generally distinguished from other types of dementia based on the presence of bilateral temporal parietal hypometabolism, and as you can see, the inter-rater reliability was substantial for FDG-PET for discriminating Alzheimer's from frontotemporal dementia and

moderate to substantial when discriminating Alzheimer's from other dementias. We only identified one study that looked at intra-rater reliability. It reported a Kappa. There was a mean Kappa across three raters of 0.52, which suggests moderate agreement for differentiating Alzheimer's from other dementias.

Two studies used HMPAO SPECT to differentiate Alzheimer's from frontotemporal dementia. The inter-rater reliability was much lower for this than it was for FDG-PET, and neither of these studies adequately described the specific regions of interest that were used to differentiate between those diseases.

Next, looking at DTBZ-PET, this allows visualization of the nigrostriatal dopamine terminal and it correlates with regional blood flow and it was… there was almost perfect reliability or agreement for distinguishing between Alzheimer's, frontotemporal dementia, and dementia with Lewy bodies in one study.

Two studies reported inter-rater reliability of CIT SPECT or DaTSCAN to differentiate between Lewy body dementia and other dementias with the larger of the two studies showing almost perfect agreement and the other study reported good inter-rater agreement.

Strength of evidence, the context questions asked about the diagnostic accuracy of functional neuroimaging. For diagnostic accuracy, we limited studies to those that use the gold standard of autopsy and this allowed us to provide the most accurate information available. This is an overview of the evidence base, and only four studies met our inclusion criteria. So, starting at the top again with FDG-PET two studies compared the diagnostic accuracy of FDG-PET to autopsy results. A diagnosis of Alzheimer's was made based on the presence of temporoparietal hypometabolism on FDG-PET, and as you can see, the sensitivity for diagnosing Alzheimer's was high, and it was higher with FDG-PET alone than with the clinical diagnosis alone. In contrast, the specificity of FDG-PET alone was lower than that of the clinical diagnosis alone, and neither of the studies, or actually none of the studies here reported the diagnostic accuracy of imaging plus clinical diagnosis use together.

OK, next looking at HMPAO SPECT, one poor quality study evaluated the diagnostic accuracy of this technology for diagnosing Alzheimer's, and this was based on the presence of regional hypoperfusion in the temporoparietal lobes. The study found that HMPAO SPECT had good sensitivity and specificity for diagnosing Alzheimer's.

OK, lastly, looking at CIT SPECT or DaTSCAN, the results suggested that DaTSCAN had better sensitivity and specificity for diagnosing dementia with Lewy bodies than the clinical diagnosis alone.

OK, so key question one asks about the diagnostic accuracy of functional neuroimaging for the differential diagnosis of Alzheimer's, frontotemporal

dementia, and Lewy body dementia, again based on the gold standard of autopsy.

OK, so for this key question, we specifically looked for studies that were trying to distinguish between patients with two different possible types of dementia or patients that, you know, they couldn't distinguish clinically, and overall six studies met our inclusion criteria. All of them were conducted retrospectively. Two studies were considered to be at moderately-low risk of bias, and three at moderately-high risk of bias. One was considered to be at high risk of bias. There were no studies identified for DTBZ-PET, DaTSCAN, or FMRI.

OK, so three studies were found that used FDG-PET to discriminate between Alzheimer's disease and frontotemporal dementia. So, note that the sensitivity of an Alzheimer's diagnosis here is equivalent to the specificity of a frontotemporal disease diagnosis. These are all presented in terms of the sensitivity and specificity for diagnosing Alzheimer's.

So, overall, we concluded that there was low strength of evidence. The FDG-PET scans interpreted visually had high sensitivity and moderate specificity for discriminating between these diseases, and you can see here how imaging compares to clinical diagnosis alone or imaging plus the clinical diagnosis.

Craig Blackmore: Sorry, I just want to interrupt for one minute.

Robin Hashimoto: Yeah.

Craig Blackmore: And then we're going to get into some trouble with terminology. When you say clinical diagnosis here, you mean clinical plus structural imaging.

Robin Hashimoto: Yes.

Craig Blackmore: When you say...

Robin Hashimoto: Yes.

Craig Blackmore: …imaging, you really mean functional?

Robin Hashimoto: Functional, yeah.

Craig Blackmore: Yeah, I just wanted...

Robin Hashimoto: Sorry.

Craig Blackmore: …to verify, thank you.

Robin Hashimoto: Good distinction. OK, and then there was insufficient strength of evidence on FDG-PET scans that were interpreted using automated software, which is a newer technology, and this was based on one very small study.

OK, regarding HMPAO SPECT, one low quality study reported insufficient strength of evidence on the ability of HMPAO SPECT to distinguish Alzheimer's disease from frontotemporal dementia.

Going back to FDG-PET, looking at patients with… who are believed to have either Alzheimer's disease or dementia with Lewy bodies, there were two studies at moderately high risk of bias, and they reported insufficient… there was insufficient strength of evidence on the ability of FDG-PET to differentiating… to differentiating between these diseases.

OK, so key question two asks about the ability of functional neuroimaging to predict disease to progression and clinical outcomes. It also asked about whether one type of functional neuroimaging is better at doing this than another, but there were no studies identified to address the second question.

So, for this key question, we sought studies that evaluated disease progression, or clinical outcomes in patients who had been diagnosed using functional neuroimaging. For inclusion, we were looking for longitudinal studies and studies that were designed specifically to look at disease progression. We required the studies use criteria developed a priority to diagnose patients with functional neuroimaging. So, overall we found 13 studies that met our inclusion criteria and nearly all of them evaluated the ability of functional neuroimaging to predict progression for mild cognitive impairment to Alzheimer's disease or dementia. No studies were identified that looked at the ability of functional neuroimaging to predict progression or patient outcomes in patients who were presenting with dementia rather than mild cognitive impairment.

OK, so starting with FDG-PET regarding its ability to predict progression from mild cognitive impairment to Alzheimer's or dementia. So, just briefly for this key question, nearly all of the outcomes were reported in terms of specificity and sensitivity. So, to do this, a prediction or diagnosis was made using FDG-PET and then the reference standard used was the presence of disease at follow-up.

So, we found moderate strength of evidence based on two small studies that were at low risk of bias that… those should actually be CoE-1, I apologize. That visual assessment of FDG-PET scans could predict progression from MCI to Alzheimer's disease or dementia with high specificity and moderate sensitivity… high sensitivity and moderate specificity. Sorry.

Patients who presented with mild cognitive impairment were followed for about one and a half years, and 25 to 50% of patients progressed. Scans were interpreted in a manner that was blinded to clinical diagnosis and clinical outcome, and then the clinical outcomes were evaluated, blinded to FDG-PET results. For these studies, clinical outcomes were based on diagnosis of Alzheimer's disease using the NIN CDS ADR DA criteria or on a diagnosis of dementia based on the global clinical dementia rating scale with a score of one or higher.

We found low strength of evidence based on one small study, that visual assessments of FDG-PET scans could predict progression from mild cognitive impairment to further cognitive decline with moderately high sensitivity and specificity. For this outcome, or for this study, progressive cognitive decline was defined as a reduction in mini mental exam scores by two or more points along with clinical deterioration from a clinician's perspective, and patients were followed for about one and a half years.

OK, so we found insufficient strength of evidence based on one study that was found to be at moderately high risk of bias that used FDG-PET scans and interpreted them visually to predict cognitive decline.

In this study, FDG-PET was used to predict whether patients with mild cognitive impairment were likely to progress, and they found that at three and a half years follow-up, mini mental state exam scores were significantly lower in patients who had FDG-PET positive scans versus those who had normal scans, and this is all the evidence we have regarding the ability of FDG-PET to predict patient progression or health outcomes.

OK, so now looking at SPECT, we found insufficient strength of evidence based on three studies at moderately high risk of bias on the use of SPECT to predict progression from MCI to Alzheimer's disease or dementia, and for these studies in generally, progression to Alzheimer's was diagnosed using the NIN CDS, AD, RDA criteria. No other evidence was found regarding the ability of SPECT to predict progression or health outcomes.

So, across the whole evidence report, we found only one study on functional MRI that met our inclusion criteria, and it provided insufficient strength of evidence from a high, moderately high risk of bias study that functional MRI could predict progression for mild cognitive impairment to dementia or Alzheimer's.

Craig Blackmore: So, I'm sorry. I want to interrupt just for one...

Robin Hashimoto: No, go ahead.

Craig Blackmore: …minute. This is procedural. We… we post an agenda and in the agenda it says that we would accept public comments from 9:00 to 9:20, and we were ahead of that schedule. So, I want to make sure if anybody called in and they called in during the window, they were expecting to be able to address the committee that we give them the opportunity to do that, so we'll just check the phones real quick.

So, this is the Washington State Health Technology Clinical Committee meeting. Is there anybody on the phone who wanted to address the committee, this would be your opportunity to do so? So, hearing no comments, we will move on. Thank you.

Robin Hashimoto: OK, so moving on to key question three. Key question three asks whether the results of functional neuroimaging impact therapeutic decisions or clinical management compared to those that were made for patients who were diagnosed in the absence of functional neuroimaging, and no evidence was found to address this key question.

Key question four asks about the short and long term harms of diagnostic functional neuroimaging, including the harms that could result from a missed diagnosis or from a false-positive diagnosis and very little information was found.

Overall, there was insufficient evidence that short term or procedural harms were relatively uncommon. No studies were identified that reported on long term harms or harms from an incorrect diagnosis, and no studies were found that evaluated any harms in HMPAO SPECT or functional MRI.

Key question five asked about whether functional neuroimaging can perform differently in subpopulations, but no evidence was found.

The last key question is key question six and it asks about the cost-effectiveness of incorporating diagnostic functional neuroimaging into the comprehensive diagnostic workup.

So, we found evidence on FDG-PET as well as on SPECT. We'll start with FDG-PET. Overall, three studies met our inclusion criteria. One study was a cost utility study and this reports cost per quality adjusted life year and then two studies were cost-effectiveness studies, and they report cost per improved outcome. Across all studies, population evaluated was a simulated cohort of hypothetical mild to moderate dementia patients. The diagnostic tests compared were the comprehensive diagnostic workup in the presence or absence of FDG-PET and the diagnosis being made for all of these studies was Alzheimer's disease.

So, one cost utility study was included. It was conducted from a U.S. perspective and used an 18-month time horizon. The cost included the cost of patient care, which could be either home care or nursing home care, as well as medication and the study found that the addition of FDG-PET to the diagnostic workup was more costly and did not improve quality adjusted life years.

Two cost-effectiveness studies were included. One was conducted from a U.S. perspective and used a six-month time horizon, so it's pretty short. The other was conducted from a European perspective. The time horizon wasn't reported, but the study in general seemed to be using the same methodology as the first study. For these studies, the cost of care was generally not included, unless there was a false-negative diagnosis. In that case, the cost of nine-month's care was included based on the assumption that during the time… during that time the patient would decline any additional care. Otherwise, the

cost of care wasn't included, presumably because patients wouldn't be receiving… or would otherwise be receiving treatment and presumably wouldn't decline significantly during the six-month time horizon. Overall, both studies found that the addition of FDG-PET to the diagnostic workup was cost effective. It resulted in a diagnosis that was less costly overall and resulted in increased accuracy versus a conventional workup alone.

David McCulloch: Sorry. Can I… can I challenge you in that? I mean, that… that is ludicrous if… if you're saying that cost-effectiveness study… reports on cost have improved outcome. You're giving us no data that having improved accuracy improves clinical outcome. These studies didn't include the cost of care? Well, I mean, that's certainly going to reduce your overall costs. I mean… I mean… there are no… you've showed no evidence to suggest using this improves clinical outcome.

Robin Hashimoto: Mm-hmm.

David McCulloch: So, I… I… so they are not cost effective by any… any sensible definition, no?

Robin Hashimoto: I'm just reporting what the studies reported.

David McCulloch: Well, but you're also giving us a spectrum, you're hired and paid to give us some [inaudible]. Is that a reasonable conclusion? Do you think it's reasonable for those studies to include that the addition of FDG-PET is cost effective per improved outcome?

Robin Hashimoto: I think that the… for these studies, not including the cost of care is problematic.

David McCulloch: Yep.

Robin Hashimoto: I think that using a six-month time horizon is problematic.

David McCulloch: Agreed.

Robin Hashimoto: I think that using a hypothetical cohort of patients is problematic.

David McCulloch: Agreed.

Robin Hashimoto: And, I mean… from that they basically did a literature review and looked at what's reported in terms of the diagnostic accuracy. So, it's all… it's all hypothetical, so yes.

David McCulloch: Right, so that… that's… thank you.

Robin Hashimoto: Yes. OK, and then the last slide for SPECT. Two cost utility studies were included. Again, the population was a simulated cohort of patients with mild or moderate dementia referred to a specialty clinic. The tests compared where diagnostic workup in the presence or absence of SPECT, and the diagnosis of

interest was Alzheimer's disease. Both of these studies were conducted from a U.S. perspective using an 18-month time horizon. The cost did include patient care, which was either home care or nursing home care, as well as medication and SPECT was associated with slightly higher costs overall. The addition of SPECT did not result in increased quality adjusted life years, and the studies concluded that SPECT was not cost effective as an add-on to the conventional clinical workup and the diagnosis of Alzheimer's disease.

So, as you can see, there are a number of gaps in the evidence. Pretty much, for all imaging modalities looked at, all functional neuroimaging modalities, there is a lack of evidence in terms of prediction of outcomes related to many of the health outcomes of interest, such as cognition, function, behavior, psychological status, depression, caregiver burden, and global health. There is also an absence of evidence in terms of how well any of the imaging modalities of interest could predict progression for patients who are presenting with dementia rather than mild cognitive impairment. There was no evidence on how one type of functional neuroimaging compares to another in terms of prediction or patient outcomes. No evidence on the impact of therapeutic decisions and clinical management compared with diagnostic workup without functional neuroimaging. There was no evidence on the impact of a misdiagnosis or a false positive diagnosis, and that was largely in the absence of any evidence, really, for a functional MRI, and as you can see, there was an absence of data on real patient populations to address the cost-effectiveness. Thanks. I can take questions.

Craig Blackmore: Questions from the committee? I'll ask one question which is, I guess it's kind of related to key question five, but we've heard that sometimes these tests were used not sort of routinely but as a problem-solving tool in patients that are, you know, that are confusing, you know, that are atypical on some level, and so did you encounter or did you look for evidence about the use of the test in specific subgroups, like, I'm particularly thinking of the… in the Medicare definition?

Robin Hashimoto: Mm-hmm.

Craig Blackmore: Patients that meet the diagnosis… diagnostic criteria for both whether it's frontotemporal or Lewy body dementia and AD.

Robin Hashimoto: Right. We did. We looked for pretty much any subpopulation and we looked specifically for studies that reported how the test could perform in terms of disease progression, clinical outcomes and harms. So, we didn't find anything. We did look at the differential diagnosis in terms of accuracy in key question one, but, I mean, otherwise we didn't find any evidence for key question five.

Craig Blackmore: Thank you.

Chris Standaert: I had a question. I mean, I don't treat these patients directly but are… when you get to progression in key question two, you talk about clinical outcomes and that sort of…

Robin Hashimoto: Mm-hmm.

Chris Standaert: …thing, and we don't have any treatments that really impact that significantly is my understanding.

Robin Hashimoto: Mm-hmm.

Chris Standaert: But, the idea of progression is not necessarily a clinical question. It's sort of a social question for state planning and all sorts of other things going on if you can predict who would decline rapidly versus who wouldn't, it would dramatically change the behavior of affected family, as I would imagine.

Robin Hashimoto: Mm-hmm.

Chris Standaert: And so we don't… nothing here talks about that and how this...

Robin Hashimoto: Right.

Chris Standaert: ...could be used not just...

Robin Hashimoto: Right, and those were things...

Chris Standaert: ...theoretically speaking but that's a very...

Robin Hashimoto: Yeah.

Chris Standaert: ...important variable, I think...

Robin Hashimoto: Yeah.

Chris Standaert: ...for patients who are affected.

Robin Hashimoto: In terms of general planning, no, I mean, we didn't look specifically for that. It didn't fall out of any of the studies. We were specifically looking for outcomes related to caregiver burden. We didn't find anything, so.

Craig Blackmore: OK.

Robin Hashimoto: In terms of pay… in terms of how use of functional neuroimaging impacts disease progression and any sort of outcomes, I've presented everything that we… that we were able to find. We didn't exclude studies based on specific outcomes that were reported.

Chris Standaert: So, the one… so I'm look… I guess I'm looking to see if these are useful in sort of doing that for people.

Robin Hashimoto: Right.

Chris Standaert: Not so much from a medical standpoint...

Robin Hashimoto: Right.

Chris Standaert: ...from what the doctor...

Robin Hashimoto: Right.

Chris Standaert: ...but changing what the families do.

Robin Hashimoto: Uh-huh.

Chris Standaert: And so you… the only thing you point that's remotely promising is that one study of 47 people on FDG-PET as a progression tool?

Robin Hashimoto: Mm-hmm.

Chris Standaert: But that's not a lot of people and that's not a lot of time.

Kevin Walsh: In a population where 50% progress, 25-50% progress in one year.

Chris Standaert: Yeah.

Kevin Walsh: So...

Chris Standaert: This, this is what I'm after...

Kevin Walsh: ...I, I know, but I'm...

Chris Standaert: ...the details of the study.

Kevin Walsh: ...I'm asking you to ask yourself, what is it you're giving families?

Chris Standaert: No, that's what I'm asking. I'm trying to, yeah.

Kevin Walsh: Right.

Chris Standaert: Right.

Kevin Walsh: So, you're giving them maybe a year, maybe two, maybe three.

Chris Standaert: Of?

Kevin Walsh: Of certainty.

Chris Standaert: Right.

Kevin Walsh: Because 50, 25-50% of these people progress.

Robin Hashimoto: Mm-hmm.

Kevin Walsh: Per year.

Chris Standaert: Yeah, and the follow-up is only 1.3 years to 1.6 years so it doesn't really help you all that much.

Kevin Walsh: Correct.

Chris Standaert: I'm just pointing out that's our data.

Robin Hashimoto: Yeah, yeah.

Craig Blackmore: And there's potential harm. I mean, there's, there's what level of certainty...

Chris Standaert: Right.

Craig Blackmore: ...do you need...

Chris Standaert: No, I'm just...

Craig Blackmore: ...to go through that exercise.

Chris Standaert: I don't, I mean...

Craig Blackmore: It's, it's a related question. What, if you're 80% sure does that...

Chris Standaert: Does that really help you? Does that really help you to give somebody a false sense of they're not going to progress if it's not so good. Yeah.

Marie Brown: It seems like that study to do would be looking at what families do with the information from imaging once a diagnosis is made. What impact does that additional information have on their decision-making or their care plans or anything like that, that's not the providers.

Chris Standaert: Right.

Marie Brown: It's not provider initiated but family initiated.

Chris Standaert: And like Craig says, that infor… how, if that information is not terribly reliable then it can become more unhelpful than helpful for many families.

Marie Brown: Right.

Chris Standaert: Yeah.

Craig Blackmore: Other questions for Dr. Hashimoto?

Michelle Simon: It's in regard to key question two and the… the progression of this is, am I right in this that none of the studies went beyond 1.5 years follow-up?

Robin Hashimoto: I think, let's see, yeah there was one study that looked at just further cognitive decline, as measured by mini mental state exam scores, and that one was for a mean of three and a half years plus or minus a year. I think that was the longest. Yeah, some of the SPECT ones were longer ranging from a… about a year and a half to four years.

Michelle Simon: And that's on slide 27, is that right? You're referring to?

Robin Hashimoto: Yeah, 27 is the MMSE one and 28 is the SPECT, yes.

Richard Phillips: Craig?

Craig Blackmore: Alright, go ahead.

Richard Phillips: Thank you, yes on slide 25...

Robin Hashimoto: Mm-hmm.

Richard Phillips: ...what is… is there some kind of characteristic difference between the automated and visual PETs that would make the sensitivities and specificities change that much, or is it just because of the follow-up years doubling in the automated?

Robin Hashimoto: Yeah, and we also have high quality versus lower quality studies. You know, I'm surprised to see that they… they would change that much and...

Richard Phillips: Right.

Robin Hashimoto: ...in a perfect world, I mean, you would think that the automated could potentially be better and...

Richard Phillips: Right.

Robin Hashimoto: ...and more reliable.

Richard Phillips: Yeah.

Craig Blackmore: I certainly wouldn't think that, come on.

Chris Standaert: You're going to be outsourced by software.

Craig Blackmore: I believe this data entirely.

Robin Hashimoto: Or at least there's somebody that wants me to believe that.

Craig Blackmore: Yeah, Richard.

Richard Phillips: I had a question, too, actually I would probably point this question to our clinical expert, too, but actually maybe Robin can answer this and that is, is there any evidence that you found that the use of these neuroimaging functional studies influences treatment in any way?

Robin Hashimoto: We did not find any evidence.

Michelle Simon: I was hoping the clinical expert could weigh in on that.

Marie Brown: The clinical expert could respond to that, too.

Craig Blackmore: Yes, please. Dr. Silbert.

Lisa Silbert: Sure, so in certain specific circumstances, it is helpful in guiding treatment. The AD, FTD example is one, but also in an atypical patient where you're not sure if they have a neurodegenerative disease, this is very helpful in terms of whether to start them on a cholinesterase inhibitor that would be likely for the rest of their life and also in terms of prognosis and counseling. But again, in the… in the routine patient, no. It wouldn't change anything.

Marie Brown: Are those patients with mild cognitive impairment or with more significant?

Lisa Silbert: These are people with dementia, clinical dementia. In patients with mild cognitive impairment, there is no cure for preclinical Alzheimer's disease at this point. So, I wouldn't advocate the use of making that diagnosis in that population right now. So, I think it probably is helpful in predicting who will get it in the future, but I'm not sure what we would do with that information currently.

Craig Blackmore: So, I think procedurally we're kind of moving on from presentation, thank you.

Robin Hashimoto: Thank you.

Craig Blackmore: And we won't make you stand up there any longer.

Robin Hashimoto: Thank you.

Craig Blackmore: So we… procedurally, we hear the presentations and we move to a little more free form discussion among the committee members as we try to head towards… towards a decision and we, as committee members, have the opportunity to ask further questions of any of our presenters here today. So, any… any comments or thoughts or further questions from the committee members? I don't want to cut anything off here.

Marie Brown: What information would Medicare have used to make their exception that it was paid for if you were trying to differentiate two types? I think it's Lewy body and AD. What, what evidence would they have used to… to make that particular stipulation? I mean, I know… I mean, we realize we don't know.

Seth Schwartz: Yeah, how do you… why do you suppose they used evidence?

Craig Blackmore: The CMS says FDG-PET scan is considered reasonable and necessary in patients with a recent diagnosis of dementia, documented with cognitive decline of at least six months, who meet diagnostic criteria for both Alzheimer's and frontotemporal dementia. So, we don't know how they came to that.

Marie Brown: No, no, I realize we won't ever know that but, do… do we have any evidence, the clinical expert I guess is my question too.

Craig Blackmore: Do you want to comment on that?

Lisa Silbert: I don't know [inaudible].

Marie Brown: Yeah, right. I realize none of us can guess that. That was more of a… what might they have been thinking?

Lisa Silbert: Well, I can speak...

Marie Brown: I mean, there's a rationale. I just don't think that was the question I did have.

Lisa Silbert: From a clinical perspective, it's… it's an important diagnosis for counseling and for prognosis, because those two dementia diagnoses are very different and they progress differently and treatment is somewhat different, as well. So, from a clinical perspective, when I am in that dilemma, I do… I have a lot more clarity in my future management of that patient and in guiding them in their future planning when I have a diagnosis that's clear of Alzheimer's versus frontotemporal dementia. So, I can only say from a clinical perspective, it's helpful in those areas, and I don't know what CMS used to make that decision, but I… I appreciate that decision from a specialty perspective.

Chris Standaert: From our evidence vendor, so the… the slide 21, the one that addresses that, that one study, AD versus frontotemporal dementia.

Craig Blackmore: Well, I… I mean, I think we heard from Robin that there was no evidence on use of the tools in that context.

Chris Standaert: Distinguishing the different entities.

Craig Blackmore: I guess affecting outcome. Maybe there is…

Chris Standaert: Or no, I'm not looking at outcome.

Kevin Walsh: Or just look at… or just look at the sensitivity and specificity...

Marie Brown: That's all we have.

Chris Standaert: Right.

Kevin Walsh: ...versus clinical diagnosis alone.

Chris Standaert: Right.

Kevin Walsh: How much difference is there?

Chris Standaert: So that's why… I'm… I'm saying. If, so… if that's a significant issue, but this is all we get, you know, it'd be great to be able to distinguish that, but the...

Kevin Walsh: We don't...

Chris Standaert: ...test doesn't...

Kevin Walsh: ...we don't get...

Chris Standaert: ...really do that.

Kevin Walsh: ...this bang for the buck.

Chris Standaert: Right. If the test doesn't really do… if the evidence that the test actually does that, it's great to think that you can do that, but if you sensitivity and specificity really aren't that great, you still may be thinking you accomplished some distinction that you haven't actually accomplished very well, if that's… if this is really what the data says.

Robin Hashimoto: This is the data, yeah.

Craig Blackmore: Any other comments or questions right now? That's a powerful silence.

Chris Standaert: I guess I have a question for our clinical expert. So, the… you mentioned a couple times if you have an atypical presentation, but I don't see anybody talking, I don't see anybody defining atypical presentation, but how do you… what is that… do you define an atypical presentation in some way that we… that someone could distinguish?

Lisa Silbert: Well, atypical from my perspective, I mean, there are clear typical presentations of Alzheimer's disease. Alzheimer's disease is very common...

Chris Standaert: Mm-hmm.

Lisa Silbert: ...it presents in a very typical fashion for the majority of patients. So, atypical would be those who deviate from that in… in my mind. Those would be people

who are younger than age 65 who have a more rapid course or have features that are overlapping for… for other diseases. So, it's unclear what the diagnosis is.

Chris Standaert: OK.

Lisa Silbert: In, in the majority of… of dementia workup diagnoses, it's fairly straightforward. Most cases are typical Alzheimer's disease, and that's why this test is rarely needed to make that diagnosis.

Chris Standaert: Mm-hmm.

Lisa Silbert: But when the clinical course deviates from that, it can be helpful, from my perspective, to say that there is a neurodegenerative disease. Sometimes it's not. Sometimes, it's a psychiatric disease or a metabolic or infectious process.

Chris Standaert: Mm-hmm.

Lisa Silbert: And then also to delineate, if it is a neurodegenerative process, which process it is. So, those are for the atypical patients.

Craig Blackmore: The first part of that wouldn't be related to the functional neuroimaging?

Richard Phillips: No.

Craig Blackmore: Right? I mean you're going to do other… other tests, other evaluations to make sure this isn't an infectious process or etc.

Lisa Silbert: Oh, sure. However, in some patients, you… you're not going to get around those chronic diseases that could also be playing a role in their cognitive status. So, it's particularly psychiatric disease.

Marie Brown: Right.

Lisa Silbert: That is often a confounder when making these kind of diagnoses.

Richard Phillips: A question. You… you'd mentioned this… the special cases. Do elderly patients with a psychiatric components of their, as part of their dementia, are they considered, in your opinion, to be one of the more deviant groups of… or people that are different atypical, or is that…?

Lisa Silbert: Really, more often talking about younger onset patients.

Richard Phillips: OK.

Lisa Silbert: That's the only time I've ever ordered that test.

Richard Phillips: OK.

Craig Blackmore: OK, any… Marie-Annette, do you want?

Marie Brown: How much then workup would you do for other kinds of etiologies, I mean, in your differential, you would either go to imaging or other kinds of exploration for other… other diseases in your differential.

Lisa Silbert: Yeah, standard workup does include some structural imaging. That's recommendations by the American Academy of Neurology, and that could just be a head CT or an MRI to rule out other processes that could be contributing and then a standard kind of metabolic infectious workup. That's all done routinely.

Marie Brown: On everyone?

Lisa Silbert: Yeah, B12, thyroid, vitamin D, that kind…

Marie Brown: So, it sounds like the psychiatric history is where it's most… or questionable psychiatric history or?

Lisa Silbert: Psychiatric history is a major confounder, yeah. That's, that's probably… for young and old patients that is… makes it difficult to tease out the history as to whether there's an actual neurodegenerative process. So, functional...

Marie Brown: OK.

Lisa Silbert: ...imaging can be helpful.

Marie Brown: OK.

Chris Standaert: For our vendor, do any of… you only have two studies on diagnostic accuracy of FDG-PET. Did they draw distinctions by age and psychiatric illness in their inclusion criteria? Did they include patients with those? Did they even mention that?

Robin Hashimoto: [inaudible]

Chris Standaert: OK.

Lisa Silbert: I'll say, I'll just add, I'm sorry to interrupt, but these PET studies, even if they aren't distinguishing Alzheimer's from FDG, I mean, from F… from frontotemporal dementia, they can at least indicate neuronal degeneration, in general. So, in that case it points to a neurodegenerative process regardless of the actual diagnosis, as opposed to some other non-neurodegenerative disease that's contributing to their cognitive decline. So, it may not just be distinguishing one from the other but identifying areas of neuronal loss or neuronal degeneration or neuronal dysfunction in someone who is declining in their cognitive status.

Chris Standaert: No, I hear what you're saying because I'm looking to see if there's some evidence that came forth that sort of says that they… that they looked to see that they… that they can do that, that it… in the data set that they would look through did they look at that question? Did they not look at that question? Do the studies include those patients who are not, do they draw a line and define them as such from our standpoint?

Michelle Simon: And that's something that you wouldn't pick up on a structural exam of any sort, correct?

Lisa Silbert: There's soft signs on structural exam. We do look for atrophy and atrophy is a sign of neuronal loss, and that's why most of the time we don't need functional imaging, because if we see that specifically, that gives us the answer, and then sometimes it, this is visual inspection, and sometimes it's not clear, particularly with older individuals. You do have atrophy.

Michelle Simon: OK.

Chris Standaert: So, I guess my question then would be, do we have data on the differentiation of neuronal degeneration from non, from not distinguishing people that have some sort of disease on the spectrum from those who don't at all, not just distinguishing within them?

Robin Hashimoto: Right, and that, that's the [inaudible].

Chris Standaert: OK.

Robin Hashimoto: Slide 18.

Marie Brown: Could you talk a little louder?

Robin Hashimoto: That's the diagnostic accuracy question for the… the context question, and that's slide 18.

Craig Blackmore: I'm hearing, I'm not hearing anything. Are there any other questions, or else I'm going to have us move on. Why don't we take a five minute, well, ten-minute break. I think Robin's looking up some things for us. So, we'll come back at… come back at 10:00 and proceed with our decision making.

I want to call the meeting back to order, if I could just get the committee members to take their seats, please. Alright, we'll call the meeting back to session here… back to order. Any other questions from the committee members that have come up in the break that they'd like to bring up at this point? Michelle, do you have a question?

Michelle Simon: Yeah, I had a question on slide 18, this is about the context question, and if we look at the clinical diagnosis alone, that third column in the FDG-PET versus the

third one down, which also has a comparison to clinical diagnosis, the sensitivity and specificity on those, shouldn't they be the same, I mean, for each other? Because we're still looking at dementia in the patient population is the same, and the only difference there is the size of the sample study and the specificity on the second one is 42% versus 88%. That just doesn't really make a lot of sense.

Kevin Walsh: The third row is looking at Lewy bodies.

Michelle Simon: But it's still dementia, right?

Kevin Walsh: They're two different...

Michelle Simon: They're different...

Kevin Walsh: ...that's the whole...

Robin Hashimoto: It's different studies and different...

Kevin Walsh: They're not just making a dementia diagnosis. They are trying to make it [inaudible] diagnosis.

Robin Hashimoto: Yeah, it's Lewy body.

Michelle Simon: OK, so with Lewy bodies we are not able to do any kind of... the specificity is a lot worse clinically than for that? So, is that we're assuming from this?

Robin Hashimoto: According to that study, yes.

Michelle Simon: OK. That helps, thank you.

Craig Blackmore: And then, Robin, were you working on some stuff for us?

Robin Hashimoto: Yeah, I'm reviewing the inclusion and exclusion criteria for some of the major studies.

Craig Blackmore: Any other questions? OK, well at this point we sort of transition to the decision-making process, and it has been useful to have one or more members of the committee sort of ground us, get us started, summarize where we are. Is there anybody who's willing to take a stab at that right now?

David McCulloch: Oh, I can say a few things, Craig. I mean, I… these are fascinating technologies, absolutely fascinating, and I'm an optimist. I can imagine sometime in the future when we have some specific treatments, biologics, or some new monoclonal antibody that can actually attack and change the process, at which time these may well come out to be... these are derivatives of the amyloid spectrum. I mean, it's a very fascinating field. That having been said, at this point to me, it seems absolutely clear that other than adding cost and adding

fascinating new data for researchers and people who work in this field, they don't add anything. I mean, I'm baffled by CMS's criteria and I suspect that it's influenced much more by politics and lobbying than by evidence, but I mean, I think the NIH should be sponsoring lots of studies, including these things. I assume they are. So, as a research tool I think they're incredibly valuable, but as a tool to help with management of patients, I don't… I haven't seen any evidence to…

Craig Blackmore: Does anybody want to respond, expand, contrast with that? Richard?

Richard Phillips: Yeah, I came here thinking I can't find any reason to cover this for any reason, except… and I've sort of been maybe alerted to the fact that maybe there are some cases where maybe permissions would be granted, or maybe we should be thinking of coverage under conditions but frankly, at this point, it doesn't seem to influence any of the treatments that are given to patients and therefore it seems to me it's very difficult to justify any coverage as a regular basis. At least that's where I come from.

Craig Blackmore: Carson, you had your hand up?

Carson Odegard: Yeah, I just think that, well… one of the things that I noticed in reading the report was that... one of the things that kind of gleaned and stuck out was one sentence that just summed it up that this was probably most appropriate for the… for that appropriate use, or for the most appropriate use. So, whatever… whatever that means, I don't know, but it… there was a sentence in there that… that stated that there are circumstances where this test would be appropriate, appropriately used, but it's kind of in conflict with what Medicare states because the… when you look at the Medicare coverage, it goes through a lot of… a lot of different requirements that really don't really address the population that it's used for. So, it's my understanding that it's used for mostly a younger population, and it doesn't address the Medicare population, as much. So, it's just interesting how they come up with all these requirements, three pages worth, that isn't used in their particular population.

Female: [inaudible]

Josh Morse: Can you make sure that microphone's on. Thank you.

Marie Brown: It doesn't sound like it.

Chris Standaert: Yeah, I mean, I'm struggling… I'm sort of where Richard was. I'm struggling with... how we could define this as applicable? I mean, I think the sensitivity and specificity stuff is interesting, and I think there are lots of diagnoses and medicine for which our tests are not 100% on either end by any means, and we certainly have sort of gestalt diagnoses where you sort of, you know, you kind of line your ducks up. You get a bunch of things, and I could see this being thought of in that spectrum. I thought of something like ankylosing spondylitis, you try to line your ducks up and then you do have a treatment. You have drugs you

can use that are... could be relatively toxic, even for people that don't have the disease, but they actually do modify the disease in the right person. So, there is some value to using tests that aren't perfect and using overlapping ranges of sensitivity and specificity to get to some relative certainty, but in the end game is either you don't have a treatment anyway that really would work that way or you really can't predict reliably enough to tell people how to plan their lives in one way or the other. You have to tell them... one way or the other, they have to live with the uncertainty that we don't really know, and if the tests don't really help you give them better certainty, as to whether they should know or not, I don't know that it really helps in the end, and it's still... that degree of uncertainty still lingers, and it doesn't really clarify it enough to any point that there is tremendous utility on it. I ask... when they... when they're looking for inclusions and exclusions stuff, I was just asking if there was some population that was excluded from the studies that was distinctive that clinicians had identified as we don't quite know what to do with these. They are different and then maybe our discussion wouldn't apply to them and that would leave you some out for the outliers, but if they're not even drawn out anywhere then I don't know how to do that.

Robin Hashimoto: Yeah, so there are a handful of studies that excluded patients with major psychiatric disorders or with major depression in terms of looking at the diagnostic accuracy. The majority of studies did not exclude on that basis. However, for key question two, those two studies that contribute to the moderate strength of evidence, that FDG-PET can predict progression from MCI to Alzheimer's or dementia. Those two studies did exclude patients with major psychiatric problems. Otherwise, I would say there weren't major exclusions in special populations.

Craig Blackmore: Other thoughts? OK, well I'm not hearing a lot of enthusiasm for cover without conditions. I see some nods of heads. We try to head down so that we have more of a binary choice, because it's hard to vote when you have three choices, and then this one, it seems like we're not heading towards a cover unconditionally. I'm looking for an opportunity for people to disagree with me. I'm not seeing it. So, then the… the two choices then become cover with conditions or not cover at all. So, what we've done in the past is talk about what conditions would look like if we wanted to cover with conditions, what would those look like and I think it's worth going through that exercise a little bit and it may be that that exercise informs our decision on its own. So, the question for the group then is, if we were to cover under some specific condition, what might that look like and let's see if there's some coalescence around something… if at all. So is there a committee member who would like to put forth kind of a straw dog hypothesis of this is what a condition might look like if we were to have one? Richard?

Richard Phillips: I have a question, more of an operational question, but is it… if you're only doing… if you're only 20 cases per year that are coming to the state, is it possible that just prior approval is an adequate way to drill this? Say noncoverage with prior approval only? Is that an option or should we... I guess

I was wondering if that's not a reasonable way to go versus just say covered with conditions. Is 20 too much... 20 cases per year too much for them to operationalize? I guess that's my question.

Craig Blackmore: I mean, I think it's a fair question because it's... obviously we're not doing this on most of the people and the system may not be broken in that sense. I think, you know, our job is not to just say do what you want to the agency directors but to provide them some guidance. So, I think it would be fine if we said there's a condition for coverage and had the expectation that they use preapproval or some process to determine eligibility under that condition, but I still think it's our responsibility to say what that might look like, but I agree with you. It not being used much so it may not be used inappropriately. I don't know. Joann?

Joann Elmore: I see no evidence from our review to justify coverage with any conditions. I see data showing the reliability is fair. I see data on 'accuracy' that these studies are biased and small. There is no data that has been presented to us that has been published showing that functional neuroimaging improves anything for the patient, to help the patient have a better life, to help the patient do better planning. These are important things. My father, at a very advanced stage, was demented. I wish that these were better, but I see no evidence that we have been presented with this morning in a very detailed evidence review that shows that there are any conditions in which it is justified, based upon the evidence. Theoretically, I can see why potentially CMS felt well, maybe with unusual case presentations a young person, you can't differentiate Alzheimer's disease from frontotemporal problems, but CMS may have made that decision, obviously, without any evidence, and I think we are supposed to weigh our decisions based upon scientific evidence, and I don't see... I wish that there was data showing it was helpful, but even the data trying to distinguish between Alzheimer's disease and frontotemporal dementia and I pulled a couple of the articles. They are small. They are biased, and they do not show it helps the patients. So, I'm not certain that there are any conditions in which we should consider.

Craig Blackmore: So, just procedurally, what... in the past we've gone through this exercise. It's come up a lot of times where we've... it's been clear we weren't going to do a complete coverage. It was going to be between no coverage and coverage with conditions, and we had a lot of discussion around what conditions might look like, and then we had an eventual vote and I'm trying to be consistent in that process. I'm not saying... I'm not pushing for coverage with conditions. I just want to make sure we discuss what the potential sort of options are for our decision making and then we can make a decision and then maybe there isn't that we need to talk about here, but I want to make sure we have a sort of parallel process to what we've done in the past, and then we have the opportunity to talk about these different scenarios. So, that's where I am, Richard.

Richard Phillips: The question about the... if we go to a noncoverage, do we not have to provide some kind of evidence, specific evidence to address the national coverage determination from Medicare... their decision to cover certain things?

Craig Blackmore: We have to state why we disagree and our disagreement might be that we looked at the evidence and there wasn't any and our charge is to make decisions based on evidence, or it might be we've identified some specific piece of evidence that contradicts. In this case, it would probably be that we simply looked at the evidence and there was nothing there to support, in our opinion, the current evidence. The best evidence didn't support that and so that's why we did what we did. We have to say why and it should be based on evidence, but it can be based on the absence of evidence, as well as sort of positive evidence.

Marie Brown: I mean, I think what we're talking about is diagnostic flexibility and the studies that we eliminated might have included more about differential diagnosis, about how it might assist with diagnostic accuracy.

Craig Blackmore: Well, I'm not… I mean, what studies did we eliminate that might have contributed to that?

Marie Brown: All studies who didn't have a postmortem component of diagnosis. I mean, I think the reason to build in cover with conditions is for clinical diagnostic flexibility but we don't have any studies that address that.

Craig Blackmore: Yeah. I mean, I think, you know, the one issue is there are these small number of unusual cases in which there is a perception that this tool might be useful, and I'm not pushing that. I just think we need to explicitly discuss it.

Michelle Simon: We have heard that, but we actually haven't seen any evidence in those populations that shows its efficacy. We heard from the clinical expert, though. So, that carries weight, for sure, but there isn't evidence, per se.

Chris Standaert: So, I guess my issue there is sort of, I don't… I have trouble finding someone to give me a condition to define, but at the same time, that question of if... there are other times where we've said, well, our coverage determination only applies within this scope. We say we don't cover, but we're not really addressing this particular question. So, if patients with severe psychiatric comorbidity are excluded from our studies, then that may be the subpopulation where the clinicians find it helpful. We could say, it's not covered but our decision doesn't apply to that group and they could then decide whether they want to do preauthorization for those… but that's not the population we looked at. If our external validity isn't such that we can say we looked at that population, we have trouble… we may have trouble, that'd be the only way I could see it.

Craig Blackmore: So I...

Chris Standaert: But I have trouble with any of the people studied. I don't see a condition to define. It's just [inaudible].

Kevin Walsh: Help me if I'm not understanding this correctly, but logically, if you've excluded people with other variables, and you're still not showing evidence that this helps, how is it going to help when you throw in more variables?

Chris Standaert: What do you mean, throw in more variables?

Kevin Walsh: Well, you've excluded the people with major psychiatric disease. So...

Chris Standaert: Mm-hmm.

Kevin Walsh: ...you don't have to try to distinguish them, you know, you don't have to make two diagnoses or try to tease this out of another diagnosis, right?

Chris Standaert: No, all I'm saying... I'm not even getting there. I'm just saying from an operational standpoint of coverages determination. So, if we...

Kevin Walsh: But I'm, I'm talking about the evidence. I'm still back at the evidence.

Chris Standaert: Right, but we don't have it yet.

Kevin Walsh: But logically to me, if you can't prove that this stuff helps when you don't have confounding variables, how could it possibly help when you do have confounding variables?

Marie Brown: It seems like if, though... if you had a population of just psychiatric patients and studied that, that would give you some...

Kevin Walsh: But these populations are cleaner than that.

Marie Brown: Well, some of them were...

Kevin Walsh: And they still can't show benefit.

Marie Brown: ...and some of them weren't.

Chris Standaert: Well, so that goes back to... so if you have a population that's relatively clean and you can establish a decent clinical diagnosis, this doesn't help much at all, but what about populations where you can't establish a clinical diagnosis because there are too many confounding factors to help you sort through it well enough.

Kevin Walsh: But it's not, but in those situations, in my experience, it's not either or, it's both and. It's not like they don't have psychiatric disease. It's do they have psychiatric disease and dementia?

Chris Standaert: That's the question.

Craig Blackmore: So, I'm looking for committee member or members to put forth what a potential condition might look like if there were to be one, and if I can't get anybody to vocalize one and get some coalescence around it then I'm going to go to a vote, but is there a member or members of the committee who think, yes this would be a condition under which coverage should be allowed, and there's a lot of potential things and there's a lot of limitations in the evidence but is there anybody who thinks… or are we all... if not, then we're going to go a vote and we know where it's going to end up, but again, I want to make sure we have an opportunity to discuss any proposed conditions, because that's the way we've done it in the past.

Marie Brown: Significant diagnostic uncertainty for something really general.

Craig Blackmore: Margaret, fire it up there. Significant whatever that was, significant...

Marie Brown: Diagnostic uncertainty.

Craig Blackmore: ...diagnostic uncertainty.

Marie Brown: I'm thinking about what our clinical expert said. I realize that's a long shot.

David McCulloch: Yeah, it's a really big bucket.

Craig Blackmore: Any other… any other besides significant diagnostic uncertainty? Any other conditions where committee members believe there might be evidence that would support the use of this?

Michelle Simon: I think frankly I'm leaning towards no cover, but if we're having this exercise...

Craig Blackmore: I think we have to have this exercise.

Michelle Simon: I would say someone with atypical features, either young onset age, early onset, rapid progression, and possible mixed diagnoses.

Craig Blackmore: OK.

Michelle Simon: Overlapping diagnoses.

Craig Blackmore: So, similar to what is in the Medicare criteria.

Chris Standaert: Mm-hmm.

Craig Blackmore: OK, so I think we've already had discussion around this. Is there any more discussion around these in terms of what the evidence tells us about leads...

Michelle Simon: Rapid progression?

Craig Blackmore: ...and research? I mean, we've heard from Joanna who doesn't think there's evidence at all, and I think there's a lot of…

Richard Phillips: It seems to me the only thing that… I don't know how you would define this in there but the only thing that would make a difference to me is if it's going to change the treatment. In other words, is it going to put somebody into a different kind of rehab facility or something like that? Does it make a difference?

Craig Blackmore: So, how are we going to operationalize that?

Richard Phillips: Yeah, that's... that's my problem. I don't know that... it's almost as if... it has to be a clinical decision by the doc, and I don't know... that's a dangerous thing to leave into a guideline.

Michelle Simon: Well, I think it would, perhaps, change treatment if you put somebody on, say, a cholinesterase inhibitor earlier than they might have otherwise been diagnosed.

Chris Standaert: I mean, I would think… I would think if you could distinguish significant psychiatric illness only from concurrent dementia, you might approach those people differently, because you know you'd be treating a more isolated psychiatric illness, but I don't... I don't have any data to say that at all. I'm just saying that may be excluded from the scope of what we looked at. You're shaking your head. I mean, you can explain why that wouldn't make a difference.

Seth Schwartz: Because there's no data to support it.

Chris Standaert: I know, I know, but the thing is, we didn't look at that. That's what I'm saying, it's...

Seth Schwartz: Well, but all... but all we can vote on...

Chris Standaert: ...it's limited.

Seth Schwartz: ...is what we look at.

Chris Standaert: Right, I know.

Seth Schwartz: All we can vote on is what we're given.

Craig Blackmore: Yeah, and I mean, that was included in the literature review. It wasn't that Spectrum excluded it. It was excluded from the studies that Spectrum found. It was excluded by the researchers. So, if that literature existed, we would have had it. It's just that it doesn't exist.

Michelle Simon: Good point.

Marie Brown: Well, I thought you said it was excluded from several of the studies but several of the studies it was not excluded.

Robin Hashimoto: The psychiatric disorders? That's correct. Right, we did not exclude it. So, it was the specific studies.

Craig Blackmore: So, we have that literature. It's just, you know.

Kevin Walsh: And the… and in the studies that were done that included psychiatric diagnoses, you can safely assume that if they'd been able to tease out a difference, we would have seen it, because studies are always looking for stuff you can publish, so they have to show a difference. So, there was probably no difference.

Robin Hashimoto: The studies were also small, so you'd be less likely to see something real.

Craig Blackmore: OK. Would you say that significant diagnostic uncertainty was captured under the atypical features?

Marie Brown: Yes.

Craig Blackmore: So, let's get rid of significant diagnostic uncertainty.

Richard Phillips: Let me ask a question, because I... I'm trying to get myself around the... would a patient with amyloid features, which we're not really making a decision on, would they present with something like this? Could they...

Lisa Silbert: Someone who has amyloid deposition, for the most part, is going to present, typically like Alzheimer's but there are a subset of Alzheimer's patients who are atypical. So, it wouldn't help distinguish. Let me rephrase that. It would help identify Alzheimer's disease as the etiology, yes, in an atypical patient if the scan was positive.

Craig Blackmore: But the tests we're talking about aren't able to identify the presence of...

Richard Phillips: Exactly.

Craig Blackmore: ...amyloid.

Richard Phillips: Well, I'm trying to figure out...

Craig Blackmore: That's a different type of test.

Richard Phillips: ...what our denominator pool is, and I... that's the problem I'm having. I really tend to agree with your point of view.

David McCulloch: At this point, we don't have a specific treatment to reverse amyloid deposition. I mean, the same parallel happened… type 2 diabetes. You can show amyloid...

progressive amyloid deposition in the beta cells of the pancreas. I'm damn sure we can do an amyloid SPECT scan or some other scan and actually document that and quantify it and follow it annually over time. It doesn't change, at this point, it doesn't change anything we do. So, as I say, I think these are fascinating technologies, but I don't think it should be how we spend... how the state should be spending its dollars. Sort of thinking, well, you know what, it'd be kind of interesting to know more information in diagnostic uncertainty and being tested. It'd be really cool. Well, we should just cover them. I mean, that...

Richard Phillips: Well, I agree with what you're saying.

Richard Phillips: If it doesn't influence treatment, then it's hard to justify doing it, and I guess that's where I'm coming from. I'm trying to dissect that out in the denominator that we have there. How do we define the groups that might be of concern?

Chris Standaert: In our statement it doesn't only apply to the tests they looked at that were set up in the key questions. So, I don't know if, like Dr. Franklin said, the newer test looking for amyloid wasn't part of the scope of what they were looking for. So, our statement does not apply to that. It applies to the five tests they specified in the key questions.

Kevin Walsh: And in terms of this condition, I don't remember seeing any studies that tried to look at people who presented with atypical features to support the notion that doing these tests makes any difference. So this, in my mind, this condition is total supposition.

Craig Blackmore: OK. Any other comments before we move on? OK, so we'll turn to our decision-making tool. It is in your packets, and you've seen this all before and this tool has a lot of text about how we make our decisions and also contains some information for discussion and one of the things it talks about is the outcomes that the committee considered in their decision-making process in the Health Technology Assessment staff have prepopulated this with outcomes we considered. I ask you all to turn to page three of your document and safety outcomes listed, injection-related harms, missed false diagnoses, are there other safety outcomes that we're concerned about? I guess radiation would have to be included as a safety outcome that we would consider, since most of these tests involve radiation. Efficacy, effectiveness outcomes, sensitivity, specificity, disease progression are the things we talked about. Are there other clinical outcomes that we were concerned about? We talked about potentially providing counseling, prognostic information for families, caregivers, as well as patients themselves, as something we considered as important to outcomes. Special populations, we talked about, and then cost. We are also charged with looking at how our decision-making corresponds specifically with Medicare national coverage decisions. We also look at local coverage decisions. We look at what other payers do. We have had a lot of discussion about that, particularly about the Medicare National Coverage Decision, which, I understand, was based on HRQ data review back in 2002, and that's one of the

considerations for our decision making. There are a bunch of clinical guidelines that we've heard summarized and eventually I will get to the actual decision-making part of this document. Here it is, and then we proceed with the decision-making process. It's a two-step process. First, we have our yellow cards, which are nonbinding votes, an opportunity for the committee members to give their perspective on where they are in terms of safety, effectiveness, and cost-effectiveness and that might guide us to our final decision or it might put us in a position to have more discussion.

So, I'd like to proceed now with the first voting question, nonbinding. Is there sufficient evidence under some or all situations that the technology is, and we'll start with effective. So, this would be... well, I guess I need to back up. I need to say, are we going to discuss them each individually, each of these technologies, or are we going to lump them, and I think our discussion has been pretty lumped, and I'm going to go with sort of considering them all as a group, unless I see us nodding otherwise. OK, so we'll keep it all together. So, you'll be voting whether you believe that any or all of these technologies are more… if the evidence tells you that they are more effective than clinical exam and standard structural imaging, less effective, equivalent, or unproven. So, that's the first vote.

Josh Morse: Ten unproven.

Craig Blackmore: Well, that was easy. Are they safe?

Josh Morse: Six unproven, three less, one equivalent.

Craig Blackmore: And then cost-effective?

Josh Morse: Nine unproven, one less.

Craig Blackmore: So, based on those votes if you will, is there… is there other discussion, any further points anybody wants to raise? OK, then we'll proceed with our second vote, which is whether we are covered, not covered, or covered under certain conditions, and the condition that we have specified, should we vote that way, would be atypical features, early onset overlapping diagnosis and rapid progression are listed, and I'll say that we can wordsmith that a little more if we need to after the vote, but let's see how the vote goes first. Is that OK with everybody, or do we need to see a final? OK. So, cover, no cover, or cover with conditions?

Josh Morse: Ten no cover.

Craig Blackmore: So, how does that compare with the Medicare decision and… well we are mostly in agreement with the Medicare, but the piece that we didn't agree with them was around their limitation of coverage for patients who met the diagnostic criteria for both Alzheimer's and I think it was Lewy body dementia, and the committee had a lot of discussion about the evidence just simply not being

there to show us that there would be some improvement in outcome or even really good diagnostic efficacy information in that circumstance, and I think that barring somebody else giving other input that that is why the committee went in that direction, and do I need anything else?

Josh Morse: If you could comment on the professional society guidelines, the differences.

Craig Blackmore: So, again there were a lot of professional society guidelines, and there's a lot of professional society guidelines, and I think the same... the same issue held as we went through the discussion, and that's really... there's a lot of ways you can hypothesize how this might be useful, but the committee is charged with acting on the best evidence and we, as a committee, did not see any real data that showed us that there was an improvement in the things that we thought were important, which were clinical outcome, even changes in treatment or some other family caregiver-related improvement. So, we recognized potential for use of it under some of the conditions that were specified in these guidelines, but we didn't see evidence to show that that was really demonstrated at this point. Is that a fair summary?

Josh Morse: Thank you.

Craig Blackmore: Alright, we move on, and we're a little bit ahead of schedule, which is good. So, do we... so because we're ahead of schedule, I think we need to think a little bit about the agenda. We have an open public comment period scheduled for 1:15. It is always good to try to keep that as close as possible so that when people have an expectation of being able to address the committee in that timeframe, and we don't want to... we don't want them to lose that opportunity. However, we also have a lot of time before lunch. So, I think we should get started. So, why don't we start with the agency utilizations and outcomes. Do you have your team here to do that? Yeah, OK. So, let's move on with appropriate imaging for breast cancer in special populations.

Daniel Lessler: Good morning. For the record, I'm Dan Lessler. I'm the chief medical officer at the Health Care Authority and I was going to talk with you today about the agency medical director's recommendations around appropriate imaging for breast cancer screening in special populations.

First, just by way of background, so breast cancer… I think as people know, is the most common form of cancer in women and really mammography is the mainstay of screening for breast cancer. Since 1990, the overall rate of mortality from breast cancer has declined by 28% and while there is some controversy, I think the general statement that somewhat less than half of the decline is due to early diagnosis with screening mammography. I would also mention that the recommended age and frequency of screening for mammography varies across differing organizations. So, as it turns out, women who have increased breast density both have an increased risk of breast cancer and the sensitivity of mammography, screening mammography, in those women is less in terms of its ability to detect small lesions, and it's estimated

that about 50% of women have dense breasts. Digital mammography, at this point, really is the standard across the United States for screening mammography and is more sensitive than film for imaging of dense breasts. Finally, the most important harms of mammography, in terms of mammography screening, are false-positive results and the potential for over diagnosis.

So, as I thought about this and, you know, as a clinician in terms of attributes, desirable attributes of new approaches to screening mammography, what I thought about were really these three key points that ideally one would like to decrease false positives, since that is one of the potential harms, increase cancer detection; however, with the caveat that it's hard to know if you're over diagnosing in terms of whether or not you're finding cancers at a point in time that it really... anything you do wouldn't really affect ultimately the outcome, and that you want to find approaches that area reasonably cost-effective.

So, with that in mind, what we're going to look at are new approaches to breast cancer screening, and I do want to underscore here that we're talking about screening and not follow-up diagnostic studies of any sort. So, all the new approaches we're talking about are in the context of screening. I think that's… that's just very important to keep in mind.

So, first digital breast tomosynthesis or DBT is a relatively newer way of imaging that creates a 3D image of the breast and essentially allows, in some cases, a clearer picture, a better picture and definition, particularly of small lesions. It's approved by the FDA in the United States for screening and earlier, meaning... what I should say is, at this point, DBT does not, in fact, expose a woman to increased radiation because the way this is typically done now is there is a digital image that's created, and it can be reconstructed in... as 3D or as more traditional 2-dimensional imaging.

There are supplemental modalities. Again, this is in the context of screening that we're looking at today. MRI, magnetic resonance imaging, handheld ultrasound, and automated whole breast ultrasound.

With respect to the agency medical directors' concerns here, concerns for safety were low, but concerns for efficacy were high, as were concerns for cost.

The key questions that were asked to consider today, first has to do with the effectiveness of DBT as… versus digital mammography for screening, second is the comparative effectiveness of handheld ultrasonography, automated ultrasonography, and MRI imaging when used as a supplemental modality to screen women with dense breasts relative to standard digital mammography and then looking at potential harms of these tests and differential effectiveness and safety in special populations, and finally, cost and cost-effectiveness.

So, this shows current... sort of the current state agency policy, but there is one. I'm going to turn to Suzanne, one correction, I think, which was on breast ultrasound in the UMP population is... does not require prior authorization for...

in screening. OK. This is screening, not diagnostic. It's not... at this point, prior authorization is not required.

So, I'm going to walk through here, just sort of current utilization. This is all mammograms over the last few years. I would note that you see that change between 2010/2011. That is actually when there was a transition from UMP into Regence and to be quite frank, I don't have an explanation for the decrement except that they're differing data sources, etc., and this is all mammograms. This would be screening and diagnostic mammograms across Medicaid and the PEBB/UMP population. This actually is an interesting slide, which shows the use of DBT in these two populations and actually you can see that in relative terms it has increased quite a bit in both the PEBB/UMP population and the Medicaid population.

This is MRIs and again, this would be MRIs across the board for... so this would be high risk. This would be in all situations for screening and diagnostic for women across PEBB and Medicaid populations, just to give people a sense, you know, I think of... generally, of the volumes that we're looking at in these populations.

Then, finally this is breast ultrasound. Again, this would not just be screening. This would be screening and diagnostic and I think the data just gives people a sense of the order of magnitude with which these tests are done more generally.

So, the way I thought about this is really to begin with these supplemental strategies and DBT, their commonalities in terms of uncertainties and in terms of harms. So, I've... what I've done is presented these initially and then we'll take the… talk about the specific screening modalities. So, first is that for all technologies under consideration, sufficient follow-up data is lacking to estimate sensitivity and specificity, I think an important point, and there are no data on more definitive outcomes of morbidity and mortality. In the case of MRI and handheld ultrasound studies have been done in high-risk populations that happen to include women with dense breast tissue, but have not been done exclusively on women with dense breast tissue. So, the results are not specific to women with dense breast tissue only. There is very limited data on automated breast ultrasound and the study populations pretty much across the board are heterogeneous and so there is... there's no way to really pull together data and take a meta-analytic approach.

In terms of harms, obviously there's potential harm just in terms of false positive results affecting psychologic well-being and then there is the risk that a woman will go on... in a case of a false-positive will go on to further diagnostic workup and end up getting a biopsy that is a negative biopsy and is obviously subject to the risks thereof in terms of bleeding and infection and so forth. As I mentioned, at this point, my understanding is that the radiation exposure from DBT is now thought to be comparable to digital mammography. So, there really doesn't seem to be an incremental risk in that case.

What I want to do now is I'm going to actually summarize just in using tables such as this for DBT, as well as for automated breast ultrasound, handheld ultrasound and I think my... the recommendations of the MDG are... I'm going to reserve to the very end of the presentation. So, this is a summary slide on digital breast tomosynthesis, and this is comparing digital mammography to DBT plus digital mammography and then, as you can see, there's the level of certainty or uncertainty in terms of these estimates. In general, it looks like the recall rates are relatively similar per 1000. The biopsy rates, although there is moderate to high uncertainty around that, the biopsy rates look to be roughly similar. Cancer detection appears a bit higher in the DBT population. So, going from three to five per thousand to four to six, but again, there's a fair degree of uncertainty around those estimates and finally, on the other hand, there appears to be better evidence, or firmer evidence, that those women that do get biopsied have a higher chance of actually having a positive biopsy result, so called PPV3.

As we looked at this, we... and in summary, we think of DBT as a promising but really yet unproven approach to screening mammography and with available studies being generally of poor quality and questions remaining regarding rates of recall biopsy and cancer detection, as well as test sensitivity and specificity, the available economic modeling would suggest that there's a possibility of a small benefit, but this likely comes with substantial additional costs.

David McCulloch: Dan, not to…?

Daniel Lessler: Yeah.

David McCulloch: I mean, maybe we'll get some of that... nothing you've shown me shows any potential small benefit.

Daniel Lessler: Well, yeah. I mean...

Craig Blackmore: His job is not to summarize the evidence. We'll get to that.

David McCulloch: Well, but I mean, he's making a value judgment. He's saying that it suggests small...

Daniel Lessler: So, so...

David McCulloch: ...benefit. I have yet to see it.

Daniel Lessler: ...yeah, well, I mean, you know, I think reasonable people might disagree on this and you guys are going to have this conversation, but the reason we've made that statement is really the last two lines in terms of the matrix. It doesn't...

David McCulloch: They completely overlap. They overlap more than 50%.

Daniel Lessler: Right.

David McCulloch: Three to five, four to six, 20 to 25, I mean...

Daniel Lessler: OK, I said suggest possible.

David McCulloch: OK.

Daniel Lessler: So, with respect to reimbursement, I would say that in general both from the sampling that we have, you know, national payers, regional payers, do not typically cover DBT at this point. Now, we... actually, so this is an updated slide, and I want people to be aware of this, because since sort of preparing this presentation there have been… there have been some changes and I'm just going to lay this out exactly as it is stated here. It is… which is to say there are no published national or local coverage determinations with respect to Medicare for DBT; however, on December 16th, CMS did establish a payment rate for a newly created CPT code, which is for DBT mammography and according to CMS, effective January 1st of this year, so just two weeks ago, contractors shall allow payments for this code and it can only be billed when this is done in conjunction with digital mammography and Meridian, which is the regional carrier for Medicare, has published the same language and effective date.

Chris Standaert: Dan, just to be clear, for those of us who are [inaudible] impaired, G0202 is digital mammography?

Daniel Lessler: Yes.

Chris Standaert: OK.

Daniel Lessler: Yeah, that's my understanding.

Craig Blackmore: So, I'm a simple guy. What does this mean? It means that locally it's now covered, is that... but only with a digital mammogram?

Daniel Lessler: Right, so you… it needs to… and the idea here is that...

Craig Blackmore: I'm [inaudible].

Daniel Lessler: ...you're a radiologist.

Craig Blackmore: Uh, I don't do breast imaging procedures, but I am a radiologist.

Daniel Lessler: And there are other people with great expertise in the room, but the assumption is that you're using a machine that both creates the 3D image and the 2D image and so it's... what they don't want, I would assume, is that somebody does a 2D image and then does a separate imaging to create the 3D image so the...

Craig Blackmore: So, it's billed as one procedure?

Daniel Lessler: So, it's billed as one procedure, yeah.

Michael Souter: Just to follow on from what you were saying, Craig, just for making the point of simplicity. There's a payment code.

Daniel Lessler: Yeah.

Michael Souter: But that doesn't mean that there's actually a coverage determination.

Female: There is though.

Daniel Lessler: So...

Michael Souter: I mean, if you got a bill for this tomorrow, would you pay it?

Daniel Lessler: Well, Medicare would, yeah. Medicare would pay it.

Joann Elmore: 57 extra dollars.

Daniel Lessler: Right.

Joann Elmore: They pay for the baseline screening digital exam and then if you add on this code they will pay an additional 57 dollars.

Daniel Lessler: Right. That's right. So, I'm going to just move on with the supplemental... other supplemental screening modalities here, and note that the… this is a slightly different data element. We're talking about digital. In this case, we're looking at MRI, and we're talking about digital mammography and then we have... this is not a direct comparison. This is the incremental yield with MRI that we're looking at. So, it's a little bit different than the previous display of data and you can see here that, again, there is a high level of uncertainty across the board with respect to these. That said, with respect to the recall rate, there would be some increase in the recall rate and some increased incremental digital mammography in the biopsy rate but likewise a considerable increment in terms of detection rate of cancers and of biopsies being positive amongst those women who actually go to biopsy but again, there are very high levels of uncertainty and the... I think one of the core issues here is the heterogeneity in the populations that have been studied with MRI are not just women with dense breasts, but it's women with dense breasts and then also there are women with other risk factors to put them at higher risk for breast cancer. So, it's difficult to tease out the relative value in women with dense breasts alone. This data is presented similar to the MRI data. This is the supplemental... this is for supplemental screening with handheld ultrasound and again, you can see the recall rate. This would be incremental to digital mammography. So, there would be 30 to 100 estimated additional women recalled. The uncertainty of

this estimate is high. Biopsy rate would go up, but there would possibly be some increase in the cancer detection rate and I would note here actually there would be a decrease in the positive biopsy rate among total women biopsied, and obviously that begins to factor into when you start thinking about cost-effectiveness here. That plays a big factor, because you're going to have a lot of additional cost for no real yield. I would say, and the AMDG concluded, that for automated whole breast ultrasound, there just... the same data is... or the data is presented in the same way as for the two previous modalities, but the uncertainty is very high and really difficult to reach any conclusion whatsoever, we would argue.

So, in summary with respect to supplemental screening, MRI has limited evidence in women with dense breasts... dense breast tissue but who are otherwise at low risk with a high relative cost. With respect to handheld ultrasound, there is inconclusive evidence across multiple studies, especially with respect to recall rates and cancer detection rates and handheld ultrasound as an adjunct to screening mammography in women with dense breasts made modestly increased cancer detection but it increases the risk of false positive findings leading to additional breast biopsies and we think there really is inadequate evidence with respect to automated ultrasound to really comment.

Available economic modeling is limited. Available modeling for MRI and handheld ultrasound suggests a possible small benefit with substantial additional cost and the benefit would likely be greatest in women with dense breast tissue who have additional risk factors, as well.

This is data on third-party coverage for supplemental studies for breast ultrasound and breast MRI and there is no information from Health Net, Premera, or Regence and in the case of Cigna, Humana, United Healthcare consider breast ultrasound experimental for any type of screening here. So, again, we're just talking about screening. With respect to breast MRI, Humana and United Healthcare cover breast MRIs and adjunct mammography when heterogeneous or extremely dense breast tissue is identified. Aetna, UniCare, WellPoint/Anthem cover it as an adjunct in women with dense breasts and a personal history of breast cancer. So, those would be people with other risk factors in addition to dense breasts.

There is no coverage decision with respect to the use of breast ultrasound for screening mammography and likewise for breast MRI as a screening modality in breast cancer screening. So, these are the state agency recommendations. Based on that would be for digital breast tomography noncoverage, MRI noncoverage, handheld ultrasound noncoverage, and automated breast ultrasound noncoverage.

Chris Standaert: So, I have some questions on semantics here. So, when I... first of all, the topic it said breast cancer screening for special populations, and I envisioned dense breast tissue. I envisioned genetic markers. I envisioned prior surgery. I envisioned other anatomic things. That isn't what we're talking about.

Daniel Lessler: We're talking about dense related...

Chris Standaert: No, I mean, you have two totally separate issues. You have DBT...

Daniel Lessler: Right.

Chris Standaert: ...by itself.

Daniel Lessler: Right.

Chris Standaert: Which has nothing to do with special populations.

Daniel Lessler: Right, right. That's...

Chris Standaert: [inaudible].

Daniel Lessler: ...right. Yeah.

Chris Standaert: That has nothing to do with the title of what you guys wanted.

Daniel Lessler: Yeah.

Chris Standaert: Which... I'm just making sure that's what we're talking about, and then even for special populations, it looks like we're talking about supplemental screening in women with dense breast tissue.

Daniel Lessler: Right.

Chris Standaert: That seems to be the focus of it, and then even within that, you talk about MRI, but we made a decision on breast MRI before, and I don't know how you see this interacting with that, I mean, I'd be very uncomfortable using this data set to change our prior decision on coverage of breast MRI, because we had an entire report on that one topic.

Daniel Lessler: Yes, so...

Chris Standaert: ...and so to use this as a supplemental, I mean, we're going to be in... are we going to be in conflict with ourselves, or we... how, we can't... I don't think we can supplant...

Craig Blackmore: No, we're...

Chris Standaert: ...our prior decision on breast MRI.

Craig Blackmore: We're not...

Chris Standaert: So...

Craig Blackmore: ...we're not going to supplant our prior decision on breast MRI. So, this... the prior decision on breast MRI was that we would cover it in women who have… who are at high risk and we defined high risk explicitly in the decision. So, those women are not a part of our consideration for the discussion today. The discussion today is about women who, at least the MR discussion, is about women who don't qualify for MR because they are at high risk.

Chris Standaert: OK.

Craig Blackmore: So, they would be women who are… specifically have dense breasts, and we are excluding the women with dense breasts who are high risk for other reasons, because they are covered under the prior decision. So, when we talk about MR, it's the women who have dense breasts but are not at high risk by other groups.

Chris Standaert: So, as we talk about it, so we're...

Craig Blackmore: So, not the...

Chris Standaert: ...talking about simply supplemental screening for women with dense breast tissue then application of these modalities absent consideration of other risk factors.

Craig Blackmore: Well, we never talked about... we never looked at ultrasound...

Chris Standaert: No, no, no...

Craig Blackmore: ...in any form.

Chris Standaert: ...no, I know.

Craig Blackmore: So when we talk about ultrasound we would be including women with dense breast at high risk and women with dense breast not at high risk.

Chris Standaert: Whatever the literature found.

Craig Blackmore: We have never...

Chris Standaert: OK.

Craig Blackmore: ...explicitly looked at that, but really our purpose is to look at dense breasts as a sole indicator of high risk, or dense breasts who do not have these other factors that would put them at a greater than 20% risk on the Gail model. It's a little convoluted, but it's important, and that's why this idea of the literature that exists on MR might include high risk women so that's not exactly the population that we're deciding on. The population we're deciding on is high-risk, sorry, high breast density but not otherwise at high risk. So, we have to figure out how that evidence applies to our group, which is a little bit different.

Marie Brown: So, I assumed our special population was women with dense breasts.

Daniel Lessler: Right, that's...

Marie Brown: OK.

Daniel Lessler: ...that's...

Craig Blackmore: But that's... for the ultrasound MRI question, that's not for the DBT question, which is all women who are getting screened. Richard?

Richard Phillips: I have a question about the definition of screening. An example is, if you get somebody to bring in, and they get recalled and they get attached another test because of their recall or something of that nature, at what point does the screening become a special, a nonscreening interest? And I'm having a little bit of trouble... you know, do they actually follow up in...

Craig Blackmore: So...

Richard Phillips: ...three months, is that a nonscreening?

Craig Blackmore: ...we are specifically asked to look at screening, I believe, effectiveness of screening. So, that would mean imaging that is done based on some time schedule rather than on some anatomic finding. So, if you see something on a screening test and you work it up with an MR or whatever, that's not a screening examination. A screening examination would be, I look at you. I don't look at your imaging, I look at you, and I say you're a woman of a certain age, we should do this test. It's not...

Richard Phillips: I see.

Craig Blackmore: ...you have a lump? It's not you have some other symptom. It's not you have a finding on another imaging study. It's, you are otherwise asymptomatic, not known to have disease, and we're going to do this test.

Richard Phillips: But somewhere in the implementation, somebody's coming, it's going to be interpreted as a screening no matter what.

Craig Blackmore: No, there's codes. There's different codes.

Chris Standaert: So, these are for...

Craig Blackmore: That's are established. These guys do that now for everything, for MR and follow-up mammograms and everything else.

Chris Standaert: So this population would be women with dense breasts on... who on standard mammogram… it's a relatively nondiagnostic study.

Craig Blackmore: Well, it's not a nondiagnostic study.

Chris Standaert: It's a...

Craig Blackmore: It can be a perfectly valid diagnostic study, but the mammogram has the ability to say your breasts are dense or not dense.

Chris Standaert: ...right.

Craig Blackmore: And so, it's a mammogram finding that equates with high risk, which we'll hear about how much high risk and how strong that evidence is, I think, and it equates with some decrease in the performance of the mammogram, at least that's...

Chris Standaert: Right, it is then coupled to...

Craig Blackmore: ...we, again...

Chris Standaert: ...some other tool to supplement the screening to make it a more [inaudible]...

Craig Blackmore: ...so the question is, if you've got women who are at slightly higher risk and in whom the mammogram may not perform as well, and again, I'm summarizing the problem not summarizing the evidence, is there value to adding another study as a screening tool, ultrasound, ABUS, MRI, whatever it is. So, it's a... it's a huge issue but our focus is actually very narrow.

David McCulloch: That's very helpful Craig. So, just... since this is not my field, clarify for me. So, let's say a woman... routine screening, gets a digital mammogram and it comes back with an equivocal finding, not sure what I see in the upper left quadrant, I'd like to bring her back and do a "fill in the blank".

Craig Blackmore: That is no longer screening.

David McCulloch: OK.

Craig Blackmore: That is diagnosis. Are you our clinical expert?

Christoph Lee: I'm Christoph from the University of Washington [inaudible]. Screening is for asymptomatic patients. Once they have a lump, they go into the diagnostic realm.

Craig Blackmore: OK. So, back up, welcome. If you could introduce yourself, which you just did, which is great.

Josh Morse: Turn the microphone on.

Craig Blackmore: Turn your microphone on. The way this works is, we have a clinical expert here because we're not breast imagers. We are clinicians, and we're evidence-based medicine people, but we don't have specific expertise in this field. So, we're very glad you're here. We will not ask you to make a specific presentation, but we will have tons of questions, and we'll let you know. So, here we go. So, anyway, that's kind of scope, and this one is a little tricky. So, that does make sense to people, the question we're asking? OK.

David McCulloch: Yes, but before I forget the train of thought, another question.

Craig Blackmore: Yeah, go ahead.

David McCulloch: So, I like what you said, but you said, now as soon as the woman's got a lump, then it becomes diagnostic. No, she doesn't have a lump, she has some vague shadow on an image.

Christoph Lee: So, either a symptom or a finding. So, once a symptom or a finding is present.

David McCulloch: Right, that's not a lump.

Christoph Lee: Correct.

Craig Blackmore: However, dense breast is a finding on a mammogram, but it might trigger more screening. You wouldn't go get additional views just because you had... clarify if I'm wrong.

Christoph Lee: An abnormal finding, an abnormal finding. So...

Craig Blackmore: OK.

Christoph Lee: ...dense breast is a normal...

Craig Blackmore: Normal.

Christoph Lee: ...finding.

Chris Standaert: Normal. Alright, OK.

Craig Blackmore: Good point, OK. So, any specific questions for Dr. Lessler about the agency?

Michelle Simon: Yeah, usually we see the utilization data, but there's no cost data here. I'm just curious if you could maybe talk a little bit about that, incremental costs for DBT or what things are running?

Daniel Lessler: So, do you know what the... what we're paying for a screening mammogram right now?

Female: No, I don't know right off the top of my head.

Daniel Lessler: A screening mammogram is about $135, digital mammogram.

Michelle Simon: And then the DBT would be... I hear it's being paid...

Christoph Lee: $56.57.

Michelle Simon: ...at $57.

Daniel Lessler: $57 I think is what Medicare, yeah.

Joann Elmore: And approximately how many screening mammograms are covered, about 100,000 per year? The reason why I'm sort of thinking of it at the population level, if it's $57 a pop to add on an extra tomo, that would be $5.7 million per year extra.

Suzanne Swadener: I'm not sure that I can pop it off the top of my head, but what I could say is, we'd have to kind of separate it out, our Medicare population and our non-Medicare population.

Suzanne Swadener: Exactly, yeah, because we were lumping them all together and I'm thinking, I think a little bit of [inaudible].

Josh Morse: Suzanne, can you please use the microphone? Thank you.

Suzanne Swadener: So, my name is Suzanne Swadener. I am the PEBB clinical program manager nurse consultant and I work with Dr. Lessler to assist in managing the UMP and the other PEBB programs. I don't have a specific number right off the top of my head to provide to you, I'm very sorry, regarding utilization annually. What I can... what we were discussing earlier is the need to kind of separate out our non-Medicare population from our Medicare population because of screening rules around age. When we looked at this data, I think we looked at this and saw that if we made a gross assumption that about 200,000 folks are in UMP. In any given year about a third of those are in retirement age, so pop that down to about say 70,000. Half of those are women. We don't see women coming exactly every year, so we're probably talking on the average of 30,000 to 50,000 women in any given year.

Craig Blackmore: Thanks. OK, any other question for the agency? OK, we are... we're still well ahead of schedule, but I see Dan has arrived. Are you ready to go an hour early here or not?

Daniel Ollendorf: We're ready to go.

Craig Blackmore: Alright.

Daniel Ollendorf: My question for Josh is, does that mean I have more time to present now?

Craig Blackmore: You know, I think if you need more time to present it, that probably would be a good use of the committee's time. So, why don't... again, I'm going to... usually at this point we would have the public comment but I think we should try to push that back closer to where the window is on the agenda to be fair to the people that would wish to present to the committee. So, yeah, if we can go ahead with our vendor.

Josh Morse: We did move lunch ahead.

Craig Blackmore: OK, and when's lunch.

Josh Morse: In about 20 minutes.

Craig Blackmore: Lunch is in 20 minutes.

Josh Morse: Yeah.

Craig Blackmore: Can you give us part one for 20 minutes?

Daniel Ollendorf: I can do that.

Craig Blackmore: OK.

Daniel Ollendorf: OK, so thank you for having me today. I'm wondering if you're asking all presenters to start off by saying Go Hawks? I'm from Boston, so I have to say that with a little bit of trepidation. So, we're going to be talking about appropriate imaging for breast cancer screening in special populations today. We'll review the scope and, in all likelihood, we'll talk about the scope and the setup of the review before we break for lunch. We'll break for lunch, and then we'll get into the findings.

I'll also talk about the status of breast density legislation, an important component of this review both here and nationwide, and we'll go over the systematic review of the evidence as well as our comparative value analysis and analyses done by others, including Dr. Lee, our clinical expert, and time permitting, we'll go over the evidence ratings that ICER produces as part of its reviews, summarize payer coverage policies and clinical guidelines.

So, just a bit of background. I'm sure it's not news to all of you, breast cancer is the most common form of cancer found in women, so a very common cancer in general, as well. It results in about 40,000 deaths annually; however, mortality has been in decline for the past 25 years, and most analyses suggest that about half of this decline is due to early detection from mammography and about half from improvements in breast cancer therapy. There are certainly other opinions on both sides of the fence, however, as to what the relative contribution of each has been.

So, those benefits of screening mammography were established in nine RCTs of over 600,000 women who were followed for 10 to 20 years and demonstrated 20-25% reductions in mortality after 15 years of follow-up in women aged 50 to 69. So, you've probably also heard about the controversy about screening women who are younger than 50, and that is, in part, because these women were not studied in these RCTs.

In terms of evolution of the technology itself, film mammography, film screening mammography, was replaced, essentially, by digital technology in the mid 2000s, and this was done to improve the precision of the image, as well as contrast resolution, in particular, in women with dense breast tissue. We're going to be talking a lot about women with dense breast tissue, as we move through this presentation.

The next evolution, after digital mammography, is a very recent one. It is digital breast tomosynthesis, which is also described by some as 3D mammography. So, this is an extension of digital mammography and the image is acquired through multiple images taken in an arc around the breast as opposed to a flat image taken with traditional mammography. There is software used to reconstruct individual slices or tomograms in addition to a standard 2D mammogram. So, you need to think about DBT as digital mammography plus, and this virtual 2D image can be created so that the radiation exposure, this is a relatively recent development. The virtual 2D image is created as part of the same process the tomosynthesis images are created and initially this was not the case, so there had to be two different exposures to radiation for the screened woman, but now because this virtual 2-dimensional image can be created, radiation exposure with DBT is approximately equal to that of digital mammography. The technology is being adopted very rapidly. I think there was a recent survey published suggesting that over a third of centers nationwide have already replaced their digital mammography units with DBT, and CMS has announced the creation of a CPT code specifically for DBT that was effective this month.

So, this is just an image that describes... that shows the difference between a digital mammography image and a DBT image. So, the images were taken and again, I won't be able to do justice to it clinically, so we'll... you can ask more detailed questions of Dr. Lee, but the tissue behind and in front of an abnormality is not as highlighted in DBT, so the breast cancer or abnormal mass is easier to visualize, and so that's what denoted by this circle.

The issue with breast density is that areas that absorb more x-ray energy and appear white on mammography have to do with denser breast tissue and so because abnormalities also appear white on mammography, there is the possibility that dense breast tissue can mask cancers... mask abnormalities. This is categorized using a four-category qualitative scale. The top two levels of that scale are heterogeneously dense and extremely dense. The two taken together are what most people described as dense breast tissue, and heterogeneously dense breasts are known to obscure small masses on

mammography and extremely dense breasts may actually lower the sensitivity of mammography. This was a particularly strong issue when film mammography was the standard of care. That has been mitigated somewhat by the introduction of digital mammography, which has less of a masking effect, but there is still a masking effect present.

Breast density is also an independent risk factor for breast cancer. So, comparing these two top categories to scattered densities, which is the next less dense category. Relative risks of about 1.5-2.0 have been observed. So, there's controversy around this, as well, though because breast density taken alone doesn't necessarily provide the entire picture of risk for the patient and breast density is also correlated with age. So, breast density lessens as a woman ages but overall breast cancer risks also increases, as a woman ages.

So, in terms of visualizing breast density on mammography itself, the four categories are displayed here, and you see, as you go left to right, as the tissue becomes more dense, the areas that appear white become more prevalent, and so visualization is more difficult potentially.

In terms of breast density legislation, about five or six years ago there was a national advocacy effort that was sparked, primarily by the efforts of a breast cancer survivor who had a missed cancer on mammography. She created an organization called areyoudense.org. She had dense breast tissue and that was, in part, described as the reason why the cancer was missed. Through the efforts of this organization, and others, 19 states have now passed legislation requiring notification of dense breast tissue with a normal mammography result and two of those 19 states also require insurance coverage for supplemental screening. That's a topic we'll be talking about.

In terms of your own state, there was a bill introduced for notification in January of 2014. It actually never made it to the state house or senate floors for debate, and the major concern that is being described with these notification efforts are that these legislative mandates, this is not necessarily uncommon with legislative mandates. These mandates may, at times, outpace the accumulation of scientific evidence, and in addition there are concerns voiced by others that widespread notification of women with breast dense tissue without a full conversation about overall breast cancer risk may cause undue anxiety and unnecessary resource utilization.

So, supplemental modalities that will be part of our review that are commonly used to screen women with risk factors, including dense breast tissue include MRI, which technically uses a similar process to DVT but uses strong magnetic fields instead of x-ray energy but does reconstruct these detailed cross-sectional views and handheld and automated ultrasound, which are also commonly used. Handheld ultrasound has been used for a number of years, specifically in women with dense breast tissue, automated ultrasound is a much newer technology.

So, how are we doing on time? We have a little bit more time, OK. So, the key questions were really around the comparative effectiveness of DBT as a frontline screening option relative to digital mammography, and we included in our scope those women in the younger age bracket, age 40 to 49 as well, and the second key question was around the effectiveness of the supplemental screening modalities, both handheld and automated ultrasonography and MRI. We also tried to obtain information on harms and harms of interest for this evaluation included over-diagnosis and/or overtreatment, unnecessary biopsies as a result of false-positive imaging, patient anxiety, and radiation exposure.

We also, as we normally do, look to see in our evidence base if there was any evidence of differential effectiveness according to specific subgroups of patients. They are listed here, and then we evaluated both the published literature on cost and cost-effectiveness and created our own... or modified our own population based model to try to ascertain what the potential impacts would be for screening eligible women in the state of Washington, and I should probably note... I should have noted this at the outset, my apologies, that this work, in part, was based on prior work that ICER did with the California Technology Assessment Forum. I also need to thank some external coauthors, so Dr. Jeff Tice at the University of California-San Francisco was the author of the original evidence review and consulted on this update and Dr. Jamie Lee who is now at the University of Washington when the entire process started was still at Mass General in Boston, also helped both ascertain the evidence and develop the model.

So, we kind of talked about the scope already. All asymptomatic women who are screening eligible in that age range were our target population. We did not broach the topic of annual versus biannual screening as part of our evidence review. Our focus was on the technologies themselves, so that's why we have one to two years listed, and we also looked at both DBT and the three supplemental screening tests of interest.

In terms of the comparators, we did allow film mammography as a comparator to DBT, because certainly in other geographies, film mammography is still widely used, and in terms of supplemental screening, we compared these modalities, if they were evaluated head to head, and we also compared... or our primary comparator was digital mammography alone, i.e. no supplemental screening.

Outcomes, as you might expect, breast cancer mortality and overall mortality, health-related quality of life, cancers detected and/or missed by these technologies, rates of recall and biopsy. So, those are two different measures in this type of evaluation because oftentimes women are recalled if there is lack of clarity in the image. Additional imaging is done, but in many of those cases, a biopsy is never ordered. So, these are not to be thought of as equivalent. Biopsy is a subset rate of the rate of recall. Other test characteristics, sensitivity and specificity, positive predictive value is defined multiple ways in breast cancer screening. We will focus most of our attention on what is known as

PPV3, which is the percentage of biopsies conducted that yield a positive cancer diagnosis and the harms.

So, we evaluated literature from January 1990 through November of 2014. We did not put any limitations on duration of follow-up. That is an important consideration. Most screening studies are felt to be of good quality. A follow-up is at least as long as the interval between screening rounds, and that is a concern with some of these studies, and we excluded studies that focused only on technical performance, measures of image, fuzziness, or what have you. We wanted to focus on patient-oriented outcomes.

I don't think I'll go into a lot of detail on study quality ratings. For comparative studies, we used the USPSTF criteria that we have laid out previously in our reviews. For diagnostic accuracy measure, we used and accepted and validated measure of the QUADAS-2, but we made certain modifications to it. So, digital mammography was the preferred comparator, but again, we did allow film mammography, as well. Breast density can, even though there is an agreed upon approach to classifying breast density, this can be defined multiple ways, especially when you go outside of the U.S., and then there are other measures, as well, consecutive sample, low withdrawal rate, sufficient follow-up would be a good quality study, but we universally rated any study that did not have sufficient follow-up in that interval between screening rounds to be a poor quality study.

These are the domains that we typically use to assess overall strength of evidence, and our literature search yielded a total of 33 studies, 9 DBT studies, 18 ultrasound, 5 handheld ultrasound, 5 automated ultrasound. Only one MRI study in our target population. So, the target population for supplemental screening would be women with a negative mammogram and dense breast tissue. For context, we summarized data for the existing evidence base for MRI, which has typically been measured in women at very high risk of breast cancer. So, these are women who have genetic susceptibility who have had previous radiation to the chest or have a personal history or close family history of breast cancer and typically a 20-25% lifetime risk of breast cancer. So, should I pause there for lunch? Oh, I guess I won't pause then, or should I?

Josh Morse: No, let's proceed until a good stopping point and lunch is here.

Daniel Ollendorf: When I see the food arrive, I will stop, OK. So, in terms of overall quality of the evidence, there were no studies in our set directly measuring the impact of testing on breast cancer morbidity and/or mortality, not all that surprising given that these large RCTs had already been conducted and defined the benefits of mammography. We also identified no randomized control trials. They were comparative cohort studies to be sure, but no RCTs.

Again, as I mentioned, we used insufficient follow-up as a measure of a poor quality study and for DBT we rated all nine studies to be of poor quality. There were a couple that did have sufficient follow-up, but those had other fatal flaws,

including large imbalances in patient groups, here comes lunch, and/or other measures of selection bias, in particular because DBT had not been a covered service prior to very recently. There are concerns about volunteer bias. So, the… where the women who were willing to pay out of pocket for the extra fee for DBT is somehow different from the candidate population. We also found relatively few good quality studies of supplemental tests. There was one study of MRI, but again, it was not in our target population. Question?

Marie Brown: Your decision… I went back to the epidemiology textbook to look at... to try to understand why or what would be the practical implication for requiring another year or two of follow-up in order to interpret the results of the screening at the time and that if you had a better idea. Why would you... why does that so profoundly affect your rating of quality?

Daniel Ollendorf: Because if you, if you think about it, if you have a three or a six-month study and what you're trying to do to fully inform your measure of sensitivity is to understand how many cancers were missed, the typical clinical definition of a cancer missed would be a cancer that appears between screening rounds, and if your screening interval is one year but you're leaving six months of that year out of the mix, you are underestimating missed cancers, essentially. Does that make sense?

Marie Brown: It does.

Daniel Ollendorf: OK. So, in terms of our overall summary of strength of evidence, we summarized it as low because of the quality of studies issue, but we did find some consistencies in the results that were reported. So, it appears that DBT's test performance is incremental relative to that of digital mammography. There is an improved cancer detection rate of about 1 per 1000 women screened when additional cancer detected, and there is a reduction in recall rates. That was a variable measure, but in most of the large prospective and/or multicenter studies, the rate of reduction of recall was somewhere between 15 to 20%.

Kevin Walsh: Is that the U.S. studies only?

Daniel Ollendorf: I included the European studies as well. I know that they're... that is a different... European studies are a different animal because the adjudication of an abnormality on mammography is done differently in most European countries. Two independent reads by two different radiologists with a consensus, meeting if there is a disagreement, which does not happen here. At the same time, those are large multicenter comparative studies, and the issue we found with some of the studies reporting much larger reductions in recall rates were related to those other quality issues I mentioned. So, imbalanced treatment groups, small studies, etc.

David McCulloch: So, this is very helpful. Can you just clarify what, what's the difference between how things are adjudicated in the U.S. than versus the... are the Europeans being more stringent, or?

Daniel Ollendorf: Yes.

David McCulloch: So, what?

Daniel Ollendorf: Yeah.

David McCulloch: So, how is it done in this country?

Daniel Ollendorf: It's one read by one radiologist, typically.

David McCulloch: OK.

Daniel Ollendorf: Without any need for... there may be... in specific institutions there may be some process to adjudicate, but typically it's one read by one radiologist. OK. So, just a little more color on these studies. Those earliest large studies did come from Europe and showed about a 10-15% reduction in recall, a 30-50% increase in the cancer detection rate. Recently, there was a large U.S. multicenter study, which has informed a lot of our thinking and our modeling, as well. Thirteen centers in the U.S., about 174,000 women received DBT in this study. In contrast to some of the earlier, smaller U.S. studies, this showed, again, a similar magnitude of reduction in recall to those early European studies, but a 7% increase in the overall rate of biopsy. So, the early U.S. studies had shown a reduction in the rate of biopsy, but here we are seeing a small increase in the biopsy rate. Question?

Kevin Walsh: I need some explanation. It's described in the Friedewald study that the statistics were screen level but not patient level?

Daniel Ollendorf: Right, so these were aggregated data reported by the centers. So, they... so this may... there may have been multiple screens included in the data set on the same patient.

Kevin Walsh: So, it's really difficult to tease out... I mean, so what's the probable effect on the real rates of reduction or increase? That's the question I ask.

Daniel Ollendorf: That is probably a fair question. I know that it was mentioned as one of the limitations and...

Kevin Walsh: Because if you throw out the European studies, because they're really not comparable, the process is not comparable, we're left with this study and so if we have to… if we're going to make a decision and we're using this study as our focus, if we can't really understand what the percentages are because of that... because of the way it was quantified...

Daniel Ollendorf: Right.

Kevin Walsh: ...I'm left with, so what do we have?

Daniel Ollendorf: But I think that… and I can go back to the study and double check the way the authors described this limitation, but because the... they did do some evaluation of their screening populations at these centers year over year. They have to report certain statistics to the federal government, and found that there wasn't much change in the characteristics of the women who would have made that base... created that base of screens. So, while not having exact patient level data is a concern, it did not appear to the authors, anyway, to be a major one. I'm not sure that all the European studies were patient level either. Some of them might have been screen level, as well.

Marie Brown: So, this deals with women who... you may have a woman in this data set that comes... has come back for three different mammograms?

Daniel Ollendorf: Right.

Marie Brown: Over time, and for her...

Daniel Ollendorf: Right.

Marie Brown: ...routine screening. So, she...

Daniel Ollendorf: Right.

Marie Brown: ...counts three times.

Daniel Ollendorf: Right, but I think the... that is a challenge, but because the demographics of the population presenting for either digital mammography or DBT are comparable, the effect of that would be less pronounced if the focus is on the incremental comparison. That's not... maybe it's not appropriate to ask Christoph if he has any thoughts to add here, or? I don't know.

Craig Blackmore: Please.

Christoph Lee: Yeah, I think Dan, you did a good job of explaining it, and we should mention that the Friedewald study was retrospective. So, it was looking at when before facilities adopted DBT and after, is that correct? Then sort of a pre/post.

Daniel Ollendorf: Right, and since the publication of that study, there have been other studies published with larger sets of data from some of the participating centers in the Friedewald study that have shown very... results that are relatively consistent to the Friedewald overall results, and in terms of U.S. based studies with complete follow-up, there was one study we identified, it was a small study, had some major imbalances in terms of risk factors and other characteristics between treatment groups and I believe actually a slightly greater than 20% loss to follow-up. So that was a challenge, as well.

So, this is just a summary, and I don't want lunch to get cold so I'll just go through this summary and then we can break. This is essentially just some… there is some variability in the results, and those are noted in detail on the report, but this is kind of a comparison of those major test characteristics between digital mammography and DBT. So, you see, it is across a wide range but there is a reduction in the recall rate. Again, those more recent studies are showing an increase in the biopsy rate, a small increase in the biopsy rate, cancer detection increase as well, one to two additional cancers per 1000 and the PPV3, that positive predictive value of positive cancer diagnosis on a biopsy, is also increased somewhat.

David McCulloch: So, are these statistically significant? I mean, if you saw that as a box plot or a three diagram with... there's so much overlap. That's the question I was asking Dan Lessler before you got here.

Daniel Ollendorf: Yeah.

David McCulloch: Is that statistically significantly improved cancer detection with PPV?

Daniel Ollendorf: In some studies it was.

David McCulloch: Three to five versus four to six.

Daniel Ollendorf: Yeah, and it's three to five for digital mammography alone. So the populations do vary in terms of their underlying risk factors, and depending on the... certainly depending on the size of the study and other issues, there may have been statistical significance for some of these findings but not for others. These studies were too heterogeneous to do any sort of meta-analysis on this, but I think what we are resting our hat on is that despite the quality issues with the study, the increase in cancer detection and the reduction in recall is consistent across all nine. I know that doesn't directly answer your question, and it really... certainly in some of the larger studies, statistical significance was achieved on most of these measures, but in smaller studies that may not have been the case by nature of the size of the sample. Yes?

Richard Phillips: Could you define what a recall is? I mean, does it imply another test? Is there a cost...

Daniel Ollendorf: Yes.

Richard Phillips: ...associated with it?

Daniel Ollendorf: Yes. So, when a woman is recalled after an abnormal finding on the initial test, there is typically additional imaging done. There might be a diagnostic mammogram done as opposed to a screening one to try to get more information on the image. There may be another test done, an ultrasound or another, to try to figure out if the abnormality is suspicious enough to go further, and then if there's still uncertainty then a biopsy is done.

Richard Phillips: Will you define that as a...

Daniel Ollendorf: But the recall rate...

Richard Phillips: ...cost element...

Daniel Ollendorf: ...relates...

Richard Phillips: ...later?

Daniel Ollendorf: Yes. In our own model we evaluated the cost element and then other published models that's been incorporated, as well.

Craig Blackmore: Let's take fifteen minutes and get some lunch, convene at five after. Convene at noon. Let's convene at noon. You have 17 minutes to eat lunch. Alright, 10 after noon, 25 minutes.

Craig Blackmore: Alright, I want to just call the meeting back to order and ask the committee members to take their seats. Alright, Dan. Alright, here we go.

Daniel Ollendorf: So, the first thing I want to respond to one of the questions that was asked about the Friedewald study. We took another look and while they don't talk in the limitations section about the screened versus patient population issue, the timeframe in which data were collected was about a year and a half. So, it's pretty unlikely that many women in that sample showed up for more than one screen. So, for that purpose you can think of the screening population as essentially the patient population.

OK, let's move onto the effectiveness of supplemental screening. So, here we will talk about handheld ultrasound, automated ultrasound, and MRI. So, by far, the largest evidence base we had to work with was with handheld ultrasound, 18 studies in nearly 100,000 women but as you'll see as I go through the data in the subsequent slides, a lot of variability in findings.

David McCulloch: Sorry, Dan, just to... this is really helpful, what you're doing so far.

Daniel Ollendorf: Oh, good.

David McCulloch: But, and just define again what do you mean by supplemental screening?

Daniel Ollendorf: So, our definition was in women with dense breast tissue who have a negative mammogram, the effects of an additional screening test, one of these three tests on those tests performance characteristics. Yes?

Richard Phillips: Is that a test done at the same setting and/or at recall?

Daniel Ollendorf: Recall would be for an abnormality, so that would be a positive mammogram.

Richard Phillips: But it's at the same setting?

Daniel Ollendorf: For the most part. There were some studies where the supplemental screen was done in a different place, and there were some issues... quality issues with some of these studies where the time between the initial screen and the supplemental screen was very long. So, there were some concerns there, but by and large... but the population was negative mammogram, dense breast tissue, then appearing for a supplemental test.

David McCulloch: Right, but it... so, all women get a digital mammogram, only the subset of dense breast get a supplemental test, not a randomized control trial of women get either just a mammogram or a mammogram plus that.

Daniel Ollendorf: There was one RCT that I'll talk about.

David McCulloch: OK.

Daniel Ollendorf: But not in... not in that target population that we're focused on, but again we'll talk about it for context, because it's a large frequently cited RCT. Yes?

Richard Phillips: What percent of people get a supplemental test at screening?

Daniel Ollendorf: Well, that's highly variable based on whether the supplement test is covered, but about half of the screening eligible population has dense breast tissue.

Richard Phillips: Has?

Daniel Ollendorf: Dense breast tissue at about 50%. So, we're talking about the potential use in a… the use in a potentially large population. So, in terms of the strength of evidence for handheld ultrasound we found low to moderate strength of evidence, not because of the number of studies or the sample, but because of the incredible variability in results, which you'll see, and in terms of the direction of affect, we termed it comparable because while there is an incremental cancer detection with handheld ultrasound after a negative mammogram in this population, there is also a very high false positive reading, which I will add more color to in a minute.

A much smaller evidence base for automated ultrasound, the newer version of ultrasound, even more study heterogeneity in terms of findings with automated ultrasound. So, we felt that the strength of evidence was insufficient because of that. With MRI, a large evidence base, but in our target population of women with a negative mammogram and dense breast tissue, we only found one study. So, the evidence base generated for MRI has primarily been in women at very high risk of breast cancer.

So, let's move on to the next slide. So, again, I mentioned the number of studies with handout ultrasound. Most of these studies has used as their comparator

or as their initial test film mammography not digital. So, only four of the 18 had a digital mammogram initially. Again, a high degree of between study heterogeneity. The recall rate ranged from 20 to nearly 200 per thousand. Of note, all of the prospective studies in this set had recall rates greater than 100 per thousand. So, that is in addition to the recall rate of 100 per thousand that already exists for a digital mammogram. We need to think about that. That is essentially doubling the recall.

Cancer detection rate also ranged widely between 0.4 and 14 per thousand. So, there is a lot of variability in the underlying risk profile of these populations. The median was about 3 across these studies. Biopsy rate also ranged widely from 12 to 114 per thousand, but one of the key issues with ultrasound is its very low PPV3. So, again, the percentage of biopsies that yield a positive cancer diagnosis range between 3 and 18% and most studies showed a PPV3 of 5 to 7%. OK, so essentially what that is saying is that if you have 20 biopsies done, you'll have one positive result.

Craig Blackmore: And just… if I could get clarity. When you say cancer detection, does that include DCIS or is that invasive cancer or is it variable?

Daniel Ollendorf: That's the overall cancer detection rate. So, that would include all of those possibilities. Some of the studies will report it separately. Typically they'll put an overall rate and an invasive cancer rate. The studies were variable with respect to how much DCIS... how much of them reported DCIS.

So, that one trial that I wanted to talk about, again, not exactly in our target population was the ACRIN 6666 Trial. So, I'm getting to the point made earlier. This was done in a high-risk population, but this was a randomized control trial. Women received either mammography alone or mammography plus ultrasound in alternate order. Yes.

Chris Standaert: Are they defined high risk? What is the population? You said high risk. What does that mean?

Daniel Ollendorf: So, I can go back and double check the study but I believe it was genetic susceptibility, previous [inaudible] radiation to the chest, and the Gail Model as one of the breast cancer risk assessment models, lifetime risk of 20% or more, but Annie, maybe you can double check on the criteria used.

So, depending… there were multiple screening rounds in this study and depending on that screening round, the handheld ultrasound arm saw an increase in cancer detection of four to six per thousand. Remember, though, this is a high-risk population so you'll see more cancers for that very reason, but in that initial screening round, the recall rate more than doubled, and there was more than four-fold increase in the biopsy rate in the handheld ultrasound arm. So, this is the real key tradeoff is false positives versus increase in cancer detection. I think they're still looking that up.

Annie: High-risk was defined by at least one of the following: Personal history of breast cancer, positive for BRCA-1 or 2 mutation, a lifetime risk greater than or equal to 25%, a five-year risk greater than or equal to 2.5%, or greater than or equal to 1.7% with extremely dense breast tissue. Prior biopsy with atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ, or atypical papilloma, or prior mantle irradiation.

Daniel Ollendorf: OK. So, in terms of our yield estimates here, now we need to think about this, is incremental above what is yielded by digital mammography. So, again with that wide range in recall, we would estimate it an additional recall above mammography of 30-100 per thousand, the biopsy rate per thousand of 30 to 60 in addition to the initial biopsy rate, two to four additional cancers detected, and that low PPV3 value.

So, automated ultrasound, five studies were identified, so a much smaller set than the handheld ultrasound; 28,000 women, no randomized control trials, and an even wider range of heterogeneity seen here, recall between 23 and 2 in over 200 per thousand, cancer detection rate of 0 to 12 per thousand, biopsy rate ranging from 12 to 36 per thousand but of note, biopsy rate was only reported in three of the five studies, and PPV3 was only reported in two of the five studies. Findings that are generally within the range but a somewhat wider range to that scene with handheld ultrasound.

Craig Blackmore: So, can I drill down a little? Five studies with 28,000 women, that's a lot of women, but yet one of the studies has a PPV3 of zero. Was that thousands of women or was that study only had 50 women? See what I'm... I'm asking how big are the studies that give us these PPV values?

Daniel Ollendorf: Well, let's move to the next slide...

Craig Blackmore: Maybe it...

Daniel Ollendorf: ...talks about the study that really drove this sample size, OK? So, this is a prospective multinational study of 15,000 women. So, that's more than half of the total sample. The other four studies comprised the rest. So, here you see 35% increase in cancer detection, about two additional cancers detected per thousand, but a nearly two-fold increase in recall, and a biopsy rate of 36 per thousand, and this is the study that yielded a PPV3 of about 10%. So, it looks like you have a question.

Chris Standaert: I'm just looking at the...

Daniel Ollendorf: The last bullet?

Chris Standaert: ...the PPV of 3.6% for diagnostic mammography alone that's way lower than what you have for your digital mammography numbers of your DBT versus the M study. I just think it's really low. That's way lower than you've recorded previously for these things, but we can talk about that when you're done.

Daniel Ollendorf: That's PPV1 though. So, PPV1 would be the percentage of abnormal findings on the screening test that...

Chris Standaert: [inaudible] biopsy.

Daniel Ollendorf: ...right. Right, that's PPV1.

Chris Standaert: OK.

Daniel Ollendorf: The only point I wanted to make there is that PPV1 is actually lower for the combined approach than for digital mammography alone.

Christoph Lee: So, Craig to answer your question about the Arleo Study, that' the one with the 0% PPV3. Those were 558 AVUS exams over three months and of those, 11 women were biopsied and all were benign.

Daniel Ollendorf: So, much smaller than the Brem study. OK, so essentially we've put in the same numbers for our estimated yield for automated ultrasound, because we felt that with the wide variability and results that the estimated yield, you know, we couldn't really say anything with any definition around it beyond what's already been demonstrated for handheld ultrasound. So, we feel that the strength of evidence is insufficient at this point and we did not try to make any other estimates.

So, as I mentioned, the MRI study that we found, only one study in the target population, high sensitivity, specificity, and positive predictive value, but this was a different population. This was a European study. In this case, MRI was used as the third line screen after a normal digital mammogram and a normal ultrasound. So, again, not quite what we're focused on here, and this population was very high risk. Nearly half of women had a personal history of breast cancer, but this was the one study we found that attempted to measure the effects of MRI in women with a normal initial test who had dense breast tissue. In other populations... in other high risk populations, again that we are adding for context, you see that MRI appears to be a more sensitive test than the variant of ultrasound that we've described in a more specific test, still a wide variety in cancer detection rate, 8 to 67 per thousand, but more cancers detected with MRI and a wide range in biopsy rate as well. The PPV3 for MRI ranges widely but with a median of about 48%, which again is higher than the other modalities. The tradeoff that we'll talk about more with MRI in our modeling section will be its cost.

David McCulloch: So, Dan, what is the sensitivity/specificity detection rate in the one... in that one study, and you've given us it for when you add in other high risk, but what...

Daniel Ollendorf: Yeah.

David McCulloch: ...in that?

Daniel Ollendorf: We can get those numbers, right? Do you have the MRI study? Yeah? OK. Sensitivity, specificity, and...

David McCulloch: Positive detection rate and biopsy.

Daniel Ollendorf: Positive predictive value for the one MRI study.

David McCulloch: Yeah.

Daniel Ollendorf: So, we just kind of laid out most of these findings already, and the strength of evidence is low here because we don't have data. We have a lot of data, but it's not in the specific target population but you would see additional recall with MRI. You would see a relatively high biopsy rate, but you would also detect more cancers than with the other supplemental technologies and with a higher PPV3 value in terms of the biopsies done.

Craig Blackmore: This cancer detection rate, that's based on the higher-risk populations, or that's based on the one study that might be relevant to our [inaudible].

Daniel Ollendorf: The cancer detection rate... so, this is our estimate taking into account the fact that the... most of the data are in the high risk population. So, we downgraded our estimates, because the cancer detection rate actually could have been much higher in very high risk patients. So, this is admittedly a guess, an informed guess.

Chris Standaert: So, you had... you had some way of sorting out in that one study who was high risk and who wasn't by their data at the end? You could categorize them that way? Is that how you did this, or you just…?

Daniel Ollendorf: We were… we basically developed an estimated yield based on our assumptions around how MRI would perform in the target population recognizing that there's little to no data in the target population.

Chris Standaert: You're building the model from.

Daniel Ollendorf: Right, yeah.

Chris Standaert: OK.

Daniel Ollendorf: OK, it looks like they're still looking.

Annie: So, sensitivity was 99%, oh, 93% sorry. Specificity was 98%, and PPV3 was 48%.

Daniel Ollendorf: In that one study?

David McCulloch: That's helpful. The problem is, it's not a screening study. It's using MRI in a specific second diagnostic test in people who are already [inaudible].

Daniel Ollendorf: Right. Yeah. So, moving to the harms, we found... so again, we were focused primarily on over-diagnosis, on unnecessary biopsy, and on radiation exposure. Over-diagnosis is a difficult situation because there are data from screening studies that are provided typically among women who were invited to screen but don't get screened, so the excess cancer rate in those women. The best guess for most researchers is to the over-diagnosis rate with mammography is about 10%. Christoph, you can add any color commentary you'd like, but again, it's very difficult to know with detection of early cancers at this point which ones are likely to progress and which ones are not, and so the true rate of over-diagnosis is still somewhat of an unknown. Any other thoughts?

Christoph Lee: Just to add to that, since we're mostly talking about something that's also screened with ultrasound tomosynthesis, from the data that's available, most of the additional cancers seen after a negative mammogram with these new technologies are invasive cancers, not DCIS. So, with tomosynthesis, the 3D mechanism allows you to see the small speculated masses, rather than calcifications on mammography. So, you're finding more early invasive cancers, not calcifications that are DCIS. The same is true for screening ultrasound with finding masses, as those are better seen by ultrasound, not calcifications that are DCIS. So, most of these studies are showing that greater than 90% of the cancers that are being found, in addition to mammography screening, are invasive cancers not DCIS.

Daniel Ollendorf: So, again, no real data yet, but less likely to be a concern here. Yes?

Richard Phillips: A little clarification. When we're talking about biopsies, are we talking about open biopsies, needle biopsies, or aspiration biopsies, or all?

Daniel Ollendorf: It's all, but when I ran through these slides with the medical directors, that question came up as well, and we took another look and looked at some national survey data. A little bit more than two thirds of biopsies are percutaneous needle biopsies. So, most of them are on the less invasive side if that makes sense.

Richard Phillips: That has a lot of effect on the complications?

Daniel Ollendorf: Yeah, sure, but even in... even in studies that looked at all types of biopsies, the complication rate is still relatively low at less than 1%. In terms of radiation exposure of the tests that we have looked at in this evaluation, only DBT delivers a radiation dose, and I mentioned that the FDA approved software algorithm allows for creation of a virtual 2D image. So, the DBT test can produce a radiation dose that's approximately equal to what would be seen with digital mammography alone. We just had an offline conversation at the break, though, which was kind of interesting that the CMS ruling is for DBT as an add on test, which means that for this not to be a fraudulent claim, both DBT and digital mammography have to be performed separately. So, at least until they fix that issue, Medicare will be essentially paying for double the radiation

dose for a screening test for the next year or until the CPT codes are revisited. So, kind of an issue. In terms of actual data in the studies we identified, those are noted in the report, but there was very little information provided.

Key question four was on differential effects in subgroups and I'm going to go run to the table and get my glasses again, because I can't… Much better. OK, so the improvements in test performance seen in studies appear to be, for the most part, independent of age in those studies that subgroup the data by age. There have been concerns stated about... with ultrasound the effects of using a technologist to perform the test versus a radiologist. So, there is some variability in how that's done. In the studies we identified, that did not appear to be a significant predictor, as well. However, we did find one study, that's the Arleo study that we actually just described, of automated ultrasound. Again, a very small study but in that three-month period, or that... actually, in terms of their focus on learning curve, they assessed the recall rate with automated ultrasound in the first quarter after inflammation and compared it to the third quarter... calendar quarter after implementation and found a significant reduction in the recall rate. It was still a high recall rate, but not what it was initially.

So, moving to key question five, the cost and cost-effectiveness. So, we identified five studies that evaluated cost and cost-effectiveness again in our population of focus. Dr. Lee was the author of the cost-effectiveness analysis of DBT and found that the use of DBT in addition to digital mammography as compared to digital mammography alone met commonly accepted cost-effectiveness thresholds between $50,000 and $100,000 per quality adjusted life year gained. The study did have a focus of biennial screening and a focus of frontline screening in women with dense breast tissue only. Our evaluation was intended to look at DBTs use as a frontline test for all women, all screening eligible women, and I'll talk about our model in a bit, but that looked at a one year time horizon, so an annual framework essentially. There were four studies that evaluated the cost and cost-effectiveness of handheld ultrasound. Three of them came from single centers in Connecticut that were evaluating the additional cost of testing after the legislation was passed. A fourth study was a simulation model that found that because of its increased cost associated with false-positive findings that the clinical benefits... the modest clinical benefits with those additional cost yielded a much higher cost-effectiveness ratio for ultrasound $325,000 per quality adjusted life year gained and those three single-center studies evaluated the additional cost of ultrasound testing relative to the additional cancers detected and found ranges of 60 to 200,000. We found no studies in the target population for the other two.

So, this is just a little more color in Christoph's study and a $50 premium was assumed for DBT, so that add-on payment that Medicare has approved is about $57 nationally, so very close, and the use of DBT over multiple screening rounds resulted in the reduction in the number of deaths and a large reduction in the number of false positives and that's where the result came from.

So, let's move into what we attempted to do with our cohort model and what we tried to do was make this population based similar to the work we did in California and then in New England, as well. So, we identified the number of women in the state age 40 to 74 who would be eligible for general screening. So, those patients who have those very high-risk factors we've talked about were excluded from this set, and that was for general screening. Then, for supplemental screening the focus was as above, that general population but only in women with dense breast tissue and a negative mammogram or DBT.

So, we're trying to model what exactly would happen with those two populations, and like we've already talked about the strategies we've evaluated. Just based on timing, we didn't... we weren't able to use HCA costs for everything, so we focused on the Medicare fee schedule for these tests. We looked at all of the measures we've just talked about, recall biopsies, false positives, etc. The costs were considered over a one-year period, and they included the costs of screening, the cost of recall, biopsy, and we also assumed a cost for women who would present in the interval with a cancer so, a cancer that was missed by initial screening that would present and be diagnosed.

We stratified the results by overall breast cancer risk, again with the knowledge that we excluded the very high risk patients. We made some assumptions with the model. As with most modeling studies of screening we assumed perfect compliance with frontline and supplemental screening. We know that's not the case, but there are little comparative data to be able to use on compliance with these different screening modalities. We also assumed that supplemental screening would happen immediately following a negative result. We also assumed that all abnormal supplemental tests would result in biopsy. That's a very conservative assumption, because some supplemental tests, they yield an abnormal result. It may also result in recall and not biopsy. So, there still may be more imaging done before a biopsy is decided on. We had to make some assumptions regarding how these tests would perform in an average risk, average overall risk population, again, excluding these very high-risk women.

So, when I say high here, I'm talking about higher risk, not highest risk if that makes sense. What we did was, we stratified the population according to five-year risk of breast cancer, less than 1.7% was considered low risk, 1.7 to 3% was considered moderate, and greater than 3% was high risk, and these risks were obtained from the breast cancer surveillance consortium risk calculator, and were focused on three major elements, age, the presence of dense breast tissue, which in the case of supplemental screening would have been there for all women, and a close family history of breast cancer.

So, just a couple of results to highlight. This is the comparison of DBT to digital mammography as a frontline screen. The reduction in recall and the increase in biopsies performed with DBT comes directly from the Friedewald study, because we felt that was the most definitive of the U.S. experience, but you'll see here that the benefit of DBT comes through with a lower rate of false

positives... false positive recalls essentially. A biopsy wasn't ordered but because the recall rate is lower, that is a benefit of DBT.

The cost per woman screened, however, we assumed that $57 premium in payment that Medicare has approved for DBT and most of those... a very small percentage of those costs are offset by reductions in recall, and the reasoning is that there is a reduction in recall, but there is an increase in biopsy and while that may be clinically appropriate, a biopsy is obviously going to be much more expensive than additional imaging on recall. So, about $1 of that $57 premium was offset in the overall population.

These are... we don't really need to focus on this, because the dense breasts in the frontline screening frame were like the dense breast tissue, characteristic is somewhat less important.

So, we also did an analysis comparing multiple payment premiums for DBT. We did this before CMS made their ruling. So, the $57 is highlighted in yellow. Digital mammography costs per woman screened is all the way on the right, and again, because of that $1 offset, that's really the threshold at which DBT becomes cost saving relative to digital mammography, a $1 premium essentially.

We also did sensitivity analyses. We had made some conservative assumptions similar to assumptions that Christoph made around the increase in sensitivity and specificity with DBT. Again, because we don't have full follow-up in these studies, we don't have definitive numbers for sensitivity and specificity. So, we assumed an absolute 1.5% increase in sensitivity and specificity. So, that's the second column to the right, but we also varied that and in our most optimistic scenario we assumed that sensitivity would be 89% versus 84% for digital mammography, specificity 95 versus 90%. Here you see substantial reductions in recall, about half of recalls are averted. Biopsy rate is almost halved as well. So, accordingly, false positives are also much lower, but even here, the cost per woman screened is still about $49 higher, so a little bit less than 20% of that increased cost is offset. The reasoning is that $57 premium is being applied to every woman screened and with recall happening in 10 to 12% of cases, the reduction in recall happens to a much smaller subset. So, essentially we've talked about the potential clinical benefits of DBT, but there will be an increase in screening costs without a doubt. Yes?

Kevin Walsh: What's the difference between the DBT base case column and column C?

Daniel Ollendorf: The… we made more optimistic assumptions regarding sensitivity and specificity. So, you see...

Kevin Walsh: Just because?

Daniel Ollendorf: ...in the header. This was a sensitivity analysis. This is...

Kevin Walsh: Right, but the sensitivity we have is 85... is that right? So, the sensitivity...

Daniel Ollendorf: We don't have a definitive estimate of sensitivity or specificity, because there's not enough follow-up in these studies to have a definitive number.

Kevin Walsh: Now I see. Thank you.

Daniel Ollendorf: Yeah. So, yes?

Chris Standaert: Alright, so cost aside, one of the issues was yield, and when you went back to your original DBT slides, you talked about a yield of roughly in one case per 1000 detected.

Daniel Ollendorf: Right.

Chris Standaert: And so that's not reflected in the first number of columns. I guess that's reflected in the last one. I'm not sure if that's what's driving the numbers in the last one, and that's where they're getting their sensitivity and specificity, but...

Daniel Ollendorf: Right.

Chris Standaert: ...why in your base model on the page before did you not assume a higher cancer detection rate when you start talking about all the analyses?

Daniel Ollendorf: That was a pretty intense discussion among the coauthors about whether to do that because again, the increase in cancer detection is not likely to be modified to any extent by the inclusion of more follow-up data, as time goes on, but I think there was enough... that was initially what I had put in the base case, but the radiologist working with us felt like why don't we be conservative and say we'll assume an increase in sensitivity and specificity. We're not going to assume an incremental cancer detection rate as part of the base case, but we'll do a sensitivity analysis on it. So, because I guess all the… all the results haven't come in yet. That was the...

Chris Standaert: I mean, it's a crucial distinction.

Daniel Ollendorf: ...that's how that ended up.

Chris Standaert: That would be one of the prime arguments for using DBT is you find more cancers.

Daniel Ollendorf: Yeah.

Chris Standaert: And...

Daniel Ollendorf: Yeah, there's no question, and you will...

Chris Standaert: So, if that's the...

Daniel Ollendorf: ...you'll find much smaller increment in cancers just through improvements in sensitivity and specificity but through the better precision of the imagery, you're likely to find an additional cancer on top of that. So, we could also look at the results for column D, and there you see the improvement in cancer detection. Had we made this a lifetime model and focused on quality adjusted life expectancy, that would have had an impact, as well.

So, in terms of our modeling for supplementing screening, we don't need to go through the results in detail here, but these followed along with the clinical data that we were able to obtain, as well as our assumptions around the performance. So, there will be... any supplemental screening test, there will be an increase in biopsy, but there will be additional cancers detected potentially. We assumed in our modeling a range of 10 to 30% for over-diagnosis. Some studies have gone that far. We just decided to use boundaries to help people interpret the data, but again, I think Christoph's point is something to consider as well, that... because these new technologies seem to be detecting invasive cancers rather than DCIS, it may be less of a concern. All of the tests would detect the cancers that would be missed by initial mammography. So, typically mammography misses one cancer per thousand as a frontline screen, but these tests differ widely in terms of their incremental costs and MRI because it's the most expensive test to perform, is the most expensive on a per-screening basis as well.

So, I don't think we need... this is a couple of sensitivity analyses when we focused on DBT as the frontline test. The real interesting feature here is that if DBT becomes the frontline tool, more women will be sent to supplemental screening because of its negative predictive value. So, rather than recalling those women, it will produce a negative result and those women would then go into supplemental screening if it were offered.

So, on a population basis, we estimated the cost of screening in the state with both DM, digital mammography, and DBT as frontline tests. So, it ranged between $250 and $320 or so million dollars and then using each of the supplemental modalities would increase those costs and you see that with MRI for example, it more than doubles those costs. That is among all women with dense breast tissue and a negative mammogram.

If we focus only on those higher-risk women, and again in our set that would be defined as a five-year risk of greater than 3% and based on the characteristics we focused on, that would be older women with dense breast tissue and a family history. That's only 13% of the population. So, accordingly the costs of supplemental screening here are much less pronounced.

So, just to summarize comparing DBT to digital mammography in all screening eligible women suggests that reductions in recall do provide an offset, but only a small percentage of additional screening costs. Certainly, there would be greater cost offsets if there were more optimistic assumptions placed around

the performance of DBT over digital mammography and supplemental screening regardless of the technology would increase screening costs to the state if performed in all women with dense breast tissue and if risk-based targeting were to be done, this would result in a much smaller increase.

So, I just want to see how we're doing on time. So, our integrated evidence ratings, we use our evidence rating matrix as shown here to identify and estimate what we feel the incremental comparative clinical effectiveness and comparative value are for each of the modalities relative to a comparator. We termed the comparative clinical effectiveness of DBT as C+ so comparable or better in our framework. Because it includes digital mammography as part of the package, we felt that there was no way it could be inferior and while the data are still new and not fully in yet, we feel that the incremental cancer detection and the reduction in recall would be a benefit, so comparable or better. Comparative value really depends on the premium. We made these assignations before the Medicare payment rate was mentioned. So, A relates to a high value, B a reasonable value, and C a low value.

For supplemental screening, again, we know that we don't have detailed information on some of these supplemental tests, particularly MRI in the target population. Based on its performance in other populations, we feel that MRI would be incremental. We incorporated ratings on comparative clinical effectiveness in a risk targeted subgroup. So, if supplemental screening with MRI was reserved for women at higher risk where more of its evidence base is relevant, then it's likely to be a superior technology. Handheld ultrasound, the term sounds a little more exciting than it is. The P stands for promising but inconclusive. We used to call it unproven but with potential. So we feel that again, because there's so much variability and heterogeneity in the evidence base, it's difficult to make a lot of definitive determinations there, but it does seem to provide some incremental cancer detection. The tradeoff there is with false positives, and we feel that the evidence base for automated ultrasound is premature at this point. The value ratings really follow along the same lines in terms of this, but again, with MRI being the most expensive test, if it's not targeted to a certain population, it would substantially increase costs.

So, to summarize what clinical practice guidelines say, American Cancer Society and National Comprehensive Cancer Network note the promise of DBT. At last look, it was not a recommended service, as of yet. American College of Radiology and the Washington State Radiological Society do feel that there are benefits of DBT and encourage reimbursement of the test so that more long-term data can be collected.

The American Society of Breast Disease notes that there are still limitations with digital mammography and considered DBT an advancement. In terms of the supplemental tests, really the only one that has a recommendation associated with it is an MRI by multiple societies but again, it is still focused on the very high-risk subset of the population. And of note, with handheld ultrasound, NCCN does not recommend routine supplemental screening in women with

dense breast tissue and no other risk factors. So, again the notion of a more fully described risk conversation before going through testing.

In terms of coverage policies, so I mentioned what was going on with CMS. In terms of the other modalities, there's really only mention made of these tests used for diagnostic purposes, not screening. So, there's no specific coverage determinations.

In terms of private payers, all forms of ultrasound for this purpose are considered investigational by Humana, United, and CIGNA. I didn't find any other policies from either national or regional payers. MRI follows the guidelines, generally only covered for women at very high risk, but two payers, Humana and United, consider dense breast tissue a specific indication for adjunct MRI screening regardless of whether there are other risk factors. So, they've gone beyond the guidelines in a sense. In terms of locally, DBT is considered... is covered by Regence currently but at last check, there was no additional payment provided and is primarily considered investigational by other regional or national payers. We don't need to go through the appendix, so I think that's my presentation.

Kevin Walsh: Could we go back to slide 24, please?

Daniel Ollendorf: 24. I'm sure there's a faster way to do this.

Kevin Walsh: So, you split out the European and the American studies.

Daniel Ollendorf: Mm-hmm.

Kevin Walsh: And calculate an increasing cancer detection rate in Europe of 30-50%, which is equivalent to 1 to 2 per 1000. What's the number per 1000 in the 29% increase in the American studies? Is it the same?

Daniel Ollendorf: I think it was about 1.5 per thousand, but I can double check that.

Kevin Walsh: OK, and then in slide 25...

Daniel Ollendorf: It was definitely in that range.

Kevin Walsh: ...is that pooled data? So, are these number... are the percentage... is the PPV3 percentage, the biopsy rate, the recall rate a combined... is that a combination of the European and the American studies?

Daniel Ollendorf: This is based on all of the available evidence, yes.

Kevin Walsh: OK, thank you.

Daniel Ollendorf: But keep in mind this is a... this is an estimation that is qualitative. It is not a quantatively pooled number. So, it's based on our review of all studies but with

heterogeneity present in these studies, we didn't do any formal meta-analysis to come up with a central estimate.

Annie: 1.2 additional cancers.

Daniel Ollendorf: 1.2 additional cancers in the Friedewald study, U.S. study. Yes?

Richard Phillips: Is there such thing as a DBT as a supplemental therapy, too, or supplemental diagnostic study to DM?

Daniel Ollendorf: Yeah, actually when we first did this evaluation, which I guess was about a year and a half ago, that is the way that we were modeling it, but that made the assumption that a woman would go back or get their result of a digital mammography first before going back and getting a DBT, and it quickly became apparent that if that had been used that way initially, it was no longer used that way. It was all being done at the same time.

Michael Souter: Just going back to the studies that you looked at, am I right in thinking that you… so you haven't included the Greenberg study in here because of the risk of cross contamination with the Friedewald study, is that right?

Daniel Ollendorf: Greenburg is one of the centers from Friedewald?

Michael Souter: Yes, but there was a subsequent paper by Greenberg on the trial.

Daniel Ollendorf: We did include it in the final report, yes, but we noted Greenburg and there was...

Michael Souter: I see the data there mentioned in the studies that you had.

Daniel Ollendorf: ...well because Greenburg was a single site of Friedewald we, for the purposes of the presentation, I highlighted the Friedewald study, but in the report itself, there's a summary of the Greenburg study, and there was one other publication from another site. I don't remember the first author off the top of my head. What was that? Lorenko? I don't think so. McCarthy?

Kevin Walsh: McCarthy, Owes.

Daniel Ollendorf: We'll double check it. There was another site that had a separate publication, as well.

Michael Souter: When I looked at the... because obviously thinking, OK, well is this the same population but actually when I looked at the patients who were actually included in that the data seemed to range quite differently just from the fact that the Friedewald study was March 2010 to October 2011 whereas the Greenburg study was 2011 to November 2012. So, there would appear to be discreet populations there. There might be possibly, who knows, in that August, September, October timeframe. It could have been some crossover there, but it

would seem that there's a substantial body then... in the Greenburg study which looked at 54,000 patients with mammography versus 23,000 with DBT that's not included here, and I just think that's important when you look at, again, the consistency of direction of effect. Do you see what I mean?

Daniel Ollendorf: Yeah, well we can certainly highlight what we found in the report from that study if you want to go through that now.

Kevin Walsh: But weren't the... weren't the findings the same, Michael?

Michael Souter: Well, that's... that's kind of what I'm getting at, though, in terms of...

Kevin Walsh: The findings were the same in the two studies.

Michael Souter: ...adding to the weight of it… well showing a kind of improvement in the numbers detected and the...

Craig Blackmore: Can I ask a technical question, which maybe it goes to Christoph, one of you or both, and that's around this issue of digital mammography plus DBT versus DBT with a reformation of the digital mammography out of it. So, the technical question is, do the existing machines have the capability of generating digital mammography and in terms of what's out there and what do people do? What's the practice? Maybe it's more a question for you, Christoph.

Christoph Lee: So, currently, the practice in most centers in the U.S. is to do 3D and 2D together at the same time.

Craig Blackmore: So, on... with one acquisition, or?

Christoph Lee: Yep, so the way tomosynthesis is taken is, during the same acquisition. All the difference is in technology to simplify it is that you have an x-ray tube that usually projects a single image by mammography for your standard 2D. That x-ray tube actually just rotates above the patient and snaps several pictures. So, currently the largest vender has a device where it will do the 3D sweep first. The x-ray tube will come back to center and at the end of the study shoot the 2D mammogram.

Craig Blackmore: So, you're still… it's two acquisitions. You're not reconstructing a digital mammogram from your tomography?

Christoph Lee: Currently not. Even though the synthetic software is available and FDA approved since May of 2013, we are not using it yet, and part of that is confidence in the data that the synthetic 2D view is similar to the actual 2D acquisition. There are other reports that they are comparable, but again, not enough data for us to say we're just going to go with a 2D synthetic view.

Craig Blackmore: So, at this point it is an add-on. It's not a substitute.

Christoph Lee: It might be at the same setting. It is an add-on.

Craig Blackmore: It is an add on.

Chris Standaert: But that sounds like even clinically you would view it as an odd on. You don't just take your DBT and be done. You don't displace the DM entirely by doing the DBT and you won't even take a reconstruction of the [inaudible] image. You have to go back and get another one.

Daniel Ollendorf: So we...

Chris Standaert: So, you're already using it as an... you're already using it as an add-on test now. So...

Daniel Ollendorf: ...that's correct.

Chris Standaert: Two more than one.

Daniel Ollendorf: Yep.

Chris Standaert: Huh.

Craig Blackmore: Other questions?

Daniel Ollendorf: We do have information from the Greenburg study and the findings were very similar to the overall Friedewald results. So, about a 29% increase in cancer detection rate, which was the same as Friedewald, 1.4 additional cancers detected versus 1.2 in Friedewald, and the recall rate was 16% lower versus 17% in Friedewald.

Male: And you thought those were significant?

Daniel Ollendorf: Yes, they were all statistically significant.

Carson Odegard: I'm still kind of confused on the overlap, because I didn't read this Friedewald study, but did... one of the sites apparently had some overlap, is that? Or was it a totally separate site?

Michael Souter: I think this is one when you looked… when you compare the authors between the two studies, they share a common author in Greenburg who comes from Fairfax in Virginia, but...

Carson Odegard: Mm-hmm.

Michael Souter: ...as far as I can see, the... more importantly I think the date ranges of the patients...

Carson Odegard: Right, right.

Michael Souter: ...included were, although there's a little bit of overlap there. A substantial part of each study was in a different time period.

Carson Odegard: OK, yeah. Thank you.

Daniel Ollendorf: And there was the additional study by McCarthy... was another one of the Friedewald sites. This was the University of Pennsylvania and it looks like this was a smaller screened population, 16,000 with DBT and 11,000 with digital mammography alone. A little bit lower incremental cancer detection rate, 0.9 per thousand detected. A reduction in recall of about 15% that was statistically significant. There is no mention made of whether the incremental cancer detection rate is though.

Kevin Walsh: But I think in the study, didn't it say it wasn't powered to evaluate biopsy rates?

Daniel Ollendorf: It says the study wasn't powered to assess the statistically significant changes in cancer detection, right. So, maybe that's why there was no P-value reported. They just decided it was too small to do it.

Craig Blackmore: Other questions for any of our presenters?

Chris Standaert: I have one more for the clinical... it's off the... it's on the screening thing. So, standard of care now, if a... I'm a little... the dense breast tissue things is a bit puzzling, because it... what I'm wondering... I'm curious how that's defined? It says half the population has that, which means it wouldn't be... that would be normal not abnormal, right? It's not an abnormality. So, how that's defined and is there really a definition of what that is, if that's some sort of thing, and then what is the standard of care? So, you have a healthy 55-year-old with no particular risk factors other than being a 55-year-old female who gets a mammogram who has dense breast tissue. How is it... how are they dealt with? Are they determined to move on? Do they go get... I mean, what happens with them, and why would you move them onto something else? Why would you?

Daniel Ollendorf: Right, and that… that is the question.

Chris Standaert: Do they need supplemental screening? I mean, that's the whole... I mean, I understand screening if you have no mammogram and they've got bad... the wrong genes and they got mothers and sisters with breast cancer, I get it.

Daniel Ollendorf: Right.

Chris Standaert: But that's now who we're talking about.

Daniel Ollendorf: To answer your first question, breast density is a subjective finding based on the radiologist interpretation. Traditionally, it's been broken down into core tiles. Categories now are A, B, C, and D.

Chris Standaert: Mm-hmm.

Daniel Ollendorf: It's broken down into the amounts of fibroglandular tissue seen in the area of the breast image. So, if you're thinking subjectively that at least three quarters of the breasts in view have fibroglandular tissue there, that's an extremely dense breast.

Chris Standaert: OK.

Daniel Ollendorf: And if you saw less than a quarter of tissue within that region, an image mostly black, then you would say that they're mostly fatty or extremely fatty.

Chris Standaert: OK.

Daniel Ollendorf: But it is a very subjective finding. The new guidelines for radiologists that we use are... it's called the BIRADS manual. The new edition just came out this year and they've made it even more subjective.

Chris Standaert: So, these issues of screening people with dense breast tissue, were they using these scales and defining them as extremely dense or some middle ground? Again, it's fuzzy.

Daniel Ollendorf: Sure, the commonly quoted increased relative risk for women with dense breasts just because of their breast density is about four to six times greater risk lifetime, but that is looking at the extremes. It's looking at the 10% of the population with extremely dense breasts versus the lower end 10% of the population, which are fatty breasts. When you actually compare extremely dense women to average women, women of average density, the relative risk is more along the lines of 1.4 to 1.5.

Chris Standaert: So, clinically when you see... patients are seen, how are they decided to go onto a supplemental screen?

Daniel Ollendorf: We do not offer supplemental...

Chris Standaert: You don't?

Daniel Ollendorf: ...screening at our institution.

Chris Standaert: It's just not done.

Craig Blackmore: So, you got… you've got to put this in context, and the context is a big national discussion about what to do about women who have dense breasts, and there's a lot of advocacy and there's been, as we heard, legislation in a bunch of states that said that you, when you interpret a mammogram, have to inform a woman of her breast density. Tell me if I'm wrong Christoph, but if they... if that woman is in the top two categories of either very dense or dense, meaning half the women, they get a letter that says... in some states and proposed in our state,

you have dense breasts. That's a risk factor. It's not a big risk factor, but it's a risk factor, and then the question is, what is appropriate to do about that and there isn't a consensus. Well, I won't say this again but our job is make that decision and say, OK , in women...

Chris Standaert: I was just curious [inaudible].

Craig Blackmore: ...there isn't. It's not like there's a standard of care now. There's sort of an up-swell to do something and so some states have gone ahead and say do supplemental screening. Some states have said inform women and then don't do anything. Some states have done nothing, and our state has said send it to the HTCC and let them figure it out, and that's where we are. I'm editorializing maybe, but...

Chris Standaert: So, at the moment, the standard of care is not necessarily to do any sort of supplemental screening.

Marie Brown: Correct.

Chris Standaert: That isn't pre-established standard of care that one would think of in this state.

Daniel Ollendorf: To be a little bit fair to the notification states, the letters typically talk about the masking potential of breast density rather than the increased risk.

Craig Blackmore: OK, and I'm not making a value judgment. I'm just trying to put things into a context.

David McCulloch: I don't think that's being fair to the... that is giving them additional justification. We still do not have properly designed trials to say... you say well there's this vague thing. It could be masking something, the implication being, and if we had a really... a test that gives a much sharper picture, you'll have a better outcome, and that's what's missing. I mean, I get it. As a radiologist, I mean, who can't love the DBT picture? It's just... oh look at all this spicules and you just said yourself, it identifies more invasive cancer. Does it? If we did... if we did that on everybody, DBT on everyone, I'll guarantee you it'd identify even more funny-looking little tiny speckle things. The only relevant study is to randomize that and do long-term follow-up and say does it actually save lives and detect more little cancer. It'll... all of these additional fancier, more specific or more detailed tests, they'll definitely identify more stuff and therefore we'll do even more stuff to women. I'm not convinced that we have data, and it's depressing in a subject that's as big as this with these mass... tens of hundreds of thousands of women, we still aren't designing studies that will actually give us the answer we want and technology's changing so fast that I don't know if we'll get those studies done.

Craig Blackmore: I don't know if we will, either.

Chris Standaert: I don't know if we will.

Marie Brown: I wondered in the clinical facilities where DBT is routinely... is possible in Seattle, knowing that UW is not one of them, that... how did they... those facilities use DBT in terms of screening?

Craig Blackmore: He uses DBT. He just... they don't use it to the exclusion of digital. They do both simultaneously.

Christoph Lee: We have… we have one of our machines with DBT capability right now, and we do offer it to women for screening. We're... it's more an issue of capital costs, but I guess your question is, how do we go about distributing this technology?

Marie Brown: In other facilities where it's... in Seattle where it's used more or...

Christoph Lee: Yeah, they...

Marie Brown: ...if they have the easy facility.

Christoph Lee: The majority of institutions that have DBT capability are allowing all women that want to get it to get it, and they are not charging out of pocket for it.

Chris Standaert: They allow them to... how would a woman make that decision?

Christoph Lee: So...

Chris Standaert: We'll get more pictures and...

Christoph Lee: ...yep, so all the machines right now have the...

Chris Standaert: ...more is always better though.

Christoph Lee: ...capability just to do 2D or just to do 3D and currently, since before January, there was no reimbursement for it.

Chris Standaert: Right.

Christoph Lee: It's mostly been a great marketing tool saying that we have 3D mammography, come to us, we'll give it to you for free.

David McCulloch: Absolutely.

Chris Standaert: I wonder why Medicare paid?

Marie Brown: OK, thank you. That was helpful.

Craig Blackmore: So, procedurally again, it's about 1:15, and on our agenda we had scheduled 1:15 to 1:35 as our time for open public comment. So, I think we'll just break off where we are in this discussion, and we'll have the comment... public comment

period and then we can... we can resume with that additional input. So, did we have anybody sign up ahead who's indicated they wanted to address the committee?

Josh Morse: No.

Craig Blackmore: The answer is no.

Josh Morse: No early signups. We do have one person who signed up who's present, Dr. Smith.

Craig Blackmore: Dr. Smith, do you wish to address us on this topic?

Dr. Smith: No comments at this time, thank you.

Craig Blackmore: Thank you, alright. Yes, would you like to? I'll give you the instructions even though I know... please tell us who you are, if you're representing anybody else, and then if you have any conflicts of interest and...

Nadia Salama: I am Nadia Salama. I work for Group Health. I'm an M.D. and a clinical epidemiologist, and I don't... I'm a member of medical technology assessment. I do the evidence [inaudible]. So, I have just a couple of comments. It would be nice to have a table with number needed to screen versus number needed to harm to get the [inaudible] outcome. It would be nice to have that for... if you're giving your decision making to patients that they pick this or they pay out of pocket. That's one thing. The other thing is when we say effectiveness, I'd rather leave the word effectiveness for drugs, not for comparative diagnostic accuracy for tests. This is one we use even in our method of technology group, we have the differentiation between when we are assessing a medical technology test versus a treatment versus [inaudible]. So we keep this diagnostic test separate evaluation criteria, because we're looking at accuracy and one other thing. Accuracy is not choose so much now like likelihood ratios or predictive values. It's [inaudible] are grossly effected by prevalence. So, if it's a highly selective group, this would be overestimated factors. So, they usually use likelihood ratios now versus accuracy.

The other thing… this were… you didn't have long-term follow-up. So, there's no... in your table 49 say identify almost all cancers. We cannot make this statement because we don't know if they are really identify all missed cancers. So, unless you have long-term follow-up. The question is, what's the gold standard here that we're comparing to? We know digital mammography is not the best when we are comparing to digital mammography. So, the question you asked was, what do we do with these patients? What's the gold standard? Do we compare with MRI or digital mammography, which we know is not the perfect test. So, these are just my comments.

Craig Blackmore: Thank you. Shall we check the…? Hello, this is the Washington State Health Technology Clinical Committee. This is the public comment period. So, is there anyone who has called into the meeting that wishes to address the committee?

Alright, well hearing no comments, we will turn the phone off, and we will go back and check on the phone again, as we get to the end of the public comment period, which is actually not too far off. Anybody else in the audience that has not had an opportunity to address the committee that wishes to? Alright, we will move on with committee discussion. So, any further questions for any of our presenters? So, I have a question, which I think probably goes to the agencies, and it relates to particularities of billing and when a bill... I guess... how am I going to ask this? There's screening with digital mammography and then there's the DBT and my question is if we basically... whether or not we fund DBT does that affect the submission of a separate mammography claim? In other words... I'm thinking of the scenario described already where one might perform digital mammography on the DBT machine and submit a bill and might or might not do additional imaging that would... might not generate a reimbursable claim. Could one still be reimbursed for the digital mammography? I don't know that I'm asking this at all clearly.

Christoph Lee: [inaudible].

Craig Blackmore: Sometimes, we say no coverage, and that means that the entire procedure is not covered. Sometimes, we say coverage but it allows coverage of one aspect of something but not the additional aspect. I was thinking of, for example, the robot. We looked at robotic surgery, and we said you can do the surgery. We'll pay you for the appendectomy but we're not going to pay anything extra for the robotics, but the use of the robotics did not disqualify payment for the whole procedure. So, on some level there's some parallels here, potentially, but I wondered if they were separate codes in the minds of the agency directors such that that scenario would be relevant.

Female: They would be separate codes, because their code is separate. As to whether or not the... your decision will interpret whether or not it… whether and/or if they get payment.

Craig Blackmore: So, I guess my question, our decision will determine the DBT portion.

Daniel Ollendorf: Right.

Craig Blackmore: But whatever we decide there doesn't affect the mammography portion no matter what machine it's done on and no matter whether or not they do a DBT.

Christoph Lee: Right. Presumably.

Craig Blackmore: Presumably.

Christoph Lee: Yeah.

Female: [not at microphone] We're taking a proclamation vote, but there are two separate codes. In theory, you're absolutely correct. [inaudible] taking a look at [inaudible] if that is your determination is you want [inaudible] pay for mammography...

Craig Blackmore: OK.

Female: [not at microphone] [inaudible].

Craig Blackmore: I'm asking the question at this point. I'm not speaking for the committee.

Chris Standaert: It also wouldn't be surprising if it actually gets used a lot and then Medicare would combine them. They won't leave two separate codes if they're combined over three, two-thirds, or 75% of the time they'll bundle them quite rapidly if that's what happens, and then they'll be one code.

Female: That's why I think [inaudible].

Marie Brown: Which means somebody wouldn't bill separate... just bill for DBT.

Female: [not at microphone] I think that if they billed for just DBT, it would not go [inaudible] no coverage [inaudible], but we're looking at in from a scenario, like, as [inaudible] both those codes were on the same claim. So, you came in for the [inaudible] what happened. You come in, you go through mammography. The pictures are taken at the same time, so the codes are built on that [inaudible]. So, we're looking at whether or not this claim with those two codes would pay [inaudible] and then deny [inaudible]. So, we're trying to verify whether that [inaudible] just have tomography, which I'm not sure [inaudible]. Is that possible, or?

Christoph Lee: Only if you're willing to use the 2D synthetic software. You really need that 2D image to help you interpret the entire exam.

Female: [not at microphone] So on principle would they always be billed together then?

Christoph Lee: Currently, yes.

Female: [not at microphone] OK, another good question. [inaudible].

Craig Blackmore: Other questions?

Michelle Simon: Could I just follow up? You're saying you couldn't do just a DBT because it wouldn't make sense? You actually need the…?

Christoph Lee: You would at least need a synthetic 2D view off the 3D sweep. The 3D sweep does not help you with calcifications. It's really the 2D image that helps you with calcifications.

Michelle Simon: OK.

Marie Brown: So, you couldn't substitute it basically? OK.

Craig Blackmore: Any other questions?

Richard Phillips: Out of curiosity, Regence covers DBT, but it doesn't... doesn't Regence administer the HCA?

Josh Morse: If you could please use the microphone for the response.

Female: Pardon?

Josh Morse: Could you please use the microphone for the response? Thank you.

Female: So the question is, in the presentation you've seen Regence is indicating... the presentation indicates Regence is covering the DBT. Yes, Regence does administer the UMP and what we're doing is verifying whether or not that means UMP is getting that same coverage. In practice, under other codes, that should be the case, but what we want to do is make sure we're being accurate in what we're providing to you.

Craig Blackmore: Other questions? Alright, so we'll move on. I'm going to make a... tell me if you're supportive of this, but I think we need to deal with these separately starting with the DBT and then we'll look at the supplemental screening and the dense breasts and maybe we'll lump those together or maybe we'll separate MR and ultrasound, etc., from an organizing perspective, we'll start with the DBT question and try to deal with that one first, and I want to just... if we could just give one more shot to the phone, Christine, and just make sure everybody's had a chance if they need one.

This is the Washington State Health Technology Clinical Committee meeting and the open public comment period, and we just want to see if anybody on the phone wishes to address the committee, this would be your opportunity to do so. So, please let us know. Alright, we will close the open public comment period, and we will move on.

OK, so we'll start with the DBT question and what I'd like again is to ask if I could get one or several committee members to summarize where they think we are, not necessarily a yes or no but a summary of where the evidence is pointing at this point as a starting point. So, any volunteers? Joanne.

Joann Elmore: We need a randomized trial like DMIST, and DMIST was a randomized prospective trial that compared digital mammography to film screen mammography. Right now, digital tomo, the benefits are lower false-positive, higher cancer detection rate. It seems like it's improving the cancer detection rate of invasive, which is better than picking up more DCIS, but still we don't

know if some of that invasive is also overdiagnosis, but it does look promising, and I, obviously, care about lowering the false-positive rate because many of us work in clinical practice, and we see women with a lot of anxiety and, you know, [inaudible] the cost. There are risks associated with it. There's the cost. If we were to approve it for all the women in the state it could be a few million dollars every year as an add-on. Radiation, until CMS and other people figure out how to allow us to only do one screen, right now it's twice the radiation per exam. Those are some of the risks.

Chris Standaert: But that would never change. I mean, he's saying you need the planar picture. Unless the software gets better.

Joann Elmore: They've got software so they can synthesize.

Chris Standaert: [inaudible]

Christoph Lee: [inaudible] 2D.

Chris Standaert: Huh?

Christoph Lee: You can reconstruct the 2D image off the 3D sweep.

Chris Standaert: Right, but you said until the software becomes a little more reliable, or people are a little more competent than the software, they're not going to use it.

Joann Elmore: That's a good point. So, there definitely are risks. There's the cost and then there's also currently for all of these shocking a third of the facilities now have digital tomo, twice the radiation for women. In regards to the studies, they are... definitely have limitations. There weren't any randomized clinical trials. There's no data on mortality, morbidity. There's no data even on sensitivity and specificity. You need a year plus follow-up to find out are you missing cancers that are detected a year or two later. Two of the studies were done in other countries, in Norway and Italy, and the screening programs are quite different there. They don't screen women in their 40s and many of our women here in Washington State are in the 40s getting screened. The radiologists are much higher volume, perhaps more experienced. The standard there is to double read everything, two radiologists, and we don't do that. So, there are a lot of differences. One of those studies was a single site only. There was only one tomosynthesis machine studied in most of these, and there's many other machines. So, we don't know about the quality of the others. So, I think while CMS may have "approved" this as an add-on starting this year for $57 a pop, the announcement that I read, they cited the U.S. Preventive Services Taskforce as saying mammography has a B rating, but according to what Josh showed me for the CMS approving tomo payment, they're citing a many years old preventive services taskforce review that did not study tomo. In fact, that review was so old it didn't even study digital mammograms. So, I think that the CMS approved this without any evidence or data.

Chris Standaert: I don't know. I guess, I hear you and there's no RCT, but every study on DBT shows the same… they show the same thing, and the numbers are huge, and it says that they're good and these are improvements in very clinically important outcomes, higher detection rates, lower recall rates, higher true positive biopsies. I mean, these are… these are very important things in the management of these people. So, it's... and it's completely consistent between every study they have that they talk about pretty much. So, it makes you... and I know they're retrospective, but there is... they're comparative. They're not saying there's lots and lots of biased. It's not an enormous expense. So, it's… there's a value in there somewhat. The economic models get very tricky, because there always are so many assumptions in those that I don't really know what to make of them frankly. I appreciate all the work, but there are so many assumptions that it... your error bars get like [making crunch sound] as you go, and there's no... and when the data is like this, it's so hard to interpret.

Craig Blackmore: Other comments? Anybody on this side of the room want to weigh in?

Michael Souter: I think that obviously we'd all love a randomized control trial, and this has been said, many, many different forms in the discussions we've had before, but there isn't and we have to get on with what we have and make difficult decisions sometimes, and what we do is, we try and weigh up what the kind of the prevailing emphasis is. We're looking into grey areas, and very often, I think, that we've made decisions to cover based on less firm ground than we have here at the moment. I actually think in looking at this that the weight of effect to me is highly convincing when I look at the numbers and when I look at the consistency of direction, which is one of the greater criteria that we need to employ and I think that's important to take into account. So, to me, this is persuasive that I think we should be covering some part of the population referred to [inaudible]. I think that warrants a little bit more discussion but I am persuaded that there's a treatment benefit to be... no, I'm sorry, not a treatment benefit… but there's an overall healthcare benefit to be had here.

Craig Blackmore; Other thoughts?

David McCulloch: I would just… between what Mike said and Joanne said, I think there is some poorly designed... I mean, this data is imperfect, and it's promising and suggestive, but until you actually... there are so many ways in which it... you can get biased in the right direction, but until a proper RCT is done, I don't... I'm not convinced that it truly is improving health benefits to women.

Craig Blackmore: Richard?

Richard Phillips: I... when I read through before I even came here and listened to what was going on, I was inclined to say that we ought to approve it. I have to say that I... I've sort of backed off from that a little bit, but I do think that... I think the evidence is persuasive that there is a trend in the same direction for all the... all nine studies that makes me think that it... it probably has a role, especially if it can be done in a cost neutral way, because I don't see that there's any increased risk

from it. In other words, I almost see it as being equivalent, at least, and in that regard I tend to say I see no wrong... no problem with advocating for it. I guess the real issue is the cost and I don't know that I see that there is a substantially greater cost when you consider that you're probably adding additional diagnostics... diagnoses of cancer, which may offset it. That's very subjective, obviously.

Marie Brown: I think there was increased radiation when you do two.

Richard Phillips: Well, I think if you, what Joanne said is right. If we... if we're doing two studies, yeah, but I... that's the real question. We're sort of in an [inaudible] right now where we're... it's a developing technology and...

Marie Brown: Right.

Richard Phillips: ...who knows, maybe in two weeks it'll be all, you know, all be done with software with one study. But that, that's a legitimate point.

Michelle Simon: It is, and that's the one that concerns me, too, because if you look at this studies while the weight and the direction is kind of the same suggesting a positive benefit. These are not long-term studies. We're looking at six-month studies and that won't take into account the missed cancers, if there are any. It won't take into account the effect of radiation, which I think is... what is it, 10 milliseverts, 1:2000 people?

Craig Blackmore: No, no, no. It's much, much lower than that.

Michelle Simon: Oh, that's the one we saw in the first study.

Craig Blackmore: That was, yeah.

Chris Standaert: That was for [inaudible].

Michelle Simon: But there is some.

Craig Blackmore: Whole body CT and that.

Michelle Simon: But there's some exposure effect there if you're doubling your radiation dose for a study. So, I'm most concerned about the insufficient follow-up of these studies that we see.

Marie Brown: I think they said the mammography was equivalent to four years of environmental exposure, something like that?

Craig Blackmore: I don't have that.

Chris Standaert: What happens to women who get recalled? So, they get a mammogram and they get called back. So, that lower recall rate translates into what? People

who get recalled get another mammogram, they get an ultrasound, they get a… so I assume a biopsy... they get something, yeah. More happens to them. Again, we're... I mean, dropping the recall rate alone is a significant thing.

Richard Phillips: Right.

Chris Standaert: This stuff happens when you bring them back. They say that's a little funny. We're going to bring you back. That's always the start of more stuff.

Carson Odegard: One thing I wondered about the legislative aspect of this is… these patients get a letter and obviously it increases fear.

Craig Blackmore: Well, they don't in this state.

Carson Odegard: No, I know, but I'm just saying...

Craig Blackmore: Some states.

Carson Odegard: ...any other state, in some states, 15 states... when they get this letter, it raises their anxiety levels and you wonder how much of the recall rate is self-determined or pushed by the anxiety of the patient themselves.

Craig Blackmore: Now, does that… does that happen? I mean, do… does anxiety drive recall rate in clinical practice Christoph?

Christoph Lee: We're clarifying that this is probably a discussion for your second item, right? For supplemental screening because...

Richard Phillips: Like, the letter alone would...

Christoph Lee: So, yeah. So, in terms of anxiety provoking diagnostic workup, usually a woman will come in with an area of pain or palpable abnormality, possibly caused by their anxiety. I could see that happening, not so much sure if the DBT question comes into play.

Seth Schwartz: I disagree with that. I think this letter will drive people to come into their providers, and that will result in more [inaudible].

Craig Blackmore: Yeah, we're not, we're not in charge of the letter. I mean, we don't know what [inaudible].

Seth Schwartz: [inaudible] that someone else said. I'm not introducing...

Craig Blackmore: Yeah, no, no, no.

Seth Schwartz: ...this idea.

Craig Blackmore: I know. Whether... well, A, we're on the wrong topic, and B, we...

Richard Phillips: And we have no data on that.

Craig Blackmore: We don't know what the state will do, and we don't know what individual practices will send letters and respond.

Seth Schwartz: Not having data has never stopped us from not having an opinion.

Craig Blackmore: Yes, ma'am?

Suzanne Swagener: Hi, this is Suzanne Swagener again. I'm looking at here a clinical position statement from Regence for digital breast tomosynthesis, which notes that effective on or after July 1, 2014, Regence will not reimburse additional costs for breast tomosynthesis, as it is considered incidental to the screen and/or diagnostic mammogram. Does that address... does that address your questions? So, it will be billed but not paid.

Craig Blackmore: OK. So, what are we hearing? We're hearing one group saying there's not a randomized clinical trial. The level of evidence here is insufficient. We shouldn't probably cover this, although we aren't going that far yet. We have another group maybe saying there's no randomized clinical trial data, but we don't ever get randomized clinical trial data that often, and there's a lot of consistent... though they may be, there are consistent studies that show outcomes that, though they are not life and death, are clinically important in the sense of recall rates and etc., and then the third piece is if we agree there's a benefit, or whether or not we agree with the benefit, we do know there's a cost and it's hard to understand how that cost relates to magnitude of benefit because it's hard to even understand what magnitude of benefit would look like. So, how do we encompass that into our deliberation, as well? So, I think, I think that's kind of where we are. Does that seem like a reasonable summary of where we are?

Group: Yes.

Craig Blackmore: Does anybody want to reflect on that, because we have to decide, so. Joann?

Joann Elmore: As always, you do a nice job summarizing. We talked about the increased costs, the radiation, and we talked about how promising it looks and the importance of dropping the false-positive rate, which really does cause harm to women, to the system. It has a lot of downstream, I think issues. In thinking about potential benefits, we've been given data on the potential for increased cancer detection rate, and the one thing we haven't talked about is, is this good? Is this helping the increased cancer detection rate? You know, years ago when many of us went through our medical training, we didn't even think about the topic of over-diagnosis, but now we are, and now we don't know what percentage of these cancers will, you know, we're diagnosing them in the women and causing angst and harm and overtreatment because the cancer would have been there for the rest of the woman's life, you know, maybe even

regressed. We don't know. It is reassuring to a point that the cancers that tomo picks up on seem to be not the DCIS but more of the invasive. So, that's promising, but we do not know whether the increased cancer detection rate is going to help women and, in fact, I think most of us put more weight on the JAMA article, which was the U.S. based study and two sentences that I lifted out of that article, I just want to state again, one sentence was this study did not assess clinical outcomes. So, whether the increase in cancer detection rates is a benefit is not known, and then they have another sentence in their paper, in JAMA, that said however, assessment for benefit in clinical outcomes is needed. I mean, this looks really promising, really cool. I think it will help the field and we're going there. Whether we are there now with the evidence, I think, is something that our committee needs to decide and whether we think that it should just be automatically paid by our state, we as a group need to decide though.

Craig Blackmore: Any other comments?

Michael Souter: I understand the implications of cost and the implications of harm and possibly introducing more invasive management than would otherwise be warranted, but I also think that we've got the possibility of being able to look at the effect of... or rather, introduce this not into the kind of the entire general population but perhaps into the population that does have the difficulty with accuracy and screening, i.e. the dense breast population and that offers some ring fencing perhaps to constrain some of the concern for harm, whether it be to the public purse or to the individual.

Joann Elmore: Key question one had to do with the entire population, not just women with dense breasts.

Chris Standaert: Right.

Joann Elmore: And in fact, I personally don't like the wording of key question one because it uses the word versus. What is the effectiveness of screening with digital breast tomosynthesis versus digital mammography among women aged 40 to 74 who are candidates for screening? So, I guess two points. One, this is asking us about tomo in everybody not a narrower patient population, and secondly, it really should be worded what is the effectiveness, or we should use other words than effectiveness, of digital breast tomo integrated with digital mammography versus digital mammography alone. It's a subtle point, but I wish we had clarified it in the questioning.

Chris Standaert: I mean, the studies seem to be an integrated thing.

Joann Elmore: All the studies...

Chris Standaert: The studies seemed...

Joann Elmore: ...were integrated.

Chris Standaert: ...to be integrated. They seemed to be and I hear, also it's a little torn. I mean, it would be nice to have that study, but it's going to take 20 years because you're going to have to follow longevity. You're going to have to follow life. You're going to have to follow... you know, this could take a decade. You're going to have follow death rates, mortality. Is it going to impact that? I have no doubt that's important. Frankly, whatever we do, the ecosystem will sort itself out. There are probably people doing this already and not getting paid because they use it as a marketing thing and for the $50 they will pull people in, because actually it's probably not even the mammography they make their money, it's all the other stuff they do that comes out of it that they make their... the breast center, the money is elsewhere, I suppose. So, it's... the ecosystem will sort itself out, and some people may just start do... they may do it as an add-on, and it may be one code and they might get paid, and again, if it's... if Medicare pays it, people are going to do it, and then Medicare is going to change it to one code within five years, because that's just what they do. So, the ecosystem will solve the problem before the RCT is done, I suspect. It's going to do what it's going to do. So, I get it, but I... you know, it's what's going to happen. I'd love the data, but I don't think we're going to see it, and I think the thing will be sorted out before we ever get there.

David McCulloch: I agree with you, Chris, except I wouldn't say the ecosystem will solve the problem.

Chris Standaert: I didn't say solve it.

David McCulloch: Well, you said solve the problem.

Chris Standaert: No, I said sort it out. I did not say solve it.

David McCulloch: Well, I don't think...

Chris Standaert: They're very different words.

David McCulloch: ...well, I don't think it'll do either. I think...

Chris Standaert: The ecosystem will do what it will do with it is what I'm getting at.

David McCulloch: Right, it'll...

Chris Standaert: Yeah.

David McCulloch: ...push it in...

Chris Standaert: Right or wrong.

David McCulloch: ...a certain direction whether there's evidence or...

Chris Standaert: Right, right.

David McCulloch: ...benefit or not.

Chris Standaert: Right.

David McCulloch: Yeah.

Chris Standaert: Yeah, and it'll do it before the evidence is there.

David McCulloch: Right.

Chris Standaert: Because that's just what's going to happen. It's evolving too fast.

David McCulloch: The ecosystem has not done man in this country a great deal to do with prostate cancer.

Chris Standaert: No. I agree with you.

David McCulloch: It's, you know, a hugely profitable, damaging, over-diagnosed, and over-corrected.

Chris Standaert: And I, you know, I go back to where Mike was. I don't see any subpopulation here. I don't see any data that tells me it's more effective in women with dense breasts or not. I have a very hard time with that. I think it's so subjective anyway, but I don't see that in the data so I don't know how I would draw that out but compared to all the stuff we see, we don't have the RCT, but we have improvement in things that are highly important to people, which we almost never have. You know? I think of a lot of the other things we do. We don't see improvements in things that are this meaningful to people, such as a 30% increase in cancer detection and a drop in recall, and an increase in effective... accuracy of biopsy or true positive in biopsy. So, it's… it's like I said it's compelling to look at, even though it isn't the perfect data, but everything sort of lines up in the right way to make it... these are the things you would want it to do, and they're big numbers, still.

Craig Blackmore: So, I want to get back to what Michael said about sort of different populations and it gets to our cover, no cover, cover with conditions and we've been dealing for the most part with this as a cover or no cover sort of framework and the question… my next question is, is it even worth considering coverage with conditions? Are there conditions that we could define? We heard about breast density as being a potential condition. Are there other, and again I'm not saying there are or aren't, I just want us to think this through a little bit before we get to the point of having to vote. So, would there be potential conditions people would think about that might affect coverage? Richard?

Richard Phillips: Can we really put conditions on a screening test, though?

Craig Blackmore: Sure. You can define the population that's allowed to get this particular...

Richard Phillips: That has what?

Craig Blackmore: You can define the population that's eligible for payment for this particular modality. You can say women over 80 could get it, I'm not proposing that at all, but you could definitely define conditions.

Michael Souter: I mean, by virtue of definition, gender is already one of the criteria, so.

Craig Blackmore: Well, yeah, it is. So is age.

Richard Phillips: The study was oriented towards age 40 to 74, isn't that right? I mean, isn't that...

Craig Blackmore: Yeah, and...

Richard Phillips: ...what the evidence...

Craig Blackmore: but are there other condition... I mean, like I say, we could say that it's only covered in women with dense breasts would be one condition. Is... are there other potential scenarios we should think about, because again, we're going to have to vote and so when we say cover, no cover, cover with conditions, what could conditions look like? Is that really viable? Again, I'm not saying yes or no, I just want… I want to have that discussion about what conditions might look like if we had them.

Seth Schwartz: Can I add one thing and ask a question?

Craig Blackmore: Yeah, yeah.

Josh Morse: In looking through some of the information about the new code, it appears that the FDA only approves the machines right now to do a 2D or a 2D plus a 3D, and I'm wondering if that software is FDA approved to do the 2D and the 3D and if that would make a difference to a coverage framework? Does anybody know that? Does the expert know?

Craig Blackmore: I didn't understand your question.

Josh Morse: So, the FDA... one of the limitations and the reason they added the code as an add-on code is because the FDA approval for the machines, according to ACR's news release, states that… and the FDA site confirms this on at least one device, is that you can do a 2D or you can do a 2D plus a 3D, but you can't do a 3D alone per the FDA.

Craig Blackmore: So, I think we heard that you wouldn't do a 3D alone, or is that... I mean, Christoph, is that what you were saying earlier that 3D alone wouldn't be...

Christoph Lee: We personally are not comfortable doing that; however, the FDA has approved that synthetic view.

Josh Morse: OK, that answered my concern, thank you.

Craig Blackmore: So, are there any conditions, people, that we should discuss? So, the only one on the table is then breast density and I heard one voice saying that breast density didn't resonate as something we had data on for this particular technology. Other sentiment that that might be a legitimate consideration or should I... when we try to narrow things down, should we try to narrow things down to cover or no cover instead of cover with conditions? Am I making sense? So, is that... is it viable as a consideration using breast density as a condition? I'm getting a few nods and a few shakes. Alright.

Theresa: This is Theresa from the Health Care Authority. We would have a hard time. It may be easier for the UMP population, but in Medicaid it would be hard to do this on a single visit. We wouldn't necessarily... we would be able to pay for the mammogram, but then if in the course of that investigation have decided we need to do the DBT as well, we wouldn't know beforehand that that woman had breast dense. So, they'd actually have to come back a second time because we'd want to make sure that only women who were at higher risk got that additional testing, so that would require two visits, it sounds like, with both technologies. Similarly, once a woman was diagnosed as... or subjectively found to have dense breasts, it appears that that would change over time. So, we'd have to think about how that might influence future testing if she was once identified as having dense breasts. So, from a programmatic implementation piece, I would just share with you those thoughts.

Craig Blackmore: So, the framework for the second half of our discussion today will be about supplemental screening in women with dense breasts, and that's a call back. That's a second procedure.

Kevin Walsh: No, she's trying to make a point.

Craig Blackmore: No, that's in the second half of the discussion, whereas if we were to use fatty breasts as a condition for DBT, which should be done in the same setting, it's a different model.

Kevin Walsh: She's trying to… she's trying to tell you it's not going to be done in the same setting for...

Craig Blackmore: Right.

Kevin Walsh: ...Medicaid patients.

Craig Blackmore: Right. We're saying the same thing.

Theresa: [not at microphone] And that's because it's going to be their first mammogram or the first mammogram in this particular place for Medicaid. I mean, that is the main difference between the UMP. Right, they may be new to that facility. I would mention if you're [inaudible] with more than just the presence of dense breasts [inaudible] visualization [inaudible] finding there and at that time then you [inaudible] enhance the viewing [inaudible]. That would be easier.

Michael Souter: But then that's [inaudible]...

Craig Blackmore: Then, that's not screening.

Michael Souter: ...risk category wouldn't it?

Craig Blackmore: That's a diagnostic study. That's not a screening study.

Michael Souter: So move to switch to screening. I mean, the… OK, granted that, you're not going to have the psychic capacity to recognize that this woman has got dense breasts before she gets a mammogram, but it's not as if we're talking [inaudible] about one soft visit in the life of that patient. I mean, with the serial screening you're going to have second, third, fourth, and fifth visits possibly. This may allow greater accuracy of diagnosis over time, and that's the concept behind looking at people who it's more difficult to image.

Christoph Lee: So, I'm sorry, can I make a point? Across all studies, in Europe and the U.S., they gave overall increased cancer detection rate and overall decreased recall rate, not stratified by density, and of the early analyses coming out of the prospective trials, the only prospective trials that are happening in Europe right now, there is no difference in terms of benefit across densities. So, even women with fatty breasts and scattered fibroglandular densities are finding benefit in terms of increased cancer detection rate and decreased false positives.

Craig Blackmore: I mean… I thank you for that. I'm going to agree with some of the voices we've heard that we just don't have any data, and it's hard, I think, to come up with a condition when there's nothing to support it. I mean, why did you come up with that? It seems to make sense, I agree, but...

Michael Souter: I was just coming up with it because it was mentioned as kind of part of the original agency presentation [inaudible].

Craig Blackmore: Yeah.

Michael Souter: [inaudible].

Craig Blackmore: And because I asked people to come up with potential conditions. So, we could shoot them down. Joann?

Joann Elmore: I would appreciate it if our expert could say a word about ongoing prospective clinical trials and anticipated dates, that the information would be available.

Craig Blackmore: Do you guys know? Any of our presenters over there?

Daniel Ollendorf: Just... at least I can talk a little bit about TMIST, which is sort of like DMIST. There's a lot of excitement and hopefulness that a randomized control trial would happen in the U.S. Unfortunately, there are a lot of obstacles, and it's still just a hope rather than a reality. I think [inaudible] and folks are talking about different collaborations, having partners in industry, but it isn't a reality yet, and if we've learned anything from history, we had Medicare cover digital mammography and CAD back in 2000, 2001, and the DMIST trial started around that time, and the data didn't come out until 2005, 2006, and the cost-effectiveness analysis didn't happen until 2008, and by that time, over 80% of the facilities were digital. So, I don't think you're going to see a randomized control trial in the U.S. in the next decade. There are other trials going on in Europe and I think that was in the review summary.

Daniel Ollendorf: Yeah, it looks like there's a Malmo trial. There's a couple of other trials that look like they're going to be completed in 2015, late 2015 and 2016, but again, these will not be long-term follow-up studies. These will be the same kinds of studies that we've already talked about.

Craig Blackmore: Alright, any other discussion, or I'm going to move us on? OK, so we'll find our decision tool in here somewhere. OK, so this is our coverage and reimbursement determination tool and sort of the standard spiel. It talks about the basis we use for making our decisions and sort of moving ahead to kind of the meat of the issue, which is the... it starts with the evidence identification and it discusses some of the outcomes that the committee thought was important in making a decision. For safety outcomes listed on here already are radiation, over-diagnosis, unnecessary workup. Are there other safety concerns other than those that need to be mentioned? I guess unnecessary work up would include procedures and biopsies and that sort of thing.

Under efficacy or effectiveness outcomes, we have mortality, quality of life, detection of cancers, recall, biopsy rate, sensitivity, specificity, positive predictive value, other effectiveness outcomes that we think are important that aren't on here, anyone? Alright.

Special populations, we discussed fatty breast, and we talked a little bit about age but the data maybe wasn't there to help us.

And then cost, cost-effectiveness, cost utility we talked about what data exists and modeling. We are also charged with looking at what Medicare has decided, and we heard about Medicare's code and decision, although it's not really a national coverage decision, I guess, but their decision to allow coverage, and boy we have... so that moves us ahead to our voting decisions, and the first is the nonbinding determination of sufficient evidence, and this will hopefully guide us, as we go to our more... to our coverage decision.

So, the first question is, is there sufficient evidence under some or all situations that the technology is effective? And so this would be then the use of digital breast tomography in addition to digital mammography versus just digital mammography alone, and if you think it is proven to be more effective under any circumstance, you should vote more and similarly less or equivalent or unproven, and I guess that would affect any of the outcomes.

So, nonbinding vote.

Josh Morse: On effectiveness?

Craig Blackmore: This is on effectiveness.

Josh Morse: OK. Six more, four unproven.

Craig Blackmore: And then safety.

Josh Morse: Six unproven, four equivalent.

Craig Blackmore: And then finally the cost-effectiveness question.

Josh Morse: Seven unproven, one less, and two more.

Craig Blackmore: OK, so based on that, does anybody have any further comments? Does that trigger any further discussion?

Michael Souter: Just again, I'm just, when we're looking at the tool, I would just encourage us all to think about what's there and sufficiency of the evidence, and we have to kind of weigh all that out, but it's not just randomized control trials. I think that's something that's... we have to be mindful of. That's our responsibility to make decisions in the absence of randomized control trials. So, I encourage everyone to think about the amount of the evidence, the consistency, and the recency and I think those are all important things to bear in mind.

Craig Blackmore: Any other comments? Alright, we...

Seth Schwartz: I just want to say in response to that, promise is not evidence. Promise is promise.

Craig Blackmore: Any other comments? OK. So, breast digital tomography, we haven't actually... you have three choices, cover, not cover, or cover unconditionally and we didn't specifically dismiss cover under conditions. If we go that way, we'll decide later what the conditions are. I didn't get the sense that's where we were headed. So, we'll move on. So, the vote.

Joann Elmore: What's the question?

Craig Blackmore: This is screening... do I need to check the key question to make sure we're OK?

Josh Morse: Yeah, this is key question one, right? Screening DBT?

Craig Blackmore: Yeah. What's the question actually read?

Josh Morse: So, this is...

Joann Elmore: What is the effectiveness of screening with digital breast tomosynthesis versus digital mammography among women aged 40 to 74 who are candidates for screening mammography?

Craig Blackmore: So, this is coverage for digital breast tomography, in addition to digital mammography in women aged 40 to 74 who are eligible for screening.

Chris Standaert: Thank you.

Josh Morse: There are six cover, four no cover.

Craig Blackmore: OK, we are charged with comparing our decision to Medicare and I guess we are in line with Medicare's recent actions and we have already reviewed other commercial payers and they are divergent. We are in agreement with some of them and others felt the evidence was insufficient where we seem to have narrowly thought it was sufficient to allow coverage, and in terms of professional guidelines, again, there is a lot of variability in the guidelines, and so, I think we are in line with some and others interpreted the evidence somewhat differently. OK, is that what you need for that, Josh?

Josh Morse: Thank you, yes it is.

Craig Blackmore: OK, part two of this is the issue... do you want a five-minute break before we go on? A fifteen-minute... ten-minute break before we go on? A ten-minute break before we move on to part 2.

So, we'll call the meeting back to session. We will work on the next part of this afternoon's topic, which is the issue of supplemental screening in women of increased breast density. So, does anybody want to start off sort of giving us a perspective on where we are, where they are on this half?

Michael Souter: I've been applicated for following the previous part one of that. So, I am offering support for that to cover. I find myself less convinced by this part, and I would have to say I have seen nothing compelling to actually offer any coverage in these circumstances.

Craig Blackmore: OK, so the evidence isn't there? Is that the…?

Michael Souter: Yeah, I just haven't seen anything that I think constitutes an adequate weight of evidence.

David McCulloch: I'm sorry, Craig. I'm muddled. I thought we had just, as a group, voted to cover DBT for all comers.

Craig Blackmore: Yeah, so we're done with that. We're done...

David McCulloch: So, we don't need to cover it for... well, so...

Joann Elmore: No, he's asking question two.

Craig Blackmore: We're done with DBT. We're onto...

Josh Morse: Ultrasound and MRI.

David McCulloch: OK.

Craig Blackmore: Ultrasound, MRI in women with increased breast density.

David McCulloch: Who've already know... who are now going to get DBT anyway.

Josh Morse: Right. They've already had their DBT.

Craig Blackmore: Their DBT'd if that's the way they...

David McCulloch: Absolutely.

Craig Blackmore: ...went or they're DM.

David McCulloch: Right.

Craig Blackmore: And so now, are the women with increased breast density, are they going to get something else?

David McCulloch: Something else.

Joann Elmore: I'll make one point that was left out of the review. It wasn't necessarily asked of our evidence vendor. So, I can see why it was left out, but we need to step back and point out the reliability and variability of just a diagnosis of breast density. There have been a few studies that have taken a woman's mammogram and you show it to the same radiologist at different time periods or to different radiologists and as many as one out of five will change density categories. So, you know, I think that there is both not adequate evidence to support us voting in favor of this key question two, but to step back further, you know, what is density and is that even a reliable marker?

Chris Standaert: I think that's a good question, and this one really drifts into this whole issue of when is it screening and when is it something else? Call backs, things [inaudible] something there, somebody's worried about it, they're high risk, that's a dif... we're not even talking about that. Maybe they... maybe some of

these things shouldn't be done on them either, but that's not even our place. This is just purely asymptomatic people with no particular reason to be concerned other than they fall within the age demographic who get screened for breast cancer and somehow you define dense or not dense or too dense or not too... and then… but all these tools. The MRI hasn't been studied in that population, and the ultrasound seemed to have a lot of uncertainty and lead to all sorts of bad things happening. Your biopsy predictive value is down to 6%. I mean, it doesn't just... it doesn't seem like it accomplishes what you would want a screening test to accomplish. It pushes you the wrong way.

Craig Blackmore: Carson?

Carson Odegard: I'm just wondering as a procedural thing if we should lump these together. I mean, for example, if you take handheld ultrasound, it more than doubles the recall rate. Do we want to lump that in with MRI if it's got better diagnostic rate or ability but more expense, or should we take these all separately?

Craig Blackmore: I think that's a good question. I was sort of thinking we would start off together and see where that seemed to lead us, and if there was feeling among the group that one was to be handled separately, then I'd be happy to do that. I don't... I was thinking clumping myself, but again, it's whatever... it's whatever the group wants.

Michael Souter: Let's support clumping.

Group: Clumping.

Craig Blackmore: Clumping. So, I'm hearing some concerns about the data. I'm not... I'm hearing that the data is not sufficient from some folks here. Is there anybody who wants to come across on the other side and make an argument that these are things we should cover, at least under... in some... at least one of the tests in some of the circumstances? Richard?

Richard Phillips: This subpopulation, I don't know if this affects screening or not, but MRI and high-risk patients, you know, high-risk screening, now, is that... I'm not sure that's really our topic or not.

Craig Blackmore: So, high-risk... so, we've talked about high-risk in different context. High-risk meaning the 20% Gail model women with genetic mutations, personal history. They're not part of our decision. So, they are covered under our previous decision for MR.

Richard Phillips: Right.

Craig Blackmore: Now, sometimes we've heard high-risk defined as greater than 3% or high-risk meaning different breast densities. That is our discussion, but the real high-risk, the, you know what I'm saying. The BRCAs and the... all this, etc. They're not part of the discussion.

Richard Phillips: Fair enough.

Craig Blackmore: The only risk stratification we're looking at is dense versus not dense, which is not real high-risk. There was another mention made of what if you are high breast density, which bumps up your risk a little bit, and you have some kind of family history, which bumps up your risk a little bit, then you're higher risk. You're nowhere near the BRCA 120% but you're at a, I think, greater than 3% was where Dan had it on his model. So, I don't know what term to use, but that's clearly not the group we looked at a couple years ago for breast MRI.

Chris Standaert: Yeah, but even that's different than saying that to your patient. I think that population's different than the screening population. Screening would imply to me that people would do a mammogram or a DBT and then they'd say breast tissue is kind of dense, looks fine, but I want… but I'm going to do another one just to be sure and I have no other particular reason to do it other than just staring at the mammogram... not even knowing a thing more about the patient. That would be a screening tool. Is it just... it's an extension of the screening population, but I don't see that it... I'm not sure that helps, and that's different from any consideration of with this history, with this this, with this that, with the whatever I want to look a little harder. That's a different question, and that's not a screening test, and that's not what we're talking about.

Craig Blackmore: Richard?

Richard Phillips: Could I ask a question of the clinical expert? My impression is, is that you don't do supplemental studies, is that true at your place?

Christoph Lee: We don't, no, not just for dense breasts. That alone is not enough to push us to recommend any supplemental study.

Richard Phillips: Is that a philosophy or is there, can you embellish, is there evidence behind that?

Christoph Lee: Well, I think the evidence that Dan kind of summarized in his review is pretty compelling. You know, the caveat being that women with dense breasts and other risk factors that bump them up into the high-risk category, you can make an argument that based on BCSC studies that have been done that women in those high-risk categories are not getting supplemental screening MRI and are under-utilizing it. So, in that personal conversation women have about their risk factors, if they got a letter about their dense breasts, breast density could be one risk factor that's discussed but really, if it helps push them to that greater than 20% lifetime risk, then the discussion could revolve around getting that screening MRI that is indicated

Craig Blackmore: But again, those women would then be covered under our previous decision if they're bumped into that 20% risk. OK, other comments? OK, so again, trying to kind of narrow things a little. We usually think of cover, no cover, or cover

with conditions and are there conditions that we should be talking about so that we could understand what we mean, where we devote in terms of cover with conditions. What would that look like? So, one thing we heard was something like family history on top of dense breasts that might bump you into a little bit of a higher risk category. Another one might be you're in the highest of the breast density categories, not the two highest, although all of the sort of letters and things pertain to the two highest categories. So, I'm just... I'm throwing these out for consideration. I'm not advocating. Does anybody have any thoughts on what a condition might look like, or is this not a fruitful…?

Kevin Walsh: I didn't see any evidence to allow us to get that granular in our distinctions.

Craig Blackmore: OK. Anybody have any other thoughts? Should we proceed to voting? Alright. Back to the tool. Alright, so I think we've talked about the tool already, and any other outcomes. I don't know. Is there any other safety, efficacy, or cost outcomes or any other special populations other than the ones we just mentioned? Special populations would be fatty density and family history and seeing no further comments, we will go to the first nonbinding voting opportunity and so the first question is, is there sufficient evidence under some or all situations that the technology is effective. So, this would mean, is there sufficient evidence under some or all situations that the use of... we're lumping so one of these supplemental screening modalities is more effective than screening without the supplemental modality, and if you think it is effective under any circumstance, you should vote more; otherwise, less, equivalent, or unproven.

Josh Morse: Ten unproven.

Craig Blackmore: Safety?

Josh Morse: Ten unproven.

Craig Blackmore: Cost effectiveness?

Richard Phillips: I'm sorry?

Craig Blackmore: Cost effectiveness?

Josh Morse: Two less, three less, seven unproven.

Craig Blackmore: OK. So, the initial vote can spark further discussion or we can keep going. Any other thoughts? OK. So, we'll move to our coverage decision. So, supplemental screening, including MRI, ultrasound, handheld or automated, in women who are identified as having increased breast density.

Josh Morse: Ten no cover.

Craig Blackmore: So, we should figure out if that corresponds with Medicare coverage decision and now I'm going to get myself confused. Medicare didn't have an actual ruling or decision around breast density, correct? That was just on the other things we talked about.

Josh Morse: More for diagnosis rather than screening. It indicates on page four of your decision tool.

Craig Blackmore: So, that doesn't apply to us. So, there's nothing relevant to us. Breast MRI. So, it only discusses breast ultrasound and MRI as diagnostic not as screening, so that's off, and then we examined other payers. We heard about that in the presentation and other states, and I think where we disagree is that the group who evaluated the evidence didn't see any evidence in these specific groups that there was any added benefit of additional imaging. Does that give you what you need, Josh?

Josh Morse: I'm just making sure...

Craig Blackmore: Making sure there's no...

Josh Morse: ...there's nothing in the professional guidelines.

Craig Blackmore: ...professional guidelines that are relevant. NCCN says there are studies supporting ultrasound but it doesn't give a specific recommendation, at least not in here. ACR they say consider it but not... ACS doesn't... oh, that's DBT. OK.

Josh Morse: Thank, yeah, thank you.

Craig Blackmore: We'll move, we'll move on? So, the final item on the agenda is updates.

Josh Morse: OK, so future, Christine has the slides coming up. In the back of your binder, for committee members, there is a series of slides that will describe where we are with the ongoing evidence reviews, and then we'll talk about... actually we'll talk really first about proposed new topics. So, we are currently in process for the testosterone testing evidence review. At the last meeting, we talked about this, and your comments were forwarded to the writers on that report, and they are responding to that. The draft evidence report is out now for that, and I think the comment period closes today on the testosterone testing report.

David McCulloch: So, Josh, I see that on March 20th, that's the only... we're going to spend the entire day on testosterone testing. Is that because we're expecting four or five hours of public testimony in favor?

Josh Morse: No. It is the only topic scheduled for that day. It's just the way the schedule worked out.

David McCulloch: OK.

Josh Morse: But it's not...

Craig Blackmore: So we might get out... we might have a half day.

Josh Morse: Yeah, it could very well be a half day. OK, the next topic on our list is the imaging. So, we gave a wrong date for that meeting in March this morning on one of our slides. It said March 15th, that's a Sunday. So, we won't be here that day. I won't be here that day, but the 20th is actually the Friday, the third Friday in March, and that's when we'll have that meeting. The next meeting and the next topic to highlight here is the imaging for rhinosinusitis. That happens in May, on May 15th. The draft report is scheduled for publication on February 9th, and of course we'll send you a notice when that becomes available. The same holds true for bariatric surgery. That review is in process. The authors of that are here right now actually and that is also scheduled for publication on February 9th. Again, I touched on this this morning, tympanostomy tubes, we are just starting this review now. We don't have a draft scope or key questions published yet, but we will in the next couple months. That's scheduled for next November, and the same is true for the lumbar fusion re-review. We're a little less advanced than the tympanostomy tubes on that report, but that's the next one in the queue to go forward.

So, when we have greater detail on each of these schedules, in your packet after this slide, but what we wanted to call your attention to today are the proposed technology topics. The director of the Health Care Authority identified these topics in consultation with the agencies about three or four weeks ago. We published them for a two-week comment period. It'll be two weeks ago Monday, so almost two weeks ago now. We held a conference call a week ago for stakeholders to ask any questions they had about these proposed topics. The complete document with greater detail on each of these is behind these slides in your binder. So, you'll see there's a little bit more context. There's more detail about other topics that we considered, as well. There's information on the… I think five, six topics we considered in greater detail for re-review and we have shown here. We have two re-reviews identified for the next cycle on the bottom of the slide that we have up right now, cardiac stents and spinal injections, and we have seven proposed new topics. So, I'll give you a minute to review that.

David McCulloch: These look great. Number four, pharmacogenetics seems just a tad broad. I mean, it's an incredibly, it's another tsunami coming our way because the ability to measure all sorts of little bits of the human genome and package it together and charge you $5000 for it is growing, but the evidence that that actually leads to reasonable changes in treatment and outcomes, those studies are lacking, or at least I would think need to be parsed out in individual cases. I mean, you know, BRCA-1, BRCA-2, that's a great example of a genetic test that has actually been very well… but there's no just explosion of other things. So, it's a great topic, I'm just not sure if we're going to end up being able to discuss anything without getting a little more narrow.

Michael Souter: I agree. I mean, by the time... we're not just talking about individual genes here. We're talking about all the different polymorphisms and how they can manifest themselves and the interactions therein, and it's a huge field.

David McCulloch: Yep. That's one.

Chris Standaert: Yeah, we'd have to narrow it down.

David McCulloch: Then, and then number three, Novocure. That seems so... that's self-evident. That must be beneficial. It's new and it's a cure. So... I'm sorry. I don't know what that one is, actually.

Michael Souter: So, I have just one comment about the ECMO, and I think that's one of the things that helps us when we come to the discussion is some appreciation of the duration of treatment in there, because that can often be, you know, a significant factor in whether you choose to institute a technology, the likely...

Josh Morse: OK.

Michael Souter: ...anticipated times.

Josh Morse: So, these are great comments and observations on these topics. The agencies that help to identify these topics, there is some representation here. I don't know if they want to provide any feedback. For example... Dr. Fotinos?

Charissa Fotinos: Yes.

Josh Morse: Do you want to comment on the... I have my own perspective on the pharmacogenetics topic and potential scope.

Charissa Fotinos: That's exactly what we were just talking about. We could refine that a couple of ways. I mean, one of the things that we need to do as an agency, I think across programs, is come up with a way in which to evaluate these tests as they come out, because as was said, there is a new gene sequence that can be measured everyday with some perhaps implication, but whether or not it ultimately predicts better outcomes, we don't know. So, it is... is there a possibility of coming up with a framework by which we can evaluate tests as they come out? Another possibility would be to look at those most commonly done tests to see if there is any literature to support them. I mean, we could probably ratchet that down to maybe six or eight, if that many, and see if there was anything for those, recognizing that for a lot of these, there's not going to be much literature and we don't have to bother with them. So, I think there are a couple ways in which we could go.

Josh Morse: I mean, we agree that pharmacogenetics is not the state topic, that it's got to be narrowed. We had some internal discussion about what that might look like, but we haven't focused...

Charissa Fotinos: Scoped it completely down.

Josh Morse: ...down in terms of scope.

Michael Souter: I mean, one of the kind of first questions are, are we talking about the genome or are we going to include the protean in that as well? A lot of people are looking at that in terms of drug handling and metabolism.

Charissa Fotinos: Right.

Chris Standaert: I had a similar question. PRP, that number five, I mean, you say injections, you know, there's wound healing and PRP is most commonly for tendinopathy but people use... you've got to be very precise about indication because it's for tendinopathy. People inject it in disks. They put it in arthritic joints. They use it concurrently with a brazen arthroplasties for chondral lesions in joints. It's just stuck in sort of every almost musculoskeletal indication you can think of. So, breaking that down by indication would be very helpful. If there is anything there, it's going to have to be defined, because it's used all over the place.

Craig Blackmore: Well, you might be able to lump it.

Chris Standaert: You might be able to lump it, yes. Yes, I totally agree with you. We might end up lumping it but it will help the discourse if it gets broken down by indications. You can really pin it down better that way.

Michael Souter: And my last comment would probably be appropriately the fecal microbiota installation that there's... there's been some recent papers there just looking at the significant differences and outcome just based on the kind of packaging or the delivery method, as it were. So, I think that would need to be parsed out and questioned, as well.

Gary Franklin: So, I think if you have some ideas about how to focus this, that would be really great to get those ideas, but I think where we were coming from was just everybody's talking about personalized medicine now and I think what that mostly means is drug companies targeting drugs and, you know, if we pick some really important areas like epilepsy or a few other areas, you know, that... for which a lot of these tests have been done and try to look at the literature of… are health outcomes improved from doing these tests? I think that's what we kind of had in mind, but if you have a clearer idea about how to focus that, that would be great.

David McCulloch: Well, I mean, I would... we've wrestled with this at Group Health. So, at least a straw proposal for how to go... we've come up with what we think are reasonable, you need to meet these six... here's the six things. You should look at one after the other and if it patties all of those tests, it should be approved. We can give you that if you want just to look at. It's not rocket science, and

then pick one or two of the most common examples and then say, OK, can we walk through that and see? Does that pass [inaudible]?

Gary Franklin: Right, and you look at those, you know, six or seven of the best examples. If you got something, great. If you got nothing, the rest of the stuff doesn't really matter that much.

Craig Blackmore: We can establish a precedence, right?

Gary Franklin: Yeah, so if we could get that from you, that would be great.

Josh Morse: Yeah, so this is the proposed comment piece, and there will be a... should these go forward and be selected, there'll be a 30-day comment period where we'll... we can collect more information specific to what you think, or what anybody thinks, might be included. Any other questions or thoughts on these topics? OK, that is all the information I have. Thank you.

Craig Blackmore: Alright, well thank you all, and we are adjourned.