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Health Technology Clinical Committee Public Meeting
January 20, 2017

- Chris Standaert: ...pharmacogenomics testing is Dr. Jon McClellan who is a psychiatrist at the University of Washington who, as a clinical expert, is meant to help give us clinical context to the topics we're reviewing. That being said, I keep thinking my agenda is in my folder. It's on top of my folder. That being said, we will start our meeting. We will start with some program updates from Josh Morse, and then we will go through our previous meeting business, which is our prior decisions. Then, we will get into the discussion of pharmacogenomic testing this morning. Alright, Josh.
- Josh Morse: OK, good morning. I'm Josh Morse from the Health Care Authority. If we could also start with just the committee members going around and saying their name into the microphone for the purposes of the transcriptionist. That would be great. Dr. Yen if you could start.
- Tony Yen: I'm Tony Yen.
- Seth Schwartz: I'm Seth Schwartz.
- Chris Hearne: I'm Chris Hearne.
- Carson Odegard: Carson Odegard.
- Jon McClellan: Jon McClellan.
- Joann Elmore: Joann Elmore.
- Gregory Brown: Greg Brown.
- John Bramhall: John Bramhall:

Laurie Mischley: And Laurie Mischley.

Josh Morse: Thanks very much. And, uh, one technical feature before I go through the few slides that I have here, it's been pointed out, is your microphones today have a new feature where you can, apparently, use the mute function. So, there are two buttons here, one shows the mic with a line through it, and that will turn your mic off. The one to its right with the face and sound coming out will turn it back on, OK? So, new technology there.

So, just a few quick updates. I think this might not be working. Christine, if you could advance the slide? Or maybe the computer's frozen up here. Well, really the only thing I was going to point out today, other than the topics, which Dr. Standaert has already mentioned, looking ahead, the next meeting of the committee is March 17th, and there will be one topic on that day, and that's extracorporeal shockwave therapy. I do hope that between... also on the agenda for that day will be some administrative work probably on the committee's bylaws, so a review of some updates to the bylaws in the meeting on that day. At the following meeting, which is May 19th, there are two topics scheduled, treatment of chronic migraine and chronic tension type headaches is one topic, and the other topic is varicose veins and a select number of procedures for varicose veins. In July, we have a meeting scheduled on the 14th, which is the followup meeting, a brief phone conference to conclude the work from July, and the next meeting is all the way out next November, and we don't currently have topics scheduled for that meeting, but those are likely to be the skin substitutes topic and computer-aided detection for mammography topic. That concludes my comments this morning, unless you have questions for me. OK. Thank you.

Chris Standaert: OK. We'll move on. Our first step is to go through our prior meeting's business. So, we have minutes that people should glance through if they haven't already. So, we need to approve the minutes, and then we will talk about our coverage determinations and finalize our votes on those. I had not seen any issues in the minutes myself. If people could just take a minute and glance through and make sure we don't see any concerns in there. Did you find a typo?

Where are you? So, the bottom of page 3 on the draft, the last full sentence in that paragraph says there is sufficient to make determination on this topic. Sufficient evidence I assume is the word we should have in there.

Josh Morse: OK. Noted. Thanks.

Chris Standaert: Anything else anybody sees? When people are comfortable, is there a motion to approve the minutes?

Male: OK. Approve.

Chris Standaert: Is there a second?

Male: Second.

Chris Standaert: All in favor of approving the minutes? Let's make that everybody, so that's nine.

Josh Morse: OK. All approved.

Chris Standaert: Yeah, all approved. OK. Next, we move onto our final coverage determination. So, we'll start with negative pressure wound therapy. This is on page 2 of the minutes. So, we approved it under certain conditions, and our limitations or conditions were complete wound therapy program must have been tried or considered prior to negative pressure wound therapy with discontinuation of coverage, as noted, essentially with no measurable degree of healing and after four months. We got one public comment from Dr. Franklin of Labor and Industries about the word "considered", which I think I sort of agree with. I'm sort of wondering if we've let that go by. The idea that tried or considered means somebody can just sort of say, well, I thought about it, which is probably not really our intent, I wouldn't think. I don't think we're just saying, this is just another consideration. I think we're trying to say that it either was not going to be a viable option or it wasn't successful to do some other way of treating this, not just that people thought about it. So, Dr. Franklin, in his public comment, gave us some proposed language, and this is certainly in the scope of what we can do, clarifications of our intent and language are well within the scope of what we can adjust in these decisions. A complete wound

therapy program must have been tried and failed from prior to wound therapy or the complete wound therapy programs are contraindicated. So, that means that they tried and didn't work, or we, they just are not, for whatever reason, other things are contraindicated in the patient. So, without contraindications, you have to try something else, a more conservative form of care. Is that what our intent was, do people think?

Joann Elmore: Yes.

Chris Standaert: Are we comfortable with Dr. Franklin's language, or do we want to alter that a bit?

Seth Schwartz: I think that captures the spirit of what we wanted to say.

Chris Standaert: I think so. I also suggest we put an "or" between our two conditions, which is also probably a valid statement. So, we add... we change that first sentence to Dr. Franklin's language. Do you guys see that? I'm sorry. I'm talking to our staff over there. Kris, you got it? And we're going to add the "or"? These are two separate conditions for discontinuation? Yeah? OK. So, with the amended language, we'll have a vote to approve our determination. All those in agreement with our decision, as written.

Josh Morse: All approved.

Chris Standaert: All approved. So, on the phone, is there a committee member on the phone, Dr. Walsh? I know he was driving in, but I don't know if he's on the phone at the moment.

Josh Morse: Do we have the phones muted or unmuted?

Chris Standaert: So, is Dr. Walsh on the phone by any chance?

Kevin Walsh: Yes.

Chris Standaert: Ah, we can mute him again then. Dr. Walsh, before we finalize our vote, we should have checked for you. I appreciate that, Greg. Do you have any comments, questions, or do you approve or disapprove of that decision. Would you like us to change the language in some other way?

- Kevin Walsh: I approve the language.
- Chris Standaert: So, keep him unmuted. So, our other determination was fecal microbiota transplantation, and we agreed to cover this with conditions and for patients with C. diff infections who have failed an appropriate course of antibiotic therapy, and it is not covered for treatment of inflammatory bowel disease. We received no public comments on this, correct?
- Josh Morse: Correct.
- Chris Standaert: I think our language is fairly straightforward there, and no suggestions. Are there questions or comments? Anybody want to make a statement about this? No? That being said, all in favor of approving our decision.
- Josh Morse: Is there a motion to approve?
- Chris Standaert: Is there, oh, do we do a motion? Is there a motion to approve?
- Carson Odegard: Motion to approve.
- Seth Schwartz: Second.
- Chris Standaert: All in favor?
- Josh Morse: All approved.
- Chris Standaert: Dr. Walsh? Is Kevin on the phone, still?
- Kevin Walsh: I approve.
- Chris Standaert: Thank you.
- Josh Morse: Thank you.
- Chris Standaert: Do we need to go back and get a motion for the other one?
- Josh Morse: Yes. Let's do that.
- Chris Standaert: We didn't get a motion for the first one. So, we're gonna vote, revote, on our negative pressure wound therapy with

the amended language, as proposed by Dr. Franklin.
Motion to approve?

- Gregory Brown: So moved.
- Chris Standaert: Second?
- Seth Schwartz: Second.
- Chris Standaert: All in favor?
- Josh Morse: All approved.
- Kevin Walsh: Aye.
- Chris Standaert: All approved. Dr. Walsh chimed in, as well.
- Josh Morse: Thank you.
- Chris Standaert: Thank you, Josh, keeping me straight. It's not easy. It's not easy. OK. We're then going to move on to our pharmacogenomic testing top. We are five minutes early, but we are fine. So, we will move through the Washington State Utilization and Outcomes Data, and then we'll get to the public comment, and we'll make sure that we offer public comment for people on the phone within that window that we published. So, Dr. Fotinos.
- Charissa Fotinos: Good morning, everyone. My name is Charissa Fotinos, and I'm the deputy chief medical officer for the Health Care Authority. I'm going to spend a few minutes this morning talking about the agency medical director's recommendations and thoughts around pharmacogenomics for behavioral health conditions.
- Specifically, the conditions that are being focused on today include looking at pharmacogenomic testing for depressive disorders, schizophrenia spectrum and other psychotic disorders, anxiety, bipolar and other mood disorders, attention deficit hyperactivity disorder, as well as substance use disorders.
- In terms of the reason for presenting this topic, while the safety of a blood draw, there could be consequences of

either having a false-positive or false-negative test, but overall felt that the safety aspect was low. Efficacy was high in terms of our concerns of its clinical utility, and cost medium/high.

You'll hear about this again from Hayes, but really a refresher, there are sort of two ways in which to think about how drugs travel through the body. The first is actually how it travels through the body, or pharmacokinetics, which sort of studies the absorption, distribution, metabolism, and excretion of a drug. Then, pharmacodynamics, what is the blood concentration? What are the effects or the side effects of that drug? What's the timeframe? And I think those are useful to keep in mind as we work to think about, step back, the context of using these tests in clinical practice. Other things beyond sort of the genetics of how the proteins, which metabolize the drugs, are involved are that absorption varies across people distribution, whether you're old or young, volumes of distributions vary. Disease states can change a way a drug is absorbed or excreted, and there are drug interactions. So, really, the point is knowing the genetic frame, with which a protein is built, does not necessarily explain all of the variation that may occur through the use of that drug.

The potential for the utility of genomic testing to guide treatment is exciting. If we could identify the potential for side effects in a person before we prescribe a medication, that sort of assumes that maybe they'll have better adherence, and these are sort of principles that underly this discussion. If we can predict someone who is a slow or rapid metabolizer of a drug, we can get the right dose at the right time and really, perhaps, in theory, have a more effective treatment course. Then, if we can predict the development of adverse effects, we could choose to not prescribe that drug. I think underlying this is, this is all good and important if born to be true, but presupposes that there is an equally effective alternative. If the drug that we're choosing can't be used, do we have other drugs that can be used instead that are equally efficacious?

I think the additional things to think about when talking about pharmacogenomics is that there are frequencies in the differences of the variants across different populations,

across races and ethnicities. If we look specifically at the rate of either rapid or poor metabolizers that relates to this set of drugs, these are pro drugs, which are ingested and aren't active until they're metabolized. As you can see for ultra rapid metabolizers, the prevalence of this gene varies across the different races. This is important to know, because in the case of children who were given codeine after tonsillectomies, a number of them, because they were rapid metabolizers, got a fairly toxic level of the drug highly and experienced overdose. Conversely, you can see that the prevalence rates of poor metabolizers are different. So, not just knowing whether or not a variant is present, but knowing that sort of prevalence in the population is also sort of a consideration when thinking about these tests.

I studied genomics in college, and the field has advanced tremendously. That was a long time ago. So, just some basic reminders. There are about 3.3 billion base pairs in a human genome, and as humans, we share about 99% of those, but that still leaves about 30 million pieces of the genome that are not identical across humans. So, that makes room for a lot of variation.

So, as we, again, take a step back again and think, I can order a test. I would like to order a test. So, what can we do with that test? Well, first we make a diagnosis, and let's just depression as an example. Talking with the patient, we either decide that medications are appropriate for that depression or perhaps they want to try a nonpharmacologic therapy first. If we choose medications, then the next step in this flow would be, am I going to order this pharmacogenomic test before deciding what treatment to use, or am I going to just do my usual standard treatment with medications that I'm used to using and are indicated for this condition? If we do test, one of the first questions to ask ourselves is, is that test reliable? What's the sensitivity, the specificity, the positive and negative predictive value? Is it reproducible? So, those are sort of the questions in the cascade. So, the next thing is, OK. If I have the test, is that going to make me do anything different? If it's not, one could argue, why do I do the test? So, does that test change my management? Here comes in sort of the clinical validity piece. The clinical validity says, how strong is that association of that variant with the

outcome that we're looking for? Does this variant, in fact, always mean that someone is an ultra-metabolizer? So, does the association describe appropriately any efficacy issues or adverse effects? How strong is that relationship? And I put in there a filter, because it if were just knowing the genetic makeup, that's one thing, but there are a lot of confounders that play into how effective a drug is, age for instance, the use of other drugs, concurrent disease states. So, any information we have about that test has to be filtered through all of that other information. Then, ultimately, the thing that we're most concerned about and are really looking to answer is, what's the clinical utility? Will my ordering, having the knowledge of this test, improve the care that I deliver and ultimately, the outcome that the patient experiences?

One of the sort of main ideas around genomic testing for medication use is, in the case of medicines for behavioral conditions, adherence is not great. So, if we know a testing can help better pick a drug up front, is adherence going to be improved? Well, I think that adherence is important, and that's influenced by a number of things, not just side effects and adverse reactions. Adherence really is influenced by a lot of things. Does that patient feel that medicine is the right medicine for them? How well are they thinking? Is their thinking clear, the placebo effect? So clearly, there is a lot more that goes into adherence rather than picking a right drug. It certainly helps, but again, it is a little bit more circuitous than A to B.

I show this slide, because there is a great deal of interest in this. Precision medicine is fascinating to think about, and the future of it, I think, is quite exciting. Right now, however, you can go online and find a number of businesses that offer genetic testing and sort of help you decide which ones you may want, and it's interesting if you see sort of the headlines on the website, so for Genesight, the Genesight test is a clinically proven, genetic-based decision support tool that can help get patients to the right medication faster. The next one, pharmacogenetics is a well-established science studying how an individual metabolizes medications. PharmaRisk PGx testing provides individualized insight into complex treatment scenarios. So, these are very nice websites. You can look and get a lot

more information about them. Given that there are at least 30 million base pairs that are not identical, there is a lot of business to be done there.

We talk about reviewing things from an evidence-based perspective, and I think that when we think about genetic tests of association, there are some things that we can apply, which are very similar to all of the other types of evidence we review, and this is taken from the user's guide from the medical literature, and I don't need to go through these, but really, the same issues apply. Is there a risk of bias and because there is analytical validity, as well as that clinical validity piece, this question becomes a lot more complex. How large and precise are the results? That's not different from really evaluating any other type of intervention, and then, most importantly, can the results be applied to patient care? Does the patient do better and does this really improve the outcome?

Current state policy: The Public Employee Benefit Program considers pharmacogenomic testing investigational. They are not covered. In the Medicaid Fee-For-Service Program, they are covered occasionally with prior authorization. Managed Care organizations do cover them. The coverage criteria is not known to us. Labor and Industries, they are not covered. Department of Correction covers but requires prior authorization.

This is a list of the different types of tests that can be ordered, and their attendant CPT codes. There is no point in going through these, but you can see they are testing for a number of drugs used in the treatment of depression mood disorders, as well as psychoses. Similarly, the list continues here, and you can see that the associated gene is also listed.

To take a little bit closer look at the CPT codes, these are the CPT codes and the tests that go along under them. I point you to the 81479. That's sort of a 'basket code' for tests that don't belong in there but are also ordered, as far as genomic are concerned.

This shows utilization over the last three years. In terms of these different groups. So, if we look at the most common

reason that these tests were ordered, it was for drugs or opioid dependence diagnosis with some utilization, which is the blue bar, in 2014 and quite a bit more in 2015. That certainly was the biggest group in which these tests were ordered. Managing medications, you can see the middle, again, an increase from 2014 to 2015. Then, the diagnosis associated with pain or pain diagnosis associated with tests also went up quite a bit. So, these are the diagnoses associated most often with the ordering of these tests.

This slide shows the utilization across the different programs, both in terms of individual clients, tests, and amounts of testing. I point the arrow here, PEBB really has very low utilization. The numbers have actually decreased, in terms of the number of clients who have had testing over this time period. The Medicaid Fee-For-Service is pretty steady, again, they are prior authorization. Managed care organizations, on the other hand, have approved and are doing... or paying for a lot of these tests to the tune of \$3 million dollars, quite a bit different than the other programs.

Key questions you will hear about in more detail, but essentially the same was the effectiveness. Does the clinical utility of testing inform the selection or dose in individuals diagnosed with any of the disorders we've previously outlined? Does it have improved outcomes when patients are not tested and providers don't have that information? Then, the second group of questions are harms. Are there direct harms associated with testing for genetic variants, as it relates to the administration of drugs? Are there any differences across populations, whether that's in terms of clinical history or patient characteristics? And finally the costs. What are the costs and cost-effectiveness of genetic testing in terms of guiding the selection or dose medications?

Brief review of what you'll hear in much more detail from Hayes, the different questions and the outcome of their evaluation. So, does the dose or medication change compared to no test. Do providers do something with that information, and it might change behavior, thought the quality of evidence is low, as it speaks to that. Are remission rates improved and are response rates improved? Again,

maybe. The evidence is low, but perhaps it might lead to improved remission and response rates. Then, is there improved adherence, tolerance, and fewer adverse events, which is sort of the appeal, in large part, of this. Again, improvement is suggested, but the quality and body of evidence for this is quite low.

Looking at some of the other questions that we standardly ask. Are there direct harms? Are there subgroup differences related to either clinical history or patient characteristics? Really, not any information out there to evaluate. The cost comparison, effectiveness, and utility studies, they vary in terms of the direction of effect and whether or not these are, in fact, cost-effective. So, in terms of that question, it's not clear.

National Coverage Decisions, CMS does not have a National Coverage Decision. Noridian, which is the regional sort of vendor of Medicare services, does allow psychiatrists or neuropsychiatrists, to use GeneSight Psychotropic panel for refractory depression that has failed other treatments. Testing for the cytochrome 2D6 gene is allowed when using either amitriptyline or nortriptyline for the treatment of depressive disorders. In addition, testing for the HLA-B15:02 phenotype when carbamazepine is being considered to be used in persons of Asian or Oceanic descent is also approved. This is a variant that if it is present and a person gets carbamazepine, he or she has an extraordinarily high risk of severe Stevens - Johnson syndrome.

So, in terms of the agency medical director recommendations for pharmacogenomic testing for depressive disorders, do not cover; schizophrenia spectrum and other psychotic disorders, do not cover; anxiety disorders, do not cover; bipolar or other related disorders in which carbamazepine is being considered as a mood stabilizer in person with Asian or Oceanic descents, cover the HLA-B15:02 genotype; for attention deficit hyperactivity disorder, do not cover; substance use disorders, do not cover.

Chris Standaert: So, this is our chance to ask Dr. Fotinos questions about what she just presented. The agency directors will be over

there. We can ask some questions later, but she is ready for questions at the moment. Tony?

Carson Odegard: Coming from an orthopedist, it's a little scary, but my understanding is it's no longer just genomics but actually proteomics, because even if you have the gene, it doesn't mean it's expressed. So, do we need to, is that part of the discussion today, or are we just doing genomics, I guess?

Charissa Fotinos: When we brought this topic up for discussion and nominated it for discussion, it was really around the genomics piece, because those were the tests that we were being asked to approve and that we were seeing the increasing utilization for. We did not talk about proteomics. This is an extraordinarily complicated subject, and I still can't pretend I understand it, and I'm glad the doctor is here to help us, but I think it's... sort of my point of this is, clearly it's not just about the genetics sequence. What is the proteins doing? What are the enzymes doing? What is all of it doing? There's this complex interplay. So, I think teasing out that. So, no, this was focused only on the genomic piece.

Chris Standaert: Tony? Sorry, he was.

Tony Yen: So, I have a question about the coverage recommendations for HLA-B15:02 for carbamazepine.

Charissa Fotinos: Mm-hmm.

Tony Yen: How about other conditions, such as seizure disorder? Is that under the coverage, as well?

Charissa Fotinos: It was very specific in stating, the scope of this review was really only for psychiatric diagnoses.

Tony Yen: OK.

Charissa Fotinos: Or mental health. That's why it was very specific.

Tony Yen: OK.

Charissa Fotinos: Obviously, you could extrapolate that for other circumstances.

- Chris Standaert: Can we pull this out now? I thought I saw it in the report from the people from Hayes. I thought you all made a comment that you actually excluded carbamazepine from your search, because it's an antiepileptic primarily. So, if that was excluded from the search, this is not within the scope of what we can comment upon, because... .
- Charissa Fotinos: Well, it's in the report. They do report on it in the report, as part of the clinical validity.
- Chris Standaert: They say they didn't. They had a specific line, I thought. Did I misread that?
- Margaret Piper: The carbamazepine example is in the background section of the report, only as an example. So, no. Antiepileptics were excluded in discussion from the report.
- Chris Standaert: So, that was... so if they excluded data... that was excluded from their search, they didn't look for data on that particular topic, that's outside the scope of what we can comment on. It means you can certainly cover it as you like.
- Charissa Fotinos: Sure, that's fine.
- Chris Standaert: But then, we're sort of stuck, because we don't have the data one way or the other to say anything.
- Laurie Mischley: That's fine. That just leaves out a big chunk of medications, but that's fine.
- Chris Standaert: Well, it wasn't me.
- Laurie Mischley: No. No. No. That's fine. It's just such a compelling relationship, but understood.
- Chris Standaert: No. I understand. No, but we...
- Laurie Mischley: Understood.
- Chris Standaert: ...are, we're... so, just...
- Laurie Mischley: Right.

Chris Standaert: ...we're bound by the...

Laurie Mischley: No. No. No.

Chris Standaert: ...scope of what we're...

Laurie Mischley: I apologize for putting it up there.

Chris Standaert: No. No. No.

Laurie Mischley: We're good.

Tony Yen: So, just to clarify, we are making coverage decisions regarding pharmacogenomics around behavioral disorders only.

Charissa Fotinos: Only, and that bullet can go away. So, the bullet for that should be changed to do not cover for bipolar disorders.

Seth Schwartz: I just had a question about slide number 16 where you're talking about the utilization data for Medicare, I'm sorry, for Medicaid. This is, just to understand this slide. So, this is for genomic testing...

Charissa Fotinos: Correct.

Seth Schwartz: ...by category? And it looks...

Charissa Fotinos: Correct.

Seth Schwartz: ...like the largest category is actually opioids?

Charissa Fotinos: Correct.

Seth Schwartz: Are we considering opioids for this discussion or no?

Chris Standaert: Addiction issues or opioid use, addiction to alcohol are in our scope, yeah.

Seth Schwartz: OK.

Charissa Fotinos: Yes.

- Seth Schwartz: Because it looks like that's three-fold more common than any of the other things that we're looking at, as far as use.
- Charissa Fotinos: Correct.
- Seth Schwartz: OK. Thank you.
- Chris Standaert: Yeah, Carson?
- Carson Odegard: Yeah. I have a question, unless I just missed something. On your CPT code 81380 for the HLAB, so in your utilization tables, you don't have that CPT code?
- Charissa Fotinos: Yeah. Just ignore that whole HLAB pieces. Just forget that, not in scope.
- Carson Odegard: Alright.
- Chris Standaert: OK. Other questions?
- Gregory Brown: There are multiple drugs that are used for multiple diagnoses. So, it's concerning to me that if this is a drug that is commonly used. I mean, I understand it's primarily an antiseizure disorder, but it's still commonly used for other indications, that we didn't get the evidence on that.
- Chris Standaert: I share your concern, and there certainly are other antiepileptics that are used in psychiatric care, as far as I'm... as a clinician I certainly see them. I don't... what we do about that now, I don't know, because that's... we have the scope of what we have. When they shaped their PICO tables and said this is the scope of the literature we're looking at, that's what we get. So, we just don't know what's out there or not out there, because they didn't even, they didn't look at that. That topic was excluded. So, what it does is, it means that our decision doesn't apply to that, alright? So, if we say don't cover, we're talking about the scope of testing. If they want to... if the agency... so our decision will not apply to that test. They are free to say we will cover it, as they would normally understand their processes. So, this particular decision doesn't apply one way or another to that particular type of testing.

Gregory Brown: I guess what I'm... the rationale I'm looking at is that even if we don't have the evidence, one of our requirements is to look at clinical practice guidelines and to me, if the FDA requires the test, that would trump any clinical practice guideline. So, irrespective of evidence, the fact that the FDA requires it and it can be used in a behavioral health or mental health disorder, can't we still vote to specifically include for that indication?

Chris Standaert: We're going into an area that is under the scope of our literature, right? We don't have the evidence. One way or the other, that's not within the scope of what was requested. So, if the FDA requires it, we don't... like I said, we don't control what they do with all sorts of other things that didn't fall under this, other psychiatric disorders not within this, right? Then they have to deal with whatever they want to deal with for those. This testing is used... theoretically, it could be used for lots of things other than psychiatric diagnoses, right, but we're fairly limited in this, in what...

Gregory Brown: Right.

Chris Standaert: ...we're saying, and I don't disagree with you that... I don't know the whole topic. It sounds reasonable, but at the same time, that's not being presented to us within the scope of the project, and it wasn't available for public comment. It wasn't available for review on par with the other literature that we got. So, it, but it just means that, again, we're not restricting that at all. We're just not...

Gregory Brown: Not commenting.

Chris Standaert: ...we're not commenting about management of diabetes today, either, you know? It falls in that. It's outside of our fence, essentially.

Charissa Fotinos: And we were deliberate in that, in that the scope to add antiepileptics to this consideration would have been huge and really quite broad. So, that wasn't part of what we Hayes to do.

Chris Standaert: I assume they have a policy for seizure disorders. They can have a policy for Tegretol for seizure disorders, which,

again, any antiepileptic we're not commenting because we're limited to psychiatric diagnoses listed. Other questions? OK. We're going to move on to public comment. OK. So, for public comment, this is a chance for anyone in the audience or on the phone to address the committee. We have the same two people that signed up, in the same order even. We're totally in luck. So, two people have pre-signed up. They also signed up here. Anybody else in the audience who wants to speak can after those two speak. Once the two scheduled speakers and people in the room that want to speak, we will ask for people on the phone and see if anybody on the phone wants to make a comment to the committee, as well. So, speakers, when you come up, please identify yourself. Please also discuss and disclose relevant conflicts of interest, relationships, and funding to be here speaking to us and on whose behalf you are speaking. So, first, Jim Pollard.

Nathan Roe: I'm Nathan. That's Jim.

Chris Standaert: OK. So, we're flipping. OK.

Nathan Roe: So, my name is Nathan Roe, and I am the medical science liaison for Assurex Health. So, I am employed by the company, and we make the GeneSight Psychotropic product. So, what I wanted to do a little bit was to just talk about where our data comes from, as you see it in a health assessment, to make your decisions appropriately. So, really, what we're trying to do is to combat the problem that a lot of these antidepressants are very ineffective when they're used for psychiatric treatment. This is demonstrated in the STAR*D study in that 50% of the patients respond to antidepressants first line; 16% of the patients have treatment intolerance; so really, about 50% on that first treatment are actually achieving appropriate response with these medications, but every step that you make when you switch or augment medication, change doses, the treatment response rate goes down and treatment intolerance rate goes up. So, really, we're trying to use pharmacogenomics to minimize the amount of treatment changes that somebody has to make in order to try to get more people to achieve treatment response. So, really, what makes this product a little bit different than

other pharmacogenomic products is that we're the only pharmacogenomic test with local coverage determination for Medicare. This was already talked about. We have the patented Combinatorial Pharmacogenomics type test for mental illness, and I'll talk about that in just a second. We are the only test with five completed and published clinical trials proving clinical validity, clinical utility, and cost-effectiveness as well, and those are in that [inaudible] assessment.

So, really, what do I mean whenever we talk about combinatorial? What we're trying to do is, instead of looking at the major metabolizing gene of each one of these medications, we're trying to look at 100% of the metabolism of each medication. So, even though 2D6 might be the primary metabolizer for one medication, maybe there's four other ones that are involved. So, if you're an intermediate metabolizer of one, an extensive metabolizer in another, a poor metabolizer in another, what does that actually mean for that medication and treatment in being able to use it for that patient?

The way we do this is that we look at a list of pharmacokinetic and pharmacodynamic genes. We cross-check the patient's phenotypes with what is going to be their response to every medication in our test, how important is one of those genes for each medication on our test, and assign each medication a genetic risk score. This genetic risk score ends up into a green, yellow, red category that's very easy to read by the practicing clinician who does not have a lot of time with each one patient. They know which ones have the most genetic interactions and which ones have no genetic interactions, and also we tell the clinician why each one is there in the particular risk category.

The reason why this approach is more effective than a traditional single gene testing is that when you look at improvement of depressive symptoms looking at just single gene testing, grouping them into the different metabolizer status of medications that are primary to 2D6 metabolize... or metabolized by 2D6, there is no change in predicting who is going to respond and who is not going to... or how well they're going to respond, but if you take those same

patients and put them into this algorithm adding in all those other slightly more... smaller components that have genetic variation, you get some clinical validity and predictive power in figuring out who is going to respond and who is not going to respond.

Now, of the people that come in, how many are actually those medications that are going to be poor responders, and what we found in our randomized control trial was that 30% of the patients that come into the trial are on what we call red bin medications, meaning they have the most severe genetic risk. Then, do these people actually improve? What is their improvement from those 30% that I just showed you? There is very little improvement in depressive symptoms compared to people that are on green bin medications in this particular trial.

So, then we move forward and looked at a Phase III study looking prospectively at whether the people who got the pharmacogenomic testing by GeneSight or got treatment as usual, did they actually improve? Did they have better improvement? And that's, in fact, what we found with three different rating scales. They do have better improvement with GeneSight guided treatment than treatment as usual.

Also, doctors who did get this test were more likely to use it. This is from one of our economics trials looking at congruence, and we found that the majority of people were able to change their medications to something else, either on the green bin or alter their dosing based on this genetic information. So, most people are actually making educated decisions based on this testing. So, that, I think, concludes my five minutes. So, I can take any other questions about that at this time.

Chris Standaert: OK. Thank you.

Nathan Roe: Thanks.

Chris Standaert: Mr. Pollard? Dr. Pollard? I'm not sure.

Jim Pollard: Good morning. I'm an employee with Assurex. I'm not a scientist and no worry. I'm not here to refute the evidence-

based approach you're taking. However, one of the components of your clinical chart or your health tech assessment was public comment. In that role, we took the opportunity of writing a letter to the clinicians that have used GeneSight and asked them to respond. The responses were not used because they didn't reflect evidence within the Health Technology Assessment, but they reflected their own outcomes, and I asked them to answer the three questions that were the same questions that were proposed by the Health Technology Assessment, which is what is the clinical utility of the genetic test? Does genetic test inform selection of dose and medication? Does the decision to change the dose provide clinically-meaningful improvement? We received 11 responses from clinicians that have been using the test for the past year, and to a person, they all said the test has provided clinical evidence. They use it for changing of dosing when a patient is having a negative response on current medication, and that that response has improved the outcomes. To a person, one of the many said that they spoke of the difficulty of selecting drugs through a trial and error process, and many of them commented on the questions and commented of possible improvement of overall benefits and healthcare system through reductions in medications and healthcare services. Even others commented on the speculation for the potential cost savings that may occur when the appropriate medication is chosen. We ask you to take the time to look at these 11 clinicians and look at their comments based on the fact that they were asked these three questions and responded to them, in kind. Just for instance, a response we received from Dr. Ehrlich, who is a medical director of Discovery Behavioral Healthcare, said it is useful for a variety of diagnosis, including mood disorders, psychiatric disorders, anxiety, and posttraumatic stress disorder. Medication selection and dosing are changed in response to the testing, which adds to the information from clinical exams, screening test, patient reports, and we find that testing reduces adverse medical effects, futile medical trials, and prolonged suffering due to ineffective medical choices. I hope the decision not cover the GeneSight testing is reversed to provide the service to more of our patients. In addition, Ms. Belcaster, an ARNP from South Bay Health, genetic testing definitely informs the selection and dose of medication compared to usual care, no testing. In those

cases, it decreases the time spent switching medications, ends up costing less, and gets clients to a state of better control more quickly. I could go on and on and on, but we have a very limited amount of time, but I know that you're looking at evidence, and evidence is a very mechanical and very pragmatic process, but you have to look at the effect that you're seeing from your clinicians and talk to these clinicians and ask them, is this really having or are the benefits really showing that you're telling us. I think any physician, in today's practice, that could stop and write a comment to this degree, has a very strong opinion of the technology and really wants to be listened to. That's it.

Chris Standaert: Thank you. Anybody else in the audience want to address the committee? Can we go to the phone, Christine, just unmute the phone? For those on the phone, this is the meeting of the Washington State Health Technology Clinical Committee. We're discussing pharmacogenomic testing, and we're just looking to see if somebody on the phone wants to make a public comment to the committee. If so, this is your opportunity to do that. The phone is silent. OK. Thank you.

That being said, we will keep moving. So, next, Dr. Piper, I believe, is going to give us our evidence report, yes, from the Hayes Group.

Margaret Piper: OK. For those of you that I haven't met yet, my name is Margaret Piper, and I am working for...

Chris Standaert: Can you move the mic a little closer to you, or step a little closer?

Margaret Piper: Sorry about that. Is it on? OK. So, my name is Margaret Piper. I work for Hayes and I am the main author of this report, but I'd also like to thank my coauthors that you see listed in the title slide, including Candi Wines, Candi? You know Candi from past experience. Where do I point this? Anywhere?

Chris Standaert: Do you have a pointer?

Margaret Piper: OK. Alright. So, this is the outline for my presentation starting with the background, and this is taken directly from

this report. A few items, just to illustrate, that the societal burden in general of mental and behavioral disorders is high. I don't think anyone really disagrees with that. This is, again, the list of the disorders of interest that have been chosen for this report. You've already seen it today. I did want to point out that the item of substance abuse disorder was limited for this report to opioid and alcohol abuse, because these are really the only two topics within the substance use disorder area that have been investigated with pharmacogenomics. So, in general, these areas have in common a multimodal approach to treatment, including medication. Medication effectiveness is variable, as you have already heard. Treatment can be empirical with kind of a hit or miss selection of drug and dose. It can take time that can reduce effectiveness adherence, and there may be side effects that can also affect adherence.

I was going to give you a little bit of background, and you've had some already. I was going to give you some background starting at the DNA level. Do any of you feel like you would benefit from hearing that now, or should I just move on? What is the vote here? I'm seeing one vote for moving on. Move on. OK. We'll do that.

So, as you've heard, for the area of pharmacogenomics, you're looking at altered gene products. These altered products can affect drug uptake and metabolism. So, this is pharmacokinetics, or the products may affect the targets of drug actions. For example, a serotonin receptor, so you might have an altered serotonin receptor, which no longer interacts as well with the drug that's being given, and this would be in the area of pharmacodynamics. So, examples in the area of pharmacokinetics are, as you've already heard, some of the CYP450 enzymes, and patients with variants that reduce the activity of some of these enzymes are labeled poor metabolizers. So, what happens is that a drug will build up in their system. They have increased exposure and perhaps increased adverse events. Then, there may be patients who are ultra-rapid metabolizers, because they have extra copies of these CYP enzyme genes. So, with the extra copies, they metabolize the drug more rapidly. They have reduced exposure to the drug and potentially reduced effectiveness. So, the idea is to figure out who these people are in advance of prescribing and

then either give them a different dose of the drug to equilibrate in accordance with their gene makeup, or to select a different drug that isn't metabolized by their altered gene.

However, as you've heard, it's a lot more complicated. There are many different kinds of gene variants, and there can be metabolic redundancy. So, a drug may be not be metabolized by only the one enzyme that happens to have a gene variant. There may be other metabolic pathways. So, you have to know a lot about the particular drug and how much it may be effected by a metabolic variant. Then, there are, as you know, other kinds of things that can effect drug metabolism, such as age and gender, drug interactions, and the status of liver, renal, and cardiac function. So, it's a very complicated area, as you've already heard.

As you know, when you are evaluating a diagnostic test, you want to look at clinical validity and clinical utility. Clinical validity, as you've heard, is the association of the gene variant and the patient outcomes. So, how well does the gene variant predict an outcome? It turns out that this is where the bulk of the evidence is. It's in clinical validity looking at a patient population, for example, schizophrenics who are being treated with antipsychotics, and looking at, within that population, a number of genes and their variants, and how well they predict different kinds of outcomes. Because there is so much evidence here, and because it's at the individual level of individual gene variants and a variety of outcomes, it's very hard to determine well, does any one of these have an impact on patient outcome? So, we have put this kind of information in the background and focused on the clinical utility information for the evidence.

Just to give you a little bit of a sample, we collected evidence on the clinical validity just for schizophrenia and just being treated with psychotropics and just the meta-analysis level. So, not even at the level of individual studies, and what you see in this slide is just a small snippet of the table that you have in your report. Each row is a meta-analysis, and it's showing you the odds ratio for a particular gene variant compared to its usual form and a particular

patient outcome within the population of schizophrenics treated with antipsychotic medication. So, the first one is CYP2D6 variants compared to the most common variant, and the outcome of dystonia. You can see that the odds ratio is not significant. The second one, compared to Parkinsonism, the odds ratio here is significant, but it's only an odds ratio of 1.64. That is a very small effect size. So, a single test for a CYP2D6 genotype looking to predict Parkinsonism is not going to tell you very much about an individual patient and their likelihood of having Parkinsonism.

So, what you would like to do is combine a number of genotypes and look at one outcome. So, you can see here that there are three different genes that are all looking at the association with tardive dyskinesia. So, would it be possible to combine those and get an improved effect size. The problem is, we found almost nothing in the literature that looked at combining these individual gene and outcome associations. What we do have, and as you've already heard are commercial panels that do combine the results of different genes, different genotypes for individual patients. The problem is, the combinatorial method is proprietary. So, we don't know how the combining is happening. On the other end, is an interpretive report that makes recommendations to the clinician about what drugs or what drug doses to use for an individual patient. What that means is that any evidence for one particular test cannot be generalized to the next test, which may use different genes in a different combinatorial method. Another problem to notice is that, for example, for the GeneSight test, all the evidence that we have in this report is based on a test using five genes when the papers were published. If you look on the website now, eight genes are being used for the GeneSight Psychotropic. So, the evidence and the current test are no longer exactly related. So, it's a bit of a moving target. The same five genes are in the current test, but three more have been added, and that's true of some of the other tests that we have. So, there are two tests on this slide that are being used in the evidence that are available in the United States. That's the GeneSight and the Genecept. Two of the tests are not available in the U.S., the Neuro-pharmagan test is from Spain, and CNSDose is from Australia.

Alright, moving onto the objectives of the report. Policy context is that we have lab tests available. Potential benefits are better prescribing choices. The concerns are, do these tests really result in improved treatment decisions and patient health outcomes. You have already seen the key questions, so I am not going to go through those, but rather move on to methods and search results.

So, the population is people any age prescribed medications for the conditions of interest for this report. The intervention is the test. The comparison is pharmacogenomic testing to usual care, which is no genetic testing, and the outcomes are first of all, decision making, does it make a difference in what the prescriber does? Then, does it change things like patient adherence to treatment, response to treatment, adverse events as a result of treatment, and cost-effectiveness or cost.

This is the analytic framework we use. This is just a picture of essentially the key questions. So, starting with the population, they either get the genetic test or they don't. Moving to the right is the population that gets the genetic test. So, at least some of them may get a change in their drug or dose selection. Moving from the population downwards is empiric treatment. Then, both populations get the same sort of clinical management. Then, the question that we have in the green box is, do the pharmacogenomically managed patients compared to the empirically managed patients, have improvements in their clinical outcomes? In the red box, are there any harms of testing?

So, our literature search was done mainly in the PubMed and Embase databases. It was last updated in November on the 28th. The main exclusion criteria for all the key questions is that we did not include any studies that did not have a control group, because you cannot know if there has been an improvement in outcomes if we don't compare the results to a control group.

So, as you can see, we started out with quite a large volume of results from this search, but where they were applicable at all, the vast majority of the articles, as we looked at them

in the title an abstract review, were reporting on association studies or clinical validity. So, in fact, our full text article review was quite small, and then that was narrowed down to 14 articles that were analyzed for clinical utility.

Just to remind you, we do a quality appraisal on all of the evidence studies, first at the individual study level, and these studies are rated at good, fair, poor, or very poor quality. Then, we evaluate the body of evidence, all of the studies that are available for each outcome are rated together, and these are rated high, moderate, low, or very low.

Then moving on to the findings, the first key question, part A, is about clinician decision making. So, we had four studies. These all addressed patients with depressive disorders. Two studies were fair quality randomized controlled trials. One was a controlled trial of fair quality, and one was a poor quality comparative trial. The first one listed was done in Australia with an Australian pharmacogenomic panel, not available in the U.S. The next two were done with the GeneSight panel. Actually, I've got that shown here, which is available in the U.S., and the last one was just a single gene test. The first trial just did a survey of clinicians. So, it was more of a judgment call, in that prescribers indicated that in 65% of cases, the interpretive report led to some kind of dosing change from their usual practice. The other three studies did more of a hardcore measurement that indicated the pharmacogenomic testing had made a change in prescribing practices. So, to sum up, there were some results that suggested that the pharmacogenomic testing results did change prescribing patterns in favor of the pharmacogenomic recommendations, as compared with treatment as usual. Study quality was poor to fair, and we rated the overall body of evidence as low.

We're going to be moving now into the effectiveness for patient outcomes. Most of the studies, again, addressed patients who had depression and the outcomes are generally measured with rating scales for depression. So, I just wanted to go over these scales a little bit. You see the most common ones listed here, HAM-D, QIDS, and PHQ-9.

HAM-D is typically done with a 17 item scale, sometimes with a 21 item scale. In the interpretation section, I've just given you a couple of the cutoffs for these scales. There are other cutoffs for different levels of depression. Several of the studies that we're going to be looking at have used some of these cutoffs. For example, they've enrolled patients who have at least a rating of 14, meaning that they are at least moderately depressed, and this is a cutoff that was used to enroll patients into the STAR*D Study, which was a large landmark study of patients with refractory depression, and this is kind of a real-world study that is often cited, and I think was probably used as a model for design for some of the studies that we're going to be looking at. So, the STAR*D Study did enroll patients using 14 on the HAM-D scale as a cutoff.

The primary outcome for the STAR*D Study was remission, and that was defined as the HAM-D 17 score of less than or equal to 7. Secondary outcome was response, and that was reduction in the QIDS self-reported score of greater than or equal to 50%, and this reduction of greater than or equal to 50% on any of these scales is a commonly used measure of response, as we're going to see.

So, moving on to Part B of key question 1, first of all, looking at the outcome of remission, patients with depressive disorders, we have two fair quality randomized controlled trials and one fair quality controlled trial, one poor quality comparative trial. The first trial you see, the Winner 2013, was a pretty well designed and executed trial. The problem with this trial is that it was not powered well at all. So, none of the results of this trial are statistically significant. The second trial was also pretty well designed and carried out and better powered. So, the results here for remission is statistically significant. They also calculated that the number needed to test for remission was three. So, three patients to test to get one patient gaining remission. The Hall-Flavin 2013 used three different measures. At eight weeks, they had one measure that was statistically significant. The difficulty with this trial is that they had a higher amount of losses to followup at 27% than most of the other trials. The other trials in this body of evidence has losses to followup in the range of about 5 to 15%. This one was about 27%. What they did do was some data

imputation using a maximum likelihood method. Using that data imputation, they were able to get statistical significance. The last study had a statistically significant comparison; however, the way they defined their comparison, I have questions about its clinic relevance, because to my mind it did not meet the definition of a clinically relevant difference.

So, to sum up, in all of the studies, the direction of the results suggest support for pharmacogenomic testing, but the results were not consistently statistically significant, and in one study, may not be clinically relevant. This outcome is response to treatment. Six studies addressed this outcome, four of them addressed patients with depressive disorders. One randomized controlled trial, but this is the trial that was underpowered, and so the results are not statistically significant. Two controlled trials of fair quality and one comparative trial of very poor quality. So, the two controlled trials, one of them defined response to treatment and had statistically significant results. The other one did not define response to treatment. So, they just compared reductions in the depression scales and had statistically significant results. The final comparative trial had no significant differences.

These are two other trials, also measuring response to treatment. One enrolled patients with any psychiatric diagnoses, primarily major depression, psychotic disorder, and bipolar disorder. This is the Espadaler trial, and at three months, they did not define their response to treatment, but they looked at the difference in CGI scores and found a statistically significant difference. Then the final trial looked, and this is the only trial that addresses any kind of abuse disorder, and this looked at alcohol use but it was not designed as a pharmacogenomic trial. It was designed as a trial of naltrexone for alcohol use. So, it was comparing naltrexone to placebo, and then within each of those two arms, they stratified according to a single genomic marker that they had postulated that one marker was favorable to naltrexone use, and the other not favorable, but then when they analyzed the results, it came out number one, not statistically significant, and number two, opposite to their hypothesis. So, this particular trial was not informative.

So, to sum up, aside from the alcohol trial, or the naltrexone trial, the results were in the direction of improved response for pharmacogenomic treatment, but only one study used a predefined measure of response and obtained statistically significant results.

Now, there were other trials that addressed outcomes, like adherence, tolerance, adverse events, hospital stay, healthcare utilization, but for each of these outcomes, there was, at most, one or two trials. So, the evidence here was extremely limited. I didn't want to take the time to go over each of these in this presentation. So, I will just say that the study quality for each of these was poor to fair and that the overall quality of evidence for these outcomes was very low.

Moving on to key question 2, which is the direct harm of pharmacogenomic testing, as you've already heard, we found no direct evidence for this question, but you can always postulate potential harms of false positives and false negatives. Key question 3 asked whether or not there was variation in decision making, patient outcomes, or harms by patient subgroups or characteristics. We found only one poor quality retrospective comparative study that used a multivariate logistic regression model and reported that there were no variables falling into these categories that predicted response to medication treatment. So, basically, no evidence.

Costs of genetic testing, we found four cost comparative studies. Two of these were also evidence studies, the Fagerness and the Rundell. Fagerness used the Genecept assay. Rundell used at least one of several individual gene assays. The Winner... do either of you know how to pronounce that? Is it Winner? Winner? Thank you. This is a different paper from the evidence paper that you already saw, but it does use the GeneSight assay. Then, Herbild is totally different. It's looking only at CYP2D6 and CYP2C19 pharmacogenomic testing. These looked at different ways of cost, and this is only cost comparison. So, Winner, for example, only looked at pharmacy cost. Fagerness looked at medication cost, as well as outpatient visits. Herbild and Rundell tried to look at total cost utilization. Basically, most

of these came to the conclusion that pharmacogenomic testing lowered the kinds of costs that they looked at.

We did find two cost-effectiveness studies. Both of these models were based on data from the STAR*D studies, but each of them looked at a single gene. Each of them looking at a different single gene. They had different assumptions built into their models and came to different conclusions about whether or not the testing was cost effective. So, you really can't compare them, and it's very hard to make any decisions based on these models. Then, finally, there was one cost utility study that was done in Denmark.

So, to sum up the results, in some cases, mainly the cost comparison studies, subjective cost-effectiveness suggested better cost with pharmacogenomic testing, but there was a lack of consistency overall. If you look in more detail, there were some indications that the results depended, at least partly, on the test cost and on the effect size of the clinical validity evidence that was used. Modeling results are limited by the assumptions made, the test chosen, and the quality of the supporting data.

Practice Guidelines: There is basically very little in the way of practice guidelines. The only detail comes from the CPIC consortium, which is a consortium that is in support of bringing information on pharmacogenomic testing to other groups. So, they have a certain perspective in this area, but most of what they publish is based on clinical validity, not clinical utility. Other professional group guidelines have very little detail in terms of pharmacogenomic testing.

Payer Policies: You have already had a review of that. So, I'm just going to move onto our overall summary.

There is quite a lot of data, but that data is in the realm of clinical validity, not clinical utility. When it comes to clinical utility, the evidence is reasonably consistent but somewhat limited in terms of medical decision making, but medical decision making alone is not enough to support a conclusion of clinical benefit. What we need is clinical utility in terms of patient outcomes. Here the evidence is a lot more limited and, in some cases, compromised. We have rated the body of evidence as low to very low quality

depending on the outcome measured and again, to remind you that clinical utility for one panel test is not generalizable to another panel test, because the genes are different, and we don't know how the algorithms work for interpretation.

Just to remind you of the difference between low and very low body of evidence quality compared to high and moderate. For low and very low quality evidence, we are uncertain that the direction of the estimate is accurate and would not change.

So, to sum up, we believe the evidence base is insufficient regarding the clinical effectiveness of pharmacogenomic testing to aid in the treatment of the psychiatric disorders of interest for this report, and that is the end of my presentation. I'll ask for any questions.

Chris Standaert: Thank you, Dr. Piper. I appreciate that. We'll let people digest in their heads for one second. Questions? This is our opportunity to ask questions of Dr. Piper. She will be back over there when we get to our deliberations, but we have time to ask her questions about her presentation or other questions you may have about the data.

Tony Yen: Question?

Chris Standaert: Yeah, Tony?

Tony Yen: So, I think one of these studies has a data imputation. Oh, it's the Hall-Flavin 2013 study. It required data imputation to account for 25% loss to followup. I'm kind of curious from your standpoint, as someone who is familiar with biostatistics, is that a valid methodology and does that cause you also to downgrade this piece of evidence, as well?

Margaret Piper: I'm never happy about data imputation, and the larger the losses to followup, the more you worry about the data imputation. They actually used two methods of data imputation, one was last result carried forward, which I ignored, because it's not really a good method. The one I paid attention to was this maximum likelihood method, but I am not a biostatistician. So, all I know is that's a better

method. Beyond that, I can't evaluate it very well. All I can say is that it's a better effort than making no effort.

Chris Standaert: OK.

John Bramhall: Do you know if the patients in these RCTs, and especially the ones that found statistical significance, if they were blinded to the fact that they had these tests done, or was there a sham blood draw done on the controls, as well, in other words?

Margaret Piper: Some of the trials did do blinding, and I can tell you which ones. Also, another point to make for that Hall-Flavin, they did correct for multiple testing. So, when you have these multiple ratings of depression and you're doing many tests, like three or four tests to look for statistical significance, you want to correct for the multiple tests. They did correct in that particular trial, which is a good thing. So, who was blinded? Participants were blinded in the Singh 2015 trial and the Winner 2013 trial, and I believe that is all. The outcome assessors were blinded also in those two trials, and that seems to be it. So, just in those two RCTs.

Chris Standaert: Tony, yeah.

Tony Yen: Just one more question. So, in terms of key question number two about harms, direct harms, do you know how long it takes to do these types of genetic panels, because that's one concern that I might have is that genetic panels, at least with my experience, is about two weeks, and does that delay therapy. That's the part I didn't quite... I wasn't about to quite capture with the report that you've generated over here. Would you consider that as a harm, in terms of, like, getting onto some type of therapy, maybe what that 80% probability if that's the correct therapy.

Margaret Piper: In terms of the evidence here, a lot depended on the trial. So, some were within a week. Some were within four weeks. Would we want to ask?

Chris Standaert: We have our clinical expert who might be able to help us.

Margaret Piper: OK.

- Jon McClellan: Well, you know how long your own tests.
- Josh Morse: Can you use the microphone, please? I'm sorry. Is there a microphone available if he's going to comment?
- Chris Standaert: Introduce yourself for the transcriptionist.
- Jim Pollard: I'm sorry.
- Chris Standaert: This is being transcribed. So, introduce yourself for the transcriptionist.
- Jim Pollard: Jim Pollard, Assurex Health. The question is the turnaround time on the test? Is that correct?
- Tony Yen: Yes.
- Jim Pollard: OK. The way we work, so a buccal swab is FedEx'd to our lab the night of the receipt, and within 36 hours the received specimen results are sent to the portal for a physician. So, within two days to three days, the physician has a response.
- Tony Yen: OK. Thank you.
- Chris Standaert: Thank you.
- Chris Hearne: My question is, I do genomic research, that one of the controversies in all of this is how much some of the variants, the non-cytochrome, the P450 variants, actually matter.
- Margaret Piper: Right.
- Chris Hearne: What they're supposed to do or not supposed to do. Did you get into any of that? It looks like you studied when they studied the panels themselves and not necessarily the background about why they might have chosen the long allele versus the short allele or those kind of things.
- Margaret Piper: Right. Well, that's the clinical validity aspect of is, is, you know, how strong is the association for each gene variant and outcome. So, we did the one example for schizophrenia, and there's a table in the appendix that looks, that gives examples of a number of associations, a

number of odds ratios. Then, the point I make in the background section on the clinical validity is that all of these are very low. All of these odds ratios are very low. The effect sizes are very small. So, for each one, individually, it would be a poor test. So, that's why you have to combine. And that's where we couldn't find information on how do you put these things together and what's the mathematics of it, what's the genetics of putting them together. So, no discredit to our guest, but we don't know the interpretive method.

Chris Hearne: There's another problem in that the findings are also quite variable. So, the notion of a method to add them all up assumes that they have a real effect, it's just small.

Margaret Piper: Well, that's why...

Chris Hearne: And that's not necessarily established either.

Margaret Piper: The table that you have, those are meta-analyses. So, each row represents a number of studies. So, it's a synthesis of a number of variable results.

Chris Hearne: Of what's been published.

Margaret Piper: Yes.

Chris Hearne: Yeah.

Chris Standaert: OK, any other questions? I just want to clarify one thing. So, the Singh study you put up, you put the funding for the other ones, and I found the paper. It doesn't list funding, but it looks like Dr. Singh is the founder of the company that makes the test that they're studying or the interpretive tool they're using.

Margaret Piper: Most of these had commercial funding, but one thing I'd like to point out is that, OK. So, here is my bias. I used to be a clinical lab director. So, the diagnostics industry in the past, before genetic testing took off, was an industry that was never funded to do clinical trials. The profit margin is slim, and it's not like pharmaceutical companies. Tests did not use to cost very much. So, diagnostics companies would make tests for a relatively low test and a relatively small

profit compared to pharmaceutical companies. Well, now, the landscape of genetic testing is looking different. Costs are higher, but they're being asked to show clinical utility. The problem is, nobody is paying for the trials to show clinical utility and the companies do not usually have the money behind them to do those kinds of trials. So, when they do, I think that's a very good thing, but the problem is, the clinical trials are commercially funded, and some people look at that as a bad thing. So, yes. There can be that bias, but I also think it's a good thing that we're getting some trials. Now, for this area, in a way, I regard all of these, now I'm speaking from personal bias, OK? I'm just giving you my opinion. I think of these as good pilot trials, but think of all the people who have depression, as just one area, just one of the disorders on your list for this report. What we really need now, now that there is some pilots that seem to show that this might work, what we really need are some very large trials, really large, well-designed, well-executed trials that take you through all the different steps, the decision making, the outcomes, all the different kinds of outcomes, and the cost and ask, does it really work, but I don't know where the funding is going to come from.

Chris Standaert: I don't know that either, but yeah. Yeah, and I assume there are also issues of sort of genetic variability within the population is enormous.

Margaret Piper: Absolutely.

Chris Standaert: And when you look at a very small number of people, you're just barely scratching the surface of that, and that affects...

Margaret Piper: And most of these trials enrolled Caucasian population.

Chris Standaert: Yeah, they test... and pretest probability and everything else sort of goes all over the place is what I would assume.

Margaret Piper: Yeah.

Chris Hearne: The other dilemma with all of this, with the literature, is that even saying they're all Caucasians, Caucasians are not all the same genetic founder population. So, a lot of the findings of the non-cytochrome P450 genes are arguably due to something called population stratification where if

you over sample... if you have too many Irish people in your cases and too many Swedish people in your controls, you're gonna find genetic differences. That has nothing to do with the question that you're asking.

Margaret Piper: Yeah.

Gregory Brown: You got a problem with Swedish people?

Chris Hearne: I married a Swedish person, so. Their genetics are much different than mine.

Laurie Mischley: I have one additional question. I just, if you could address the incongruence between the increase that we've seen in opioid dependence utilization of pharmacogenetics and the paucity of any data really in the preview?

Margaret Piper: Within the search parameters, it just didn't come up. There was nothing there.

Laurie Mischley: From year one to year two, almost a 3000% increase in utilization was amazing to me, but the trials aren't addressing it.

Chris Standaert: I suspect some of that's due to the intensity of the opiate problem we have, I suspect, but I don't know. I thought that was interesting, too. So, you did not find... nothing you gave us really was on opiates.

Margaret Piper: No, but it, I mean, there were search terms in our...

Chris Standaert: Nothing showed up.

Margaret Piper: Yeah.

Chris Standaert: Dr. [inaudible] did you want to make a comment?

[Inaudible Response]

Seth Schwartz: I guess along those lines, I would just... I don't think I even understand what... how they're used with opiates. I guess I would ask you, do you... our clinical expert, do you have any idea how the genetic testing is used for opiate dependence?

Jon McClellan: No. We wouldn't do it, and I don't know of any data about how you would derive it.

Seth Schwartz: Do we even know what the tests are? I mean, do we know any... do we have any information?

Gregory Brown: I don't know what the tests are specifically, but I have seen for orthopedics some companies doing genetic testing for which opioids are more effective for individual patients so that you can go to your surgeon and say this is what my pharmacogenetic profile recommends that you use for me for pain medication postop. I mean, that's different than, obviously, substance abuse, but there seems to be some body of literature on that.

Seth Schwartz: And from our utilization data, do we have any idea what tests were even ordered for those patients? I mean, it would be... it seems that it's going to be difficult for us to make any comment about any genetic testing for pain or for opioid use, since we have zero data, but, I mean, I'm just curious what the problem is that we're even looking at.

Chris Standaert: There's a whole problem of doing lots of testing, but is that actually doing anything useful at all, and even in the alcohol one they did, they had nonsignificant, it had a reverse effect. I thought they were finding data that would help them, and actually they were giving people the wrong approach based on the results, because the interpretation of the results didn't lead, didn't match with the clinical response.

Margaret Piper: We're a little limited in answering this question, because we don't know, necessarily, the prior authorization rules that the managed care plans use. We don't have that information.

Chris Standaert: How is a managed care plan so much higher than everything else? I mean, you're talking thousands to millions.

Margaret Piper: I suspect that they're not doing much prior authorization. I don't know what else to believe. So, this is enlightening. This is good. Any questions? No. Maybe we'll take... we'll...

Seth Schwartz: I guess I would ask Dr. McClellan, I guess, these are all very... these trials that we're looking at are very small, I mean, like, 25 people in a randomized trial, and just thinking about genetic variability, it's sort of difficult to understand how they found any differences at all. I guess, so the question is, do you have any, any comment about how common some of these genetic mutations are that affect sensitivity to medications or...

Jon McClellan: There's two questions. To make a genetic test, you have to really confirm that it actually does something for whatever it is that you're testing for or care about. In this field, I think there's two challenges. The cytochrome P450 variants clearly do stuff with metabolism. There is the bigger issue of whether or not psychiatric medications, whether blood levels and stuff, matter, but all the other ones, there's a lot of debate about whether or not they matter at all for whatever they're being tested for. I mean, so for example, the serotonin transporter, the long or short alleles have been studied for just about everything. As it turns out, a common allele means it's found in all human population. So, you'll find one or the other just about everywhere, but your likelihood of having it varies enormously depending on where your ancestors came from, and it's not just whether you're Caucasian or African or Asian. It's whether or not... which side of the mountain you came on, and it varies from, like, 0.1 to 0.9 across human populations. So, in sample 25, you can certainly get differences just depending on where their backgrounds are from. The way to control for it is to do sibling comparisons, but that's not what's done.

Chris Standaert: Any questions? Why don't we take a break until 10:00, and we will start back and go through our process, our deliberations.

If committee members could take their seats, we can get started. So, we're going to get started. This is essentially our question and answer. It's all one thing. So, this is our time for our committee to discuss the evidence and what we think. We still have available our people to help us, Dr. Piper over there, our clinical expert and the agency representatives. So, again, we are charged with three things. We're supposed to look at things from the perspective of efficacy, safety, and cost, and those are the

three factors we consider. We're trying to use the evidence to come to a decision that is in really the best interest of the people of Washington who are receiving care and paying for that care. That's what we're trying to do. So, those are our determinants, and again, our main source of evidence really has to be the vendor, as we found out with the carbamazepine issue, we are somewhat bound by the scope of what they went searching for. So, to pull on things that they weren't searching for or weren't looking for just becomes... you're not... it's just not... unequal perspectives on that, as opposed to a structured, systematic way of going through the literature. Then, everything is sort of viewed on par. So, we are bound within what they did, and we are bound by the question we have. This is a big topic, and we have a small piece of it, essentially. There may be other things that are valid or invalid, but we just don't know, and we don't address them, but we can only do what we can do.

Alright, and so questions on evidence? We usually start with our evidence vendor, largely. So, with that, I'll throw it up to anybody who wants to make a comment or give us some perspective of where we may be or how they're thinking about this. It's a bit complicated.

Laurie Mischley: I just have a question about the formality here, in terms of approving... trying to do all of this at once. I mean, we're covering a lot of different drugs, a lot of different indications. So, say that we, theoretically, decide the evidence is insufficient here and now.

Chris Standaert: Mm-hmm.

Laurie Mischley: And a proprietary company is able to come up with the evidence that says, hey, for depression and these drugs, here is a new set of evidence.

Chris Standaert: Mm-hmm.

Laurie Mischley: Could that be brought before the committee in a smaller chunk and slice, or would it reopen this topic the way we're looking at it now?

Chris Standaert: So, if there is new evidence that comes to light that is published or otherwise made available, it gets submitted to

Josh and the state. Then, they can decide whether that warrants a rereview of the topic. They can then reframe the topic more tightly within that, I would think. They can open up the rereview for the portion that is brought forward, but I would imagine that's really up to the state to do, but there is a process for doing that. It becomes a new report. You couldn't just sort of say, next month, we have this one study. Can you guys rethink about this one study? We can't do that. It has to go back through the whole thing again, essentially. Yeah, am I correct, Josh, or do you have a different interpretation there?

Josh Morse: No. I agree with that perspective, but typically when we do identify something for rereview, we do try to update the whole thing. We'll go and look around at one topic where we might know something may have changed and look around everything else that was reviewed to make sure that everything is kind of brought up to the same currency.

Chris Standaert: And the state does scan for new information to warrant rereview. It's mandatory that they do that for certain timeframes, but also the public, anybody in the public can submit information to the state saying, I think you should look at this again at any point. Anybody want to help orient us here? Go ahead, Greg.

Gregory Brown: I guess the way I'm looking at it is, this is an emerging field that as a researcher and knowing that virtually everything in healthcare is multifactorial, but looking at single genes is going to have no chance of success, essentially, but the multigene panels, presumably, will get better with time, but I think even though it's low or very low, there is some evidence that in depression that a multigene panel can effect outcomes. So, I would look at supporting this for depression only at this point.

Chris Standaert: And we can, part of your question, Laurie, was how do we... it's diverse, right? So, we can consider this all as one chunk, or we can consider it by diagnosis, essentially. You could say for depression, or opiates, for alcohol, for whatever. We can break it up any way we wanted, that we see the evidence takes up. That's a valid way of doing it.

- Laurie Mischley: I think the question was more along the lines of the test, the panel being the... and that's the harder thing to... you know, we're not talking about for depression or for this drug...
- Chris Standaert: Right.
- Laurie Mischley: ...but if this one particular test used in this indication is where I see potential.
- Chris Standaert: Mm-hmm. It's tricky, because they are proprietary things. So, you have one group studying one and one group studying another. The cross of variability, the population size, the inclusion/exclusion criteria are changing everything, yet you have to view it as a whole in a way.
- Gregory Brown: I guess, correct me if I'm misunderstanding, but we are not approving an individual test. That would be a Health Care Authority decision to say well we... given our recommendations, if we say that something's appropriate in a certain area, then the state would determine whether they think certain tests are more effective or not that they would pay for? Is that how it would work?
- Chris Standaert: In this case, I would think so. I would assume there may be some circumstances where you have a lot of data on one specific test that may drive you for that test. If we think that's what we have, I suppose we could that. We're supposed to consider as a whole and we don't...
- Gregory Brown: Yeah.
- Chris Standaert: ...there are multiple things...
- Gregory Brown: Well, right.
- Chris Standaert: ...on the same test.
- Gregory Brown: That's my point is that we're supposed to approve it for a specific condition, if we approve it with conditions, it's for then that specific condition, but we're not endorsing a specific test, any more than this afternoon if we approve a spinal segment arthroplasty, we're not approving a specific design. We're approving the procedure.

Chris Standaert: Yeah. And so, this afternoon we have issues of FDA approval, right?

Gregory Brown: Right.

Chris Standaert: So, FDA-approved devices, yeah, for that. Yeah, I guess that's tricky, 'cuz you'd say if you approve, what if you approve panels that haven't been developed, and people just do? We may have to say something like... do these get FDA approval or what do they get? Is there any sort of approval required for these things?

Gregory Brown: There's no FDA approval? I was going to say, I thought there was FDA approval, and that's why 23andMe got shut down, because they didn't have approval.

Chris Standaert: There's no federal regulatory body that regulates these. It's tricky.

Josh Morse: Please use a microphone, and I think Dr. Piper can comment...

Chris Standaert: Yes, Dr. Piper.

Margaret Piper: OK. So, many genetic tests are not FDA approved because they are done inhouse as laboratory developed tests, and what that means is that all samples for the ordered tests are shipped to that one laboratory. For that reason, they escape FDA regulation. They do have to... the laboratory itself has to have a CLIA license for the level of testing that is required. So, but it is not a CLIA certified test, because the test, itself, is not regulated. It must meet certain standards for process under CLIA regulations, but it is not regulated in the same way that an FDA approved test is regulated. The FDA last year was in the process of putting forth guidance for regulating laboratory developed tests. That has, apparently, been shelved. Nothing seems to be happening.

Chris Standaert: So, it does look like, for example, Noridian has a policy on GeneSight, on a specific test. It is not a concept. I did... it really depends on where we think the data takes us. I don't think we're bound one way or the other. I think we could

specify if we thought that's what should be done, if that's where we thought the data was.

Gregory Brown: Well, that's why I was asking for clarification. I didn't think it was our purview to be that specific, but.

Chris Standaert: It depends what our data says, right, really.

Gregory Brown: OK.

Chris Standaert: Yeah. Yeah. So, I mean, if you had something where you had multiple competing tests and only one of them seemed to work, why couldn't you just specify that one test is the one that is cost-effective. One may be more cost-effective and more, I mean, you could easily have a series of tests you're talking about. So, I would think we could do that if that's what we want. Joann?

Joann Elmore: I'll give my summary, because it's a little different from yours. I will start by saying, I do agree with you. I think this is a very cool topic. It has great potential in the future. I hope it will work in the future. We need all the help we can get, as clinicians, but my comments about the evidence are both as an internist but also an epidemiologist and someone who has published a biostatistics textbook and kind of that also, I think, alters my review of the literature. I found the studies... we have a small number of studies. They are small in size. One study had one out of four patients that were lost to followup. They were not all blinded. The effect sizes were small. As you two pointed out, there were different panels of tests that were used. Most of these were funded by the companies, and I must admit, when I looked at the actual journals, I know that our evidence vendor searches for "peer reviewed journals," but I think that we are beginning to stretch the boundaries of what is defined as peer reviewed for some of these journals, and I also felt that as a clinician, I care about helping patients and improving their outcome. So, I was less excited and enthused by the intermediate outcomes of, will it change the doctor's treatment, but I want to know, will it help my depressed patients. Will it help my bipolar patients? So, I was less impressed by the current existing evidence. I hope going forward, we will see higher quality, larger, bigger studies, but as it stands, I was disappointed.

Chris Standaert: Carson.

Carson Odegard: Yeah, I... well first of all I'd like to thank Dr. Piper and the Hayes team for this report, because it's a highly complex subject with a lot of variants and it was well researched and well written, so thank you. It's a good launch pad for our discussion. I have to go with both of you, with Joann and Greg on this. It's hard to discuss something that has very little evidence that points in a slight direction on the positive side, but when you don't have the significance, and especially the meaningful significance, it's hard to make decisions on that. So, I welcome the other members of the panel to jump in here, but I would have to agree with both of you. I would be willing to discuss the depression side of it and agree with Greg on the depression side, but the others I wouldn't agree with.

Chris Hearne: Something that gives me some pause is key question number two about direct harms from these pharmacogenetic tests and I think we can all think of some examples of tests that lead people to make decisions that harm patients. So, the fact that we don't have any information about whether the results of these tests cause people to make poor decisions or decisions that harm their patients is troubling to me. So, I think that, in my mind, is a big strike against this.

Chris Standaert: And you have issues of, these are, you know, the Singh study is 12 weeks, you know? It's 150 people. They have a study of 25 roughly. These are small numbers and short timeframes to find problems. It's a very good point. John, what do you think?

John Bramhall: Well, so I think it's an exceptionally broad area to look at, and I'm a little bit disappointed. This is fantastic approach. This is great. This is the future, as you said, Joann. This is the future of all kinds of therapy. I work in an operating room every day, and you know, we've long wanted to have objective information before you go in about a patient's susceptibility to the medications that we might use. This is still... it's not fantasy, it's reality in an experimental environment, and that's where I come down on this. I think it's still highly experimental, and I'm a little disappointed

that we're not being asked... and we're not being asked, to decide something a little bit more narrow. So, for example, we were chatting, if there's an incidence of tardive dyskinesia associated with a certain therapeutic intervention, it looks like it's almost, you're almost there to be able to, perhaps, predict ahead of time a rational selection of medication on a basis of a known side effect that is associated with a particular gene pattern. I mean, we're not quite there, but you know what I'm saying. And that kind of question, it seems to me, to be... that's the level of question that we ought to be at. Are there specific instances that we could approve for coverage for certain medications for certain indications that have a clear harm that you could minimize? That's the kind of question that I would like to be deciding this morning. Putting it into this enormous envelope of schizophrenia, depression, bipolar, alcohol abuse, and drug abuse, this is such an enormous range of empiric therapy that I think it's not surprising that we don't see a concrete change in prescriber behavior emerging out of this midst. So, my personal position is that the question that we're being asked today, I think this is all highly experimental. There needs to be a lot more data. The proper location for selecting what studies are done on that is probably NIH and probably the companies themselves, not the level of funding and the appropriateness of funding by a Department of Health at this point. I put in another plea for interested parties to really present information in the future that is a lot narrower that would allow us to make a pretty concrete decision in a certain area that could be very helpful to the patients that we're concerned about, but I don't think we're there yet. That's my feeling today.

Gregory Brown: I'm trying to understand the concern about picking a drug with a side effect. I mean, this is changing the drugs that we're using to treat depression. I don't know if certain drugs have significantly higher side effect profiles than other antidepressants, but in the face of we're not changing the drugs being used and no evidence that we're driving patients toward medications with higher risk profiles, to me this discussion about risk with this test or harms is pretty minimal.

Joann Elmore: I thought it was a good point you made about lack of data on harms. For example, when we get a test, you can look at false-positives and false-negatives. We don't know the underlying information on this pharmacogenomic testing. For a false-negative result, it can give you false reassurance. Your patient may then have side effects and may be late to seek medical care. For false-positives, it might cause excess cost, change in therapy, etc. So, because we don't know the underlying accuracy of the many different panels, I thought it was a good question.

John Bramhall: Let me just comment from my own world. We know... so the postoperative nausea, and I know it's a separate issue, but just as an example, we know that there's a certain genetic profile associated with the lack of response to a drug like ondansetron, which is a first line attack for nausea, for example. So, I come in as a clinician and I automatically prescribe ondansetron to my patient, and it's ineffective, and I only find that out after the harm is done, after the puking into a basin in the recovery room. Had I done a test ahead of time, I would know that there was a pretty good chance that that wasn't a good drug for that patient. So, I simply use that as an example where harm... harm is suffering, and harm is delayed therapeutic efficacy for the disease at hand, and in the case of depression, harm is not wrenching into a bucket. Harm is suicide, you know? Harm is very concrete and very substantiate. So, when you ask the question is there harm associated with these tests, I don't think the data supports that there's a lot of harm associated with them, and on the other side, I can see a lot of mitigation of harm in its broader sense.

Chris Standaert: Well, harm goes in both ways, right? So, there's harm of doing the right thing and... harm for... harm from picking the wrong drug, but it goes in both ways, right? So, if you say, well this person probably isn't going to respond to these, which are normal first line, relatively safe, relatively well tolerated drugs, we're going to pick from this list that has a higher interaction with other things, based on this test, you may be exposing more risk, and this is the unknown risk of it. I think for me, this issue of sort of, yeah, you can do a test and give it to doctors, and they will change what they prescribe, but the real question is, does that

make any difference? Right? So, that's where the data it's [crosstalk].

Gregory Brown: Can we ask our clinical expert?

Chris Standaert: Yeah. Sure.

Gregory Brown: Are there different side effect profiles for these different antidepressants?

Jon McClellan: Of course.

Chris Hearne: The dilemma is, I mean, this is a good discussion. To me, it does go back, the example, if she really had strong data that it predicted how well someone was going to respond or how well someone was going to have side effects, there wouldn't be a discussion. That's an approvable thing. The problem is, I don't think the data shows that yet. So, then it does open up other discussions. If it doesn't really tell you that much, and you start changing the way people do things based on promising findings that don't matter, does it create other problems down the road. To be honest, I don't necessarily think it's got a lot of risk, because everything we do now anyway is just sort of making it up. So, this is just continuing to do that, but it does provide a false hope about something that may or not work, and it costs money. You ought to have better data to do that.

Seth Schwartz: I think the things I'm sort of struck with is, when I look at the summary here, we have a small number of small trials with limitations funded by industry effectively, that show a small effect size with uncertainty about how that's going to impact clinical outcomes in a meaningful way. I struggle a lot with these, when we have some of these topics where we're kind of on the fence about, well, it seems like it probably works, and I think that this, again as John summarized, I think this probably is the future and it will be fantastic if we can tailor drugs in a meaningful way to individual patients, but I don't think we're yet. I struggle when we have topics where there is no alternative. We're kind of a patient where we have nothing else to offer this patient if we don't offer them the technology that we're reviewing, and that's not the case here. I think there are plenty of current clinical practices for caring for patients

with depression that are still pretty good. There are obviously problems when people don't respond well to the medications, but it's not as if there's not an alternative. So, I think that this strikes me as an experimental intervention or experimental test that we don't really know how it's going to benefit yet, even though there probably is a positive future for this. I don't get the sense that this is something we need to be funding at this stage of the game, although upon rereview in five to six years, maybe it's going to look fantastic, and we're going to kick ourselves, but I don't really struggle with that, at this point.

Laurie Mischley: I'm agreeing with everything everyone is saying here, and I love that we're so close to offering individualized personalized medicine, and I appreciate the lack of data. Where I get hung up are these examples of, you know, for instance, we have the meta-analysis that says CYP2D6 is associated with the Parkinsonism side effect when prescribed antipsychotics. So, when we are talking about antidepressants, the clinician can have a conversation with the patient and say, OK. That didn't work. You had too many side effects, let's change it. It's not quite the same as... Parkinsonism doesn't necessarily go away when you take the person off the antipsychotic for years afterwards we are treating their Parkinsonism. So, some of the side effects of these medications are much more consequential than others, and again, we're back to this is so broad that it's hard to take all of these in a single swoop. On an individual basis, if I knew that the patient who I was about to prescribe an antipsychotic for had this snip, it would absolutely influence my decision making, whether that is reflected in the data, it's not. I mean, we don't have the data for it. I can't shake that it's not an insignificant side effect that we might be able to offset.

Chris Standaert: Is your mic on?

Kevin Walsh: Our charge is to pay for what works. There's not evidence here that this works. I agree it's promising. It's bright and dazzling in the future. The science that they've done is poor. The fact that they're using proprietary methods to construct their recommendations is very suspicious to me. This is not difficult. The evidence is not here.

Chris Standaert: Tony?

Tony Yen: I'm trying to understand, you know, the evidence as best as I possibly can, and this is through the filter of knowing that most of these are commercial studies or commercially funded studies. I think the only one that's not commercially funded, at least from what I took some notes over here, is the Breitenstein 2014 study with an end of 58. That's the only one that's noncommercially funded that I can really make out and address is the clinical utility at the very end, in other words, outcomes. It shows, I believe, remission at four weeks for the folks who received that type of genetic screening was 83.6% versus 62.1% with a P of 0.005. If I was trying to, like, you know, put all the evidence together, good and bad, I think there is... and this is acknowledging that most of the good is actually commercially funded, but that still gives us significant findings, even with small studies, but I'm just trying to say, if I was to make a decision on the data alone, and I'm not being highly critical about the size behind the data, but the data alone, there are significant differences for the making a difference with depression, at least, with really a preponderance of those studies, at least, and please let me know if I'm seeing something that other people are not seeing.

Kevin Walsh: So, I just want to comment, the duration of these studies is suspect to me. So, I'll share with you the sequence to treatment alternative to relieve depression study, the STAR*D study, that tried to construct samples that were more generalizable to patients who are actually enrolled in the population, as compared to people in trials, and they found that for citalopram, for instance, which is an SSRI, 25% of people who were evaluated required ten to twelve weeks to respond. So, when you're telling me that you've got a significant finding at four weeks, it's absolutely meaningless to me.

Seth Schwartz: The other thing I worry about a lot of the search on, but I worry a lot about publication bias here, because there's obviously a million genes that you could look at, probably a million genes have been looked at, and we're basically seeing what's been picked and chosen of a few different genes where we're seeing marginally positive results. I just really worry that we're looking at statistical aberration as

opposed to a real effect, and I just don't think we know the answer to that yet, particularly with this problem.

Joann Elmore: And I just wanted to add, Tony mentioned that he thought that one of the only publications that was not funded by industry was the Breitenstein, but two of those authors held the patent for the gene that was studied in that article.

Tony Yen: OK. Thank you.

Chris Standaert: And I think something, oh, sorry.

Jon McClellan: I would just add to the methods issue that at least some studies I know of, you're not... the clinician and the patient are not blinded to the fact that they have a result, and placebo response is a huge issue in depression trials anyway, and if I, you know, you just take a thing and you tell the patient that this is going to work better, and you tell the doc it's going to work better, that's not... actually it's a good therapeutic idea, but it doesn't mean that it's science or that you should pay for it.

Tony Yen: Thanks.

Chris Standaert: And I think we do have to look at the literature critically, and these issues of internal and external validity are important, right? Is the study... can the study really stand? Does it really apply to the population we're thinking about, and again, we have very small studies with internal flaws. I think there are issues for both internal and external validity that you have to consider. Yes, Dr. Piper.

Margaret Piper: I just wanted to make a quick followup comment on followup time for these trials. I did research that, and what I found is that eight weeks was sort of considered the absolute bare minimum, which all of these trials did meet, but that twelve weeks would absolutely be better, and some of the trials did meet twelve weeks.

Chris Standaert: There is still a fairly short-term outcome.

Margaret Piper: Yes.

Chris Standaert: And, you know, these are longterm medical disorders.

Margaret Piper: Absolutely.

Chris Standaert: Right? So, depression over twelve weeks in a subjective setting, short for the scope of the disease, the timeframe of the disease process, that's a short bite of it.

Chris Hearne: To be fair to the companies, that's also what the rest of the literature looks like for depression treatment. I mean, this is the whole problem with psychopharmacology and not just this area. It's all made of short trials.

Chris Standaert: You need to get to work on that. Other questions or comments? Do we want to move onto our tool a little bit? Let's see if that helps us how to go next. We do have some differing opinions here. Let's see if we can use our tool to actually help us come to some kind of consensus. Let's have you guys go to page five. So, this is our tool. We're supposed to rely on several things, efficacy, considerations like what does the evidence say that results in more beneficial, important health outcomes. Which evidence, if it does so, compared to other comparators or alternatives? What's the magnitude or incremental benefit of the intervention, all that sort of stuff? Safety and safety concerns about what you know and what you don't know, short or long term, and cost is always tricky for us, unfortunately. It'd be nice to have clear information on costs once in a while. So, we're going to look at these for a second. So, if we go to page five, our discussion document.

So, safety, do we have safety outcomes. Actually, I think we could look at this in both ways, that there is some potential for the testing to lead to problems or to avoid problems. So, one could look at it in both ways. Do people think there's convincing evidence one way or the other, or specific safety concerns that they saw? Chris, you brought up the longer term issue, right, that maybe we don't know enough. We don't have a registry of 10,000 people, right? Any particular safety concerns? No. We saw no direct harms that anybody saw, right? We have more of an unknown concern than the knowledge of some direct harm that has occurred from having had this test, and there is some reason to think if the test really did what it was supposed to do, you would lessen harms. So, actually, it would theoretically improve safety.

Carson Odegard: This is somewhat of a nonsequitur, but one of the things that's always bothered me about genetic testing is that we check for five or eight genes and we pay all this money, and they've already got a sample and why don't we do the whole genome when we're doing a test so that that information could be used, in other words, why do we keep paying multiple times on an individual patient, potentially, rather than one time. This patient needs genetic testing for this, but as long as we're testing, we'll check for everything. Is technology to the point where?

Chris Standaert: Map people out.

Carson Odegard: Yeah.

Chris Standaert: And then you can do permutations of all the different genes that might impact something, and you might... maybe that is the Holy Grail.

Jon McClellan: You can know, at least in our lab, we can do someone's entire genome for \$1000. The problem is, you end up with millions of variants that you have no idea what they do or what they mean. You also run the risk of finding something that people may not want to know about. I mean, there's lots of issues that have to get handled with that, and you do... so in our research, I'm not allowed to go back to patients and tell them, even if I find something that absolutely seems like the cause of their illness, because I can't prove that it caused it, and I can't do anything about it. So, the technology is there. The interpretation, the data is not there, and some of the ethical dilemmas about what you do with the information, if you actually find it is not yet worked out, not to mention they'd have to make an entire database of the American population that the current administration will use for something.

Chris Standaert: Yeah. That's interesting, the ethical thing. What do you do with all that data? Alright. So, efficacy. So, they gave us five different things. We can talk about those. So, we have data on sort of treatment decision making. Does it influence people's treatment decisions, do you think? Yeah. There seems to be evidence it does do that. Is that actually an important outcome? Does it matter if you just

know that people change what they do? Is that an important outcome or a lesser importance?

Laurie Mischley: Only if it helps the patient.

Chris Standaert: So, by itself, that's not a terribly important outcome.

Laurie Mischley: Only if it's going to help the patient.

Chris Standaert: Although, there is evidence for it to do so, it's a relatively low importance, in terms of that particular outcome, and drug dosing? Did we see data on drug dosing? Does it affect drug dosing? No data. Again, we'd have the same issue. They're just changing the dose. It doesn't tell you anything if you don't know what the hell happens if you do that. So, that's also a low. Treatment adherence? So, if you stick with a drug, and that's really what you should be on, I guess that's good. If your drug doesn't work and somebody told you this will work for you because those are the right genes that probably doesn't help you much. So, there was some evidence on treatment adherence, yeah? Didn't that one study talk about treatment adherence? Yeah, so there's some. Again, considering an important outcome, it's not the outcomes you were talking about. So, again, we're in the low outcome. Response to treatment. That's a reasonably important outcome. Data on response to treatment?

Gregory Brown: I think there's some.

Chris Standaert: Low to very low quality, very low quality, but that would be an important outcome. That's really what we would like, more data, I would think. Yeah, treatment tolerance. I guess that's side effects?

Carson Odegard: I don't think we had anything.

Chris Standaert: Yeah. We don't have anything. That would be important, but I don't think we have... let's go back to what he said, tardive dyskinesia or other things that would be important if we had decent data on it.

Laurie Mischley: One thing I will just add, in terms of treatment decision making, we touched on placebo response, and even, even

these trials that did a single blind where the patient was blind, I don't know how to control for this, in terms of future study designs, but I think it's really important to blind the clinician. I mean, that increased sense of confidence of using this cutting edge technology gets conveyed to the patient.

Chris Standaert: It does.

Laurie Mischley: And just a plea for future researchers moving forward, if there is a way to somehow accommodate the double blind design, that would be a huge [inaudible].

Chris Standaert: Equal enthusiasm on both sides.

Laurie Mischley: Right. Right.

Chris Standaert: Yeah.

Joann Elmore: But that's a great point, because their definition of double blind is the patient is blinded, and then the person assessing the patient is blinded, but the physician knows all about the test results. The physician has a sense of confidence whether it's evidence based, we don't know. Yeah, I wondered about that, as well, yeah.

Chris Standaert: I heard the statement about a good clinical practice but not great research practice, just that idea of sort of helping your patient think... thinking you're going to do...

Gregory Brown: Knowing what you do does matter.

Chris Standaert: Yeah, thinking how you're going to respond or do with the treatment matters.

Gregory Brown: So, the RCT would require the trial to give random recommendations for antidepressants to the clinician thinking they were evidence based?

Chris Standaert: That's a cool, I don't know. I don't know. That's a cool way to do it.

Joann Elmore: Triple blind.

- Gregory Brown: Yeah.
- Chris Standaert: For cost outcomes, are there other efficacy outcomes that we saw, anybody saw in there that they want to bring up, or that they would like to see that we had no evidence for? Quality of life, depression, suicide rates, things like that, I think, would be important. You know, stuff like that would be very useful. So, some longterm efficacy questions would be very useful, if we could have them, but we don't have them. So, it is important to know there are the gaps in the data of what would really... from a clinical standpoint, we would really be looking for. So, cost data?
- Gregory Brown: When you don't know the outcomes very well, it's hard to see if they're cost effective.
- Chris Standaert: Our perpetual dilemma. Yes. There was some data presented, but one goes back to this idea that you have to believe the data.
- Seth Schwartz: And when you think about how cost would be effected, I mean, it's not designed to decrease costs. It's designed to target therapy. So, you're going to give these people a drug one way or the other. I wouldn't expect that it's necessarily going to reduce cost. It would be the added cost of the test, but the only thing that's going to determine cost-effectiveness is whether you improve effectiveness, and we haven't seen that proven. So, it's hard to believe we could even get that data if we wanted it at this stage.
- Chris Standaert: Again, that's our perpetual dilemma. Cost-effectiveness is dependent upon effectiveness, and then getting good cost data.
- Laurie Mischley: Or side effects. I mean, back to the antipsychotics. I mean, the tardive dyskinesia, the Parkinsonism isn't even going to necessarily present in those first twelve weeks of use. So, some of the cost savings data we're not even beginning to go into that.
- Chris Standaert: In twelve weeks, we're not even, yeah. You save hospitalizations in six months you've saved a fortune. That's where that twelve week followup is a problem. Special populations, which actually in this setting I would

think would be really important. You're dealing with genetic makeups, and I think there are ways to define those populations, but I didn't see that at all. I didn't see any attempt to split people out or talk about that. So, in this case, I think this is actually unusually important for special populations.

Gregory Brown: That's the entire problem.

Chris Standaert: Yeah, but our data on special populations is low or nonexistent.

Gregory Brown: Special populations and disease populations. That is a special population. So, if we look at depression versus chemical dependency versus whatever. So, they look at different disease populations.

Chris Standaert: Some evidence there in terms of these genetic patient characteristics or other factors, we don't have that, but we have the disease.

Gregory Brown: We have the genetic factors but again, we don't know that any single genetic factor means anything, whereas the proprietary multifactorial genetic factors presumably has some, but we don't have the [inaudible].

Chris Standaert: Right.

Seth Schwartz: This is a situation where, you know, we have the pretest probability could be dramatically changed by what population we're looking at. So, if it's a certain ethnic makeup that we know has a 30% incidence of genetic abnormality, the test may be super effective in that group of people, but if it's only 1% mutation, it's much less likely to be a useful test, and I don't think we saw that at all.

Chris Standaert: Right.

Seth Schwartz: They weren't big enough studies.

John Bramhall: And the paradox is that the special population is self-referential. It's defined, in a way, by the test itself in a way. I mean...

- Chris Standaert: In a way, yeah.
- John Bramhall: If it aligns with Caucasian ancestry, but the real issue is...
- Chris Standaert: Right.
- John Bramhall: ...that there's a population somewhere that you identify with the test itself, and that becomes...
- Chris Standaert: Right.
- John Bramhall: ...a special population.
- Chris Standaert: Right.
- John Bramhall: But it's a...
- Chris Standaert: But you'd like to do it the other way. You'd like to find the special population you can identify without having to go through the test and to get down to the pretest probability of...
- John Bramhall: Yeah. Yeah.
- Chris Standaert: ...yeah, and we just don't have that granularity. So, in our safety, we said we had some concerns, because we did, we don't know what we don't know, but we don't have any great high level safety concerns at the moment, but we'd like to know more. Efficacy, we identified data on several low importance outcomes, but very low quality to nonexistent data on higher importance outcomes to us, such as response and quality of life, and longevity, and other sorts of things. Cost, we are, once again, in our zone of fogginess it looks like. So, to move on. So, our... we take this as an informational vote or your perspective on the data essentially. These are the yellow to off white cards that you have. So, you can have five choices on these. The question... I'll go through the question and you can say unproven, meaning you just don't think there's enough data. You think the outcome is less, meaning that things are less safe, less effective than alternatives or equivalents. You think they are equivalent. You think they are better some of the time, or you think, in general, they are better.

So, safety, is there sufficient evidence that the technology is safe for the indications considered?

Josh Morse: Nine unproven, two equivalent.

Chris Standaert: Efficacy, effectiveness. Is there sufficient evidence that the technology has a meaningful impact on patients and patient care, your same five choices?

Josh Morse: Seven unproven, did I get that right? Seven unproven, three some.

Chris Standaert: Cost-effectiveness. Is there sufficient evidence the technology is... the cards are up before the question's done... is cost effective for the indications considered?

Josh Morse: Ten unproven.

Chris Standaert: Alright. So, now we move onto essentially our discussion about a binding vote. There was clearly a predominance of people who felt unproven was the theme here, and efficacy there were three of you who thought there was some evidence for efficacy, effectiveness. So, if one of you wants to speak to what you see so the other people can think, we can then consider whether we can define conditions or just take a vote on whether we're moving on and deciding. We could vote to cover with conditions and then talk about those conditions, if that's what we choose to do.

Gregory Brown: I think we were in agreement that the only condition we would consider covering would be depression. So, I think if we had a vote for that, but I think...

Chris Standaert: Condition of depression of some sort, right? Coverage under that.

Gregory Brown: Right. If that's the proposal, then anybody says vote or not cover can still vote that and... or do we... or am I misstepping preliminary.

Chris Standaert: Yeah, just when you start making a condition, we have to go, we go through the wording and all that and what people would want, but it's clear that the majority are not there. I suppose if we vote for conditions then the assumption is

that the condition would be depression, we could then talk about that, but then we have two, we can't have two binding votes, can we Josh?

Josh Morse: No. You could do a straw vote to determine if that's where you're headed.

Chris Standaert: So, how many people would like to talk about conditions? Let's make that our straw vote. One, two...

Gregory Brown: I mean, I'll talk about it. I think it's a foregone conclusion.

Chris Standaert: That being said, we will move on and if the majority say cover with conditions, we will then define those conditions. So, based on the evidence of the technology's safety, efficacy, and cost-effectiveness, it is, your choices are not covered, covered unconditionally, or covered with conditions.

Josh Morse: I see seven not covered, three cover with conditions.

Chris Standaert: OK.

John Bramhall: OK. I don't know if it's appropriate just to articulate, you know, my condition is that empiric therapy has failed. So, it would seem appropriate to me that if empiric, and all this therapy is empiric, let's just assume. You decide on a course of treatment that's standard of care. It's what you usually do to treat schizophrenia, fine, depression, fine, bipolar disease, fine... Your treatment fails. Now, what do you do? And it would seem to me appropriate if you have \$100 test to put that into the mix and use that to guide future therapy. That just seems intellectually appropriate. I'm not saying that it's supported by the evidence, it just seems intellectually...

Joann Elmore: In other words, you like the hypothesis of this, but there's no evidence to support it in clinical practice.

John Bramhall: No. I don't see any evidence to support it as a first line of attack, but I can certainly imagine the therapeutic interventions that fail now [crosstalk].

Joann Elmore: But is there evidence to support it when it has failed, as you have said, and I don't think that we have seen that either. I understand why you're saying that, because it would be nice to have a test to help these patients who are suffering.

John Bramhall: No. Your question is different to that point. I'm sorry, I don't want to get metaphysical, but your question is, well why did it fail? That's your question, and you need, you now have, as a therapist you need information to guide you. Asking the question why did my empiric therapy fail, and here's a test, which may or may not shed light on it. All I'm, and I'm being a little loosey goosy here I admit it, but it's \$100 test, and you've done six months of therapy that's cost a huge amount, both in terms of personal suffering and in terms of financial cost to the department. Now, the question is, what do we do? Do we give up on the patient? Do we try something else empirically, and it would seem intuitively to me, sensible to say what other information can I obtain that I haven't used, so far, and let's put that in the mix. So, that's my condition that I'm thinking of.

Chris Standaert: OK.

Kevin Walsh: We aren't here to parse out our intuition. We're here to evaluate the evidence. The condition that you're hypothesizing was not even evaluated. We have no evidence on which to make a decision.

Laurie Mischley: So, I agree with both of you, and I'll just that what is so interesting about this is that we are talking about something where a technology and the clinician are inevitably going to evolve much faster than the research gets done, and if we are steadfast in our waiting for high quality evidence to support what clinicians are already using and doing, I think that we are setting up a stage where a lot of people may end up... I agree that we're not there yet, but thinking forward over the next five years, we're still not going to get the double blind placebo controlled trials we want, and the technology and clinical use of these tests is evolving really rapidly.

Kevin Walsh: And so will the cost of it to the state if we approve it without evidence.

Chris Standaert: Right. So, in reality, we just voted, and the clear majority said we're not covering. So, we have a noncoverage decision. This is a process, and I'll just comment on your last comment that that is the point, right? That things that appear to make sense or appear to be of interest get pursued with abandon in clinical practice, yet have no data that they actually help anybody and may actually be harming people is the whole... that's the problem, right? That's not the solution. That's the problem. We need to be, personally, in my view, even more systematic about how we look at the effects of what we do so we're actually doing things that help people, you know, because there are limited resources... both limited resource issues and harm issues and where you invest in helping people's health be better. That's my perspective on it.

OK. So, our vote was a noncoverage decision. So...

Josh Morse: You do need to check for...

Chris Standaert: Yes, I know.

Josh Morse: OK. Thank you.

Chris Standaert: That's where my sentence is going. Are we consistent with the identified Medicare decisions and expert guidelines? And if not, what did we rely upon. Medicare does not have a National Coverage Determination. This is, the point here is that we don't have to be consistent with or be told by expert guidelines what to do. We have a different process. We have a different objective. We have different key questions, different methodology. So, if you look at things differently, you can come to different conclusions. So, we are perfectly free to say that, as long as it's supported by our methodology and decision making and evidence. So, we're not bound by some society who wants something done. That doesn't trump the evidence or our process. So, there was a Medicare local coverage determination, but we're not bound to follow them, I don't believe.

Josh Morse: No. That's true.

Chris Standaert: And there was a paucity of evidence to justify matching it, it seemed, was my interpretation of the committee's

decision. Clinical guidelines and things, they're generally supportive... many of the payers are experimental. Do people see things we're not aligned with or do you feel we're generally aligned with most of these policies are doing? Are we aligned, Joann? You're looking at them.

Joann Elmore: Mm-hmm.

Chris Standaert: Yes. OK. So, with that we'll be done for this. So, this decision will be published and released and open for public comment, and people will comment. Then, at our next meeting, we will then look through the public comments and finalize our determination.

Chris Hearne: Chris, can I say something?

Chris Standaert: Yes.

Chris Hearne: I agree that this is very promising, but apparently, something like one in five Americans experiences a severe adverse event from a drug, overall, and if this personalized medicine stuff really seriously helps us and, like, antipsychotics, for example. Three of the top ten causes of mortality are from antipsychotic use. So, if we cannot impact these serious adverse events by personalized medicine, in this case, pharmacogenomics, what are we doing? So, I would like to see studies that actually can demonstrate in the future there is an impact when these serious adverse effects not on marginal benefit.

Chris Standaert: I think we would too. I think we would agree.

Chris Hearne: The reason I waited until you made your decision was, I didn't want to say anything there, because I was looking stuff up while you were talking about how common are serious adverse drug events, and it turns out they're extremely common. I think one in five Americans has had a serious adverse drug effect, and if we're going to be spending money on this stuff, which might be worth it, it ought to impact something like that.

Chris Standaert: Well, it's complicated. So, we're done, yeah?

Josh Morse: Yes. Thank you.

Chris Standaert: OK. We're an hour ahead of schedule. Half an hour. How about this. How about while we're waiting for lunch, we do the updates, Health Care Authority reviews and progress, which was at the end of our day. We'll do that now while we're waiting for lunch, and then we'll talk a break for lunch, because we don't have anybody. We don't have our vendor. We don't have our expert. We don't have the public, and our public comment isn't until 12:50, and that's almost two hours from now. So, we're going to do that in reverse, I have a feeling. Deal with public comments here and open up the phones at that point. We'll try to get lunch, and then we'll go through our Health Technology Assessment reviews and process and at least get that done. We're not prepared to...

Josh Morse: I'll move slow, something I'm pretty good at. Deliberate, how's that.

Chris Standaert: That's a better way of putting it.

Josh Morse: So, in the back of your binder, since we don't quite have the slides up, you'll see the plan for the topics that are coming up in the next few months. The first slide that we have here shows the technology here is extracorporeal shockwave therapy, and this is for musculoskeletal conditions. The draft report... the meeting is on March 17th. We're currently in the draft report phase for this topic. So, the report should be online, if you want to read the draft report and submit comments on any concerns you have with the report. That is available now. I believe that's available until sometime in early February, a couple more weeks.

Chris Standaert: That's the only topic we're doing that day?

Josh Morse: It is the one topic that day. We will schedule that in the morning, yes. As I pointed out, we will... on the agenda will likely be some administrative work on the committee bylaws to update the bylaws.

Chris Standaert: We'll do that afterwards, yeah?

Josh Morse: We'll do that, we can add that to the agenda for afterwards and in advance of that, we will be having a... we'll have to

talk actually about the mechanics of what will happen on that day.

Chris Standaert: Is there someone who should come talk to us about that, or?

Josh Morse: No. I think you and I will work on that, and then we'll publish a draft for people to consider at the meeting. I believe our rules require a public comment process around the committee bylaws, and we'll review the process on that, but this... because it's only a half day topic, right now, that would be a good time to address the bylaws.

Chris Standaert: It would be, and you could put in a... we publish those. You could put in a time for comment, you know? Public comment frame so it's there if people want to comment on the bylaws, they can.

Josh Morse: Yes, comment there and I think there will also be a public comment period following.

Chris Standaert: No. I mean, if you want to respond. We can open up for ten minutes for anybody on the floor who wants to come on out, too. So, we can have an open public comment. So, we can get everything we need to get done with that.

Josh Morse: OK. So, the next line on here, treatment for migraines and tension type headaches. We have the final key questions. I'm not quite sure if we've published them yet, but this is for the report that started from May 19th. The same is true for the varicose veins. The final key questions have been concluded and these topics will be released here in about 60 days for the draft reports from now.

Chris Standaert: OK.

Josh Morse: And again, for the November meeting, we haven't scheduled those topics, but they are likely to be the skin substitutes review and the CAD for mammography.

Chris Standaert: And then migraines and varicose veins are specific interventions for those?

Josh Morse: Yes.

- Chris Standaert: So, it's nonpharmacologic treatment, so like botox or whatever for migraines, I assume?
- Josh Morse: Yes. I think that topic includes botox, acupuncture, massage, TMS, yeah, transcranial magnet.
- Chris Standaert: Transcranial magnet?
- Josh Morse: Yeah.
- Chris Standaert: And varicose veins is specific procedures for treating varicose veins. Is there some procedure that we're after?
- Josh Morse: I believe there are three targeted lesser invasive procedures, including well I'm not going to try to remember off the top of my head, but I think it's deeper into these slides here.
- Chris Standaert: They're defined procedures?
- Josh Morse: Yeah. So, this is the policy context for extracorporeal shockwave therapy. We are not looking at the use for lithotripsy for kidney stones. We are looking at musculoskeletal primarily tendon issues.
- Chris Standaert: Yeah, that's tennis elbow. Those are the ones I've seen the most.
- Josh Morse: So, this is the...
- Gregory Brown: So, the kidney...
- Josh Morse: Kidney stones is something else.
- Chris Standaert: It's for musculoskeletal conditions.
- Josh Morse: In this scope, yeah.
- Gregory Brown: It's bone. It's calcium.
- Chris Standaert: Do orthopedists treat that?
- Josh Morse: So, here's the more specific project plan. So, you can see, we're in the public comment period. No. Yeah. Why am I

not able to track on this? Public comment period likely ends today, January 20th, for the report. You can see that online. Was that extended, Christine? OK. So, this was the ballpark for the public comment period for the report, December 22 through January 20. I suspect it's a little longer than January 20 there. OK. Thank you, Christine, so ten more days for that.

Chris Standaert: Is that an intracorporeal shockwave treatment? I'm just wondering about the name. I know it's what it's called, but I just wonder about that. It doesn't sound pleasant.

Josh Morse: So, this is the policy context for the migraines and other type headache types, botox, transcranial magnetic stimulation, nerve destruction, acupuncture, and massage. This topic is proposed to determine the safety, efficacy, and value. So, I'll just point out the draft report target publication date is the end of February there. So, that's, that'll be the next step. So, here's the varicose veins description. So, in the original scoping, we did not get into specifics here about, oh no. There it is, chemical ablation, stab phlebectomy, and laser ablation.

Chris Standaert: No stripping or anything?

Josh Morse: That's the comparator, I believe.

Chris Standaert: Comparator, OK.

Josh Morse: Is the, yeah, and the draft report is the same schedule as the previous one. This is end of February for the report. So, any questions for me about these that are in process?

Chris Standaert: That took five minutes.

Josh Morse: I tried to be deliberate.

Chris Standaert: If we don't have our evidence... you guys can go. You're welcome to hang out, but you know. Thank you, very much.

Gregory Brown: Wasn't the [inaudible] report published?

Chris Standaert: Yeah, it's all been published, but we don't have our evidence vendor. We don't have our clinical expert. We

don't have anybody. So, it's... we're too far ahead. We're kind of dead in the water. There are definitely times when the evidence vendor, you know, we need the evidence vendor to hear that thing.

And now, we have the whole issue of sort of the... when we've done feedback... open meetings... when we've done feedback... so, we used to do these things. The people who commented first was the public. We had a bunch of complaints from the public saying, it's unfair, because the public talks first, then the agency directors, and they have more influence over us than the public does, and the public can't respond to what the agency directors said. So, the public should be able to hear... I know it's published, but you'd like, at least, to be roughly in the frame where there are people who might be thinking they're going to hear what they say. I mean, we publish these, and there are things saying this may not follow the exact timeline. So, there is notice that these things may not run, as the outline goes. We may run ahead or hopefully never behind, but we may run ahead of that.

Josh Morse: Yeah, I suggest we take a ten-minute break and then get... we could start with the agency presentation. I anticipate Spectrum will be here early.

Chris Standaert: Why don't we take a break until 11:20, and then maybe we can do sort of, we can eat and whatever. So, a break until 11:30. We'll see if lunch shows up. Let's go until 11:30, 20 minutes.

Josh Morse: Thank you.

Chris Standaert: We'll see where we are at 11:30 and who is here.

We're going to get started. We finished our other topic some time ago. We've been waiting a while, but I think people are here we need to be here. We will certainly leave open public comment time for the specified window we have there for people who come in or for people on the phone, but it would be nice to get started.

So, this is the Washington State Health Technology Clinical Committee. This is our meeting of January 20th. Our topic

this afternoon is artificial disc replacement. This is a rereview. My mute was on, sorry. So, again, Washington State Health Technology Clinical Committee from the 20th of January. This is our afternoon topic, which is artificial disc replacement. It is a rereview. What that means is, there is an existing coverage determination already that we have to consider. Just a couple of comments about this particular topic. So, we have... it's artificial disc, but we have lumbar and cervical, which really are distinctly different issues, and we have two different decisions we've already made that are related to the two of them. We have a coverage determination for cervical fusion, and we have a coverage determination for lumbar fusion, but again, they are distinctly different topics, distinctly different applications. They are different. They are under the same name, but they are really not the same. Indications and everything else are different, which we'll get through, as we get to talking about them. Again, we are, as an evidence-based process, our prime drivers are efficacy, cost, and safety. Those are the things we factor in, and we use our evidence vendor to help us with understanding the evidence on these topics, and we get input from the public and input from the medical directors, Dr. Franklin in this case. We have a clinical expert with us, Dr. Oskouian. We're very honored to have him. He took a fair amount of time out of his day to trek down here and do this. Dr. Oskouian is the director of spine at Swedish Neurosciences, a very experienced spine surgeon, and he has presented to our committee before, but we're happy to have him and his expertise with us today. With that, we'll get going.

So, first is Dr. Franklin will give us the State Agency's perspective, and then we'll have time for public comment, and public comment we have people who have signed up ahead of time. There is a signup sheet that people can sign up for today, and we will open up the phone lines for people on the phone who want to talk. OK. Dr. Franklin?

Gary Franklin:

Christine, can you bring it up on here? OK. Thanks, very much. I'm here for the agency medical directors' group. This is the topic artificial disc replacement. The background on lumbar artificial disc replacement, degenerative disc disease, can be the source of lumbar spine pain, as can other tissues in the lumbar spine, and treatment for

symptoms degenerative disc disease may include medications, physical therapy, intensive rehab, and also spinal fusion and artificial disc replacement. The Health Technology Clinical Committee reviewed the evidence of lumbar fusion in 2016 and concluded that fusion is not more effective, is less safe, and is more costly than an intensive rehab program, and the decision was to not cover fusion for degenerative disc disease in the lumbar spine that was uncomplicated by comorbidities. Artificial disc replacement has been intended as an alternative surgical approach, but it is not better than lumbar fusion for treating lumbar degenerative disc disease, and that's one of the problems.

The HTCC reviewed the short-term evidence, which was all we had, of lumbar artificial disc replacement that was available in 2008 and determined that lumbar artificial disc replacement was a covered benefit in patients who met the FDA approved indications for use, which basically were, if you met the indications for lumbar fusion at a single level, you could have a lumbar artificial disc replacement, single level. That was essentially it, and all of the evidence, almost all of the evidence, is comparing lumbar artificial disc replacement to lumbar fusion, except for one study. In cervical artificial disc replacement, it's essentially the same thing. It's cervical artificial disc replacement versus cervical fusion. The effectiveness and safety of lumbar artificial disc replacement, however, remained a concern due to the lack of long-term evidence. The other thing that was brought up the last time that we reviewed this and is still true, you'll see, is that it's not very popular. We have way more lumbar fusions and not that many lumbar artificial disc replacements, and perhaps our experts can speak to that when we get to that.

The background on cervical artificial disc replacement is quite different, as Chris intimated. Cervical artificial disc replacement may be indicated when nonoperative conservative treatments fail to prevent neurologic progression, or there, of course, may be such severe neurologic stuff going on in the neck that you need to do something more quickly. A fusion is a surgical option for the treatment of radiculopathy or myelopathy, as a result of central or paracentral disc herniations or osteoarthritis, etc. So, the bottom line is that, single level cervical artificial disc

replacement can be done in place of a fusion, and in addition to that, there is now a two-level cervical artificial disc replacement device. So, that's raised questions about whether a two-level cervical artificial disc replacement could be done, as well.

In 2008, the HTCC reviewed cervical artificial disc replacement and determined that it was covered when patients met FDA approved indications for use. That included the same indication as you had decided that would allow a cervical fusion at a single level.

Since 2008, a total of eight artificial disc replacement devices have been approved by the FDA, and as was mentioned in the last topic, when we do a review, we don't focus on one exact type of cervical or lumbar disc versus another. It's whether the procedure works or doesn't work, is effective, and is cost-effective. The effectiveness and safety of the procedure remain a concern, due to lack of long-term evidence, because these things are in for your life. In 2013, the FDA approved a device for two-level arthroplasty and that has been looked at, as well, in this report. There is now some mid-term evidence of artificial disc replacement that has become available, and that is in your report.

The agency medical director concerns for this are medium to high on safety, on efficacy, and cost, and that is about the same as it was when we first reviewed it. The current agency policy, of course, follows your decision in 2008.

Agency utilization and cost: You can see here what's happened in 2013, 2014, and 2015. We probably pay for between 300 and 400 lumbar fusions a year at L&I, there were about 9 or 10 in the L5 in 2015 lumbar artificial discs. So, as the last time you reviewed it, it's not very common and again, I think there are much more substantial safety concerns because of the anterior approach that must be done and there are concerns, especially with reoperation if there is any problem with the artificial disc, because of the issues of reoperation and coming in anteriorly. I'm hoping our experts can speak to that, as well. These are quite expensive. It's not as expensive as a lumbar fusion, but you can see the costs up there.

The key questions are classic PICO questions for safety, on efficacy, on differential efficacy, and on cost-effectiveness, of which there's not a lot of information on cost-effectiveness.

So, on lumbar artificial disc replacement, as we said the last time, lumbar artificial disc replacement appears to be comparable to lumbar fusion in the short term and the midterm up to 24 to 60 months. This is based on lower quality evidence; however, the efficacy of the comparator lumbar fusion is not established, as compared with nonoperative care for degenerative disc disease. The HTCC reviewed the evidence of lumbar fusion, as I mentioned earlier, in 2016, and concluded that fusion is no better than an intensive rehab program, is less safe, and is much more costly. Therefore, it was decided that it would not be covered for degenerative disc disease, uncomplicated by comorbidities.

Although artificial disc replacement appears to be result in greater improvement, oh I'm sorry. There's one study that was kind of different this time. It was a study of lumbar artificial disc replacement versus conservative treatment, as opposed to versus fusion, which all the other studies are, and I just wanted to say a word about that one, since it was more unusual. Although artificial disc replacement appeared to result in greater improvement in the Oswestry Disability Index than intensive rehab, it didn't exceed the pre-specified minimally important clinical difference, which was ten points. Randomization procedure still left imbalance in baseline factors with greater pain and more sick leave in the rehab group. There was no difference in other outcomes, such as return to work, SF-36 mental component, fear avoidance beliefs, and other outcomes, or drug use. There is a much higher risk of surgery, substantial amount of improvement was seen in the rehab group, as well.

There was one thing I wanted to point out. It wasn't actually found in most of the studies, but one of the studies did have some baseline return to work or work status data on these patients. It as the Charite study, and it was of interest to me that at baseline, 45 to 49% of patients were

working fulltime at the time of the surgery, and two years later after either fusion or lumbar artificial disc replacement, very few additional patients were working fulltime. It went from something like 45 to 49% to 52 to 55%, which was for somebody that works in an area that we're trying to get workers back to work, this was sort of disturbing.

The risks of lumbar artificial disc replacement are substantial. In the artificial disc replacement versus multidisciplinary study, the Hellum study, 34% of the lumbar artificial disc replacement recipients experienced at least one complication. These included things like intimal lesions in the left iliac artery, arterial thrombosis, and sensory loss at the two-year followup. The complications resulted in impairment in 8% of the lumbar artificial disc replacement patients at two-year followup, and there was a 6.5% reoperation rate, and as I mentioned, re-operating on a lumbar artificial disc replacement is not a simple thing.

The longterm outcomes of patients with lumbar disc arthroplasty need to be followed carefully, because it's a lifelong thing. The longevity of an artificial lumbar disc is not known and as I mentioned, revision surgery may be more risky.

There is stuff in the report on cost-effectiveness of lumbar artificial disc replacement. These are not high quality studies.

I'm not going to spend nearly as much time on cervical artificial disc replacement. I think the evidence here is much more solid. The quality of the evidence that cervical artificial disc replacement is actually overall higher quality evidence than in the lumbar artificial disc replacement, and cervical artificial disc replacement appears to be superior or comparable not just not inferior, as it was in the lumbar area. So, superior or comparable to fusion at 24 months and longer, up to 60 months. Also, there is some cost-effectiveness data that is a little more convincing than it is in the lumbar spine.

There is a national coverage decision that was present when we looked at this the last time, and that is that CMS for

services on or after August of 2007, lumbar artificial disc replacement was not considered to be reasonable and necessary for the Medicare population over 60 years of age. Therefore, it was noncovered in that decision. So, that decision is still intact. There is no national coverage decision for folks younger than that in the Medicare population.

So, taken together, the agency medical directors are recommending, particularly regarding lumbar artificial disc replacement that it not be covered. It's basically fallen out of favor anyway. We're paying for very few of those and we just think the safety and cost issues, as well as the lack of superiority to anything that we could find are not probably worth it. Most of the studies are artificial disc replacement against fusion. We don't cover fusion for reasons that we went into previously. Cervical artificial disc replacement we think should be covered for treatment of degenerative disc disease when that degenerative disc disease results in radiculopathy or myelopathy. So, patients that meet criteria per our prior decision on cervical fusion could get a cervical artificial disc replacement instead of a fusion at one level.

Cervical artificial disc replacement should not be covered, as previously, for chronic neck pain without evidence of radiculopathy or myelopathy. That was the prior decision. Cervical artificial disc replacement could be covered for a two-level FDA approved device when radiculopathy or myelopathy is demonstrated by objective evidence at both levels. I think that is it. I'm happy to take some questions.

Chris Standaert: Questions for Dr. Franklin from the committee?

Kevin Walsh: Can we go back to slide 17? Can you point to me the studies that we have that you think indicate that cervical artificial disc replacement is superior or comparable to ACDF in effectiveness?

Gary Franklin: Well, I'm going to let the vendor go through the studies in detail. I didn't feel like that was my job, but mostly it was comparable. There was some, there was some superiority, but in contrast, the studies in the lumbar area were of lower quality and were not as strong. That's my main point. I'll

leave it up to the vendors to discuss the comparability or the superiority.

Chris Standaert: Seth? No? That's what you get for touching your mic.

Kevin Walsh: Gary, I think, I want to push you. I mean, you've made a... you're giving us a recommendation, which I presume is based on your read of the literature, which I respect. When I look at this literature and I look at the NDI reports for one-level and two-level cervical artificial disc replacement, I'm not that impressed. So, I'm interested in what I'm missing that you're seeing.

Gary Franklin: Well, you're not missing anything. It's just that we do cover cervical fusion for the same indications, and the evidence on artificial disc replacement is that it is, at least, comparable, and so I'm not sure you're going to... and whether it's superior... whether there's enough stuff on superiority, I don't know, probably not. It's probably more comparable, but it's stronger evidence than it was in the lumbar area. My main point here is, we do cover cervical fusion. It was a tough decision. The studies aren't that great for that either, but it's a standard of care. So, now we're talking about... cervical fusion, if you have radiculopathy, if you have myelopathy, somebody's going to get a procedure and now the question is, could you do this instead of that. I don't think the evidence is compelling that that's not something you should do. I mean, that's... and whether it's superior, that's probably questionable, but there was some superiority stuff in here. There was really hardly any or no superiority stuff in the lumbar region.

Kevin Walsh: Thank you.

Chris Standaert: I just want to clear up, because somebody's going to bring this up at some point and it didn't come through, but we should probably bring it up. So, we mentioned the differences between these procedures, which I think we all should understand and just be speaking the same language here. So, when you look at a lumbar total disc, I'll ask Dr. Oskouian to clarify his perspective after I talk, but if you... a lumbar total disc, our comparator really is, there's lumbar fusion, which is one comparator, and the other is rehab. So, in that setting, there's a lot of data of lumbar fusion versus

rehab as a comparator. That was our comparator when we did the lumbar fusion topic. So, realistically, that's what we're thinking in our head, I suspect, that is there some advantage to lumbar disc and total disc replacement over fusion in terms of comparativeness to rehab to make it viable. So, in a treatment indication for lumbar disc replacement, in the context we're talking about, is for pain. It's to treat back pain. It's to treat a degenerative disc. Take out the disc, replace it with something else, and theoretically, that doesn't hurt and people feel better. That's the premise. Cervical disc is different, because really, the only comparator is fusion. In the cervical spine, the indications for cervical fusion are radiculopathy and myelopathy. There is something compressing the nerve roots or spinal cord in the spinal canal. So, in the low back, to get into the spinal canal, you can go posteriorly from the back, and there is the cauda equina. You can move it and get to the disc in front. In the cervical spine, you can't do that, because the spinal cord is in the way. So, the access to the spinal canal is from the front, and you have to essentially sacrifice the disc, or part of the disc to get there. Then, when we had our discussion on cervical fusion, they were trying to say no fusion as a comparator, which became essentially impossible. So, the idea of going in and taking out a cervical disc and doing nothing to put anything in there seemed like this is not the standard of care. This is not what's done. It shouldn't be done. So, in cervical fusion, in the cervical situation, there isn't a comparator of you're going to compare it to rehab, because really the disc is being sacrificed for access to treat the neurologic problem or the neurologic pain and they're either going to get it fused or get a disc replacement. So, the only comparator here is fusion. It's not rehab.

Kevin Walsh: Say that again. I'm not following.

Chris Standaert: OK. So...

Kevin Walsh: Why couldn't you do studies that compared rehab to disc replacement at the cervical level, as was done at the lumbar level?

Chris Standaert: So, we have studies of fusion versus no fusion for myelopathy, but essentially, the treatment then becomes

rehab and waiting. So, we have studies of cervical fusion versus no surgery for myelopathy. We have studies of cervical fusion versus no surgery for radiculopathy. Our indications when we decided to cover cervical fusion were that, were myelopathy and radiculopathy based on the data we had saying that there, there is a surgical indication to go decompress the spinal canal to help the spinal cord or the nerve root. That's the indication for surgery. It's not neck pain, it's neurologic, and that was our indication. The issue is that in the cervical spine, when you do that to get to the spinal canal and to decompress it in that way, you often have to go through the front, which means you have to take something out to get to the spinal canal, which is in the back, unless you take out the disc to get there for access. Then, you get out, you decompress the spinal canal, but you've removed the disc. So, you have to put something else back in to maintain the alignment of the spine or even improve it in some circumstances. So, in that circumstance, the only choice is, you fuse them or you put in an artificial disc. Those are the only two choices in our current state. So, the comparator for cervical disc replacement is not a comprehensive rehab program. That's not what it's compared to in the literature. They are taking people who they assume have already met indications for cervical fusion. They've met indications for decompression of their spinal canal, and then they operate on them. Then, they're either going to fuse them or put a disc in, because they have to do something. It's got to be one of those two. You can't, again, you can't take out the disc and just leave it. So, our comparators were very different. That's why what we're talking about is different. The indications are different. The low back and the lumbar disc indications we're talking about are not for radiculopathy. We're talking about for degenerative disc disease and back pain. The cervical spine, we are talking about, in the treatment of myelopathy and radiculopathy. So, this is what I was getting at earlier. They're different. Dr. Oskouian, do you want to clarify that anymore? Am I?

Rod Oskouian:

Yeah. I mean, I think that the indications for a lumbar disc replacement... the hard thing when you look at these studies is that, as Chris pointed out, is that you are comparing it to a surgical procedure, and I think this is where some of the confusion comes is that, I don't think

you, as a surgeon doing these procedures, I think it's a different population that you're looking at. When I choose a patient for let's say lumbar arthroplasty, it's not fusion or lumbar arthroplasty. It's a small segment. So, I think... but when you do a study, I think mainly because of the FDA, you have to have a comparison group. So, that's where the difficulty with a lot of these studies and even the study that Dr. Franklin referred to, a lot of the lumbar arthroplasty fusion studies, they compare things and today, you don't necessarily... it's hard to compare the two, but in order to get a study, you have to have a comparison group.

Chris Standaert: Did what I said make sense? No.

Kevin Walsh: I understand what you're saying logically. It does not make sense to me... I mean, I guess I'm going back to... I remember having a problem with the vote about cervical fusion for the same reason, that I understand it's now the standard of care. I understand we voted on it, but I get high centered there.

Chris Standaert: And you can certainly discuss the indications for why you would decompress the cervical spinal canal, right? So, what is the reason for doing that? Once you decide you have to do that, you've met the indication for doing it. So, maybe that's something we can talk about, what is the indication for that?

Kevin Walsh: Well, there's no compare... but there's no nonsurgical comparator. So, it's all a hypothetical imaginary discussion.

Chris Standaert: It's not entirely... well, in the cervical artificial disc replacement studies, they took people who met indications for decompression of their spinal canal, right? So, they're already... they aren't taking people with neck pain. That's not what we're talking about. They're not... they're taking people... they have inclusion criteria, which are typical surgical criteria for intervening on the cervical spine to decompress the spinal canal, but then, the issue is, once you do that in the neck, you're a bit stuck.

Kevin Walsh: I understand that.

Chris Standaert: So, if you agree that these people need to be decompressed, then they're either going to get fused or a disc replacement, and the question then becomes relative benefits of one versus the other.

Rod Oskouian: Maybe if I put it in a different way is that I think as a surgeon or let's say if you're... it's not one or the other. There's a spectrum of different problems and the way we see this is that some patients, as Chris was saying... let's say if they have myelopathy, and they have a large disc herniation, and they have their spinal cords being compressed, that patient is going to do well with a cervical fusion. So, that's one patient. Let's say if you have a patient who has arm pain. They have a large disc, but it's not going in the spinal canal, it's hitting the nerve, and the patient has weakness and arm pain, that's called radiculopathy. So, for me, it, as a surgeon, is OK, that patient is going to... if they fail conservative treatment, what are my surgical options. It's not... so, in that patient, you have two different options. You can do a cervical disc replacement and what we've done historically is a fusion. So, that's one, and then what if you have a patient who has a bone spur. You need to get to decompress the nerve, and you have to take the disc out, and I think that's what Chris is saying. So, to me, it gives the surgeon... you have other options available. You don't have to do a fusion. It's, like if you go to the dentist and he says, all I can do is put amalgam in and drill a big hole. It just, I think there... the spectrum of patients that you see are all over the place. As a surgeon, you don't say it's fusion or arthroplasty. At least, that's not how most surgeons are. There is a spectrum of patients that you see, and it just... it's a tool that's used for a selective population. That's how I would look at it.

Chris Standaert: That was clarity or not clarity? Other questions for Dr. Franklin? Yes?

Joann Elmore: I had a quick question about slide nine. This is the number of procedures in 2013, 2014, and 2015. The label is count of cervical and lumbar procedures, and just a quick question. Are these the total number of artificial discs, or are these fusions, or are these a combination of the two?

Gary Franklin: These are all artificial discs.

- Joann Elmore: OK. Thank you.
- Gary Franklin: There are hundreds of fusions and tens of these.
- Chris Standaert: Gary, what does... I don't know if you guys can find it in your prior report, the number on that same slide of paid per procedure? I'd be curious what the difference between a fusion and disc arthroplasty is. So, it's that same table, slide nine, and the cost by PEBB and L&I and whatever. There's paid per procedure, how much they pay per disc replacement essentially. They have it for... yeah, they're combined, but I'd be curious what the number is for fusion, which we probably have from the fusion data or for the...
- Female: What's also included in the data, if you look inside the agency data in the final report from the TAC, there are notes there that talk about the combination of an artificial disc and a fusion. Those have been put separately so that we could actually compare artificial disc to artificial disc, but there are combinations of things that occur, as well, in the final report.
- Chris Standaert: Getting two procedures done at the same time.
- Female: Yes.
- Chris Standaert: And somebody gets a fusion at one level and a disc at another level.
- Female: Same data.
- Chris Standaert: OK, but no. I was just curious about the cost per procedure of disc.
- Female: I can pull that up for you.
- Chris Standaert: Because it just doesn't... if you have it in the old reports. So, if you could find it, that'd be great.
- Female: It'll take me a sec.
- Chris Standaert: OK. Thank you. Is Dr. Franklin free to go? Yes. We'll move on to public comment. So, we have four people who signed

up ahead of time. One of them was Dr. Oskouian. So, you'll have ample time to talk to us. So, we'll remove him from the list. One person who signed our sign-in sheet to speak who was already on our list, Catherine Hill. So, Dr. Chapman and Dr. Elskens are our two who have signed up. Anybody else who wants to speak is welcome to. Dr. Channard had asked us about... we don't have him on the list, but I assume you want to speak, as well, yes? Oh, no. Certainly. So, and after that, if anybody else in the audience wants to say something, they're certainly welcome to, and we'll open up the phone lines. So, who wants to go first, Dr. Chapman or Dr. Elskens? You're just going together?

Daniel Elskens: This shouldn't be part of the comment. I'm Dr. Daniel Elskens. I'm a neurosurgeon practicing in Walla Walla. I just recently relocated from Michigan. I've been involved in arthroplasties, lumbar and cervical, since their FDA approval. I have no conflicts of interest to report.

Chris Standaert: I don't mean to interrupt you. So, I just forgot to add that when people come to speak, we do need to know your name, affiliation, and if you're representing some other group or individual or institution and if somebody paid you to be here, essentially paid for your travel and everything else to get here. That's perfectly fine. Thank you.

Daniel Elskens: We have some slides.

Jens Chapman: Dear ladies and gentleman of the committee and members of the third party payers groups, my name is Jens Chapman. I'm a practicing spine surgeon at Swedish Medical Center. I have no conflicts to disclose. I participated at my time at UW in FDA trials of disc replacements, and I have done FDA approved disc replacements, since their origins in terms of the FDA studies. I have no conflicts to report in terms of payments of any sort from any companies. I am an editor, reviewer, and a section editor and deputy editor in a number of journals, including JBJS, Global Spine, Journal Spine, The Spine Journal, and the list goes on. I am speaking here on behalf of myself, as a practicing spine surgeon with the best interest of my patient care in mind. I pass the microphone. Thank you.

Daniel Elskens: In addition, we have got the support of the major spine related professional groups in the country, North American Spine Society, which is multidisciplinary, which I'm sure many of you are familiar with, the Congress of Neurologic Surgeons, and the American Association of Neurologic Surgeons, as well as the International Spine Society. And we have nothing.

The purpose of the rereview was selected for rereview based on new literature identified, which may invalidate aspects of the previous 2008 report. The key questions were the efficacy of disc replacement over comparative therapy, the safety profile of disc replacement, the differential efficacy of safety in special populations, and the cost-effectiveness of disc replacement. Your contracted review organization has reported that since 2008 there are eight additional randomized control trials for one level disc replacement versus fusion. There are two randomized control trials for two-level disc replacement versus fusion, and that there were no randomized trials for disc replacement versus rehab. They have chosen to ignore a significant body of evidence that exists, including multiple cost-effectiveness studies, as well as the meta-analysis of all of the available U.S. studies, which actually take the non-inferiority component and make them superior, which goes to answer the gentleman on the end's question about that. Cost-effectiveness data shows that artificial disc would have to fail at 20% or more to be less cost-effective than fusion.

Your contracted organization has picked up, since 2008, that there were no additional randomized control trials for one-level disc replacement versus fusion, one randomized trial for two-level disc replacement versus fusion, and one randomized trial for disc replacement versus rehab. Again, they chose to ignore level one data in the United States, including disc replacement versus disc replacement and they have ignored the meta-analysis of the four U.S. based FDA trials in disc replacement.

Rereview of cervical disc replacement warranted numerous new trials, including trials addressing key questions that didn't exist. New technology and the devices that are existing now versus previously.

Your results indicate benefit is moderate to low of disc replacement over ACDF for both one and two-level cases and cost-effectiveness was greater with CDR over ACDF, especially for two-level cases. The data, in terms of superiority over fusion, comes more in the two-level cases. The FDA has allowed the manufacturer to basically state that the outcome of that is better, adjacent level disease is less, index level of disease is less.

Rereview of lumbar disc replacement is unwarranted. There have been no new studies, since 2008 to suggest change in coverage needed, no demonstration, however, of lack of effectiveness. Safety profile with longer-term has been the same. No additional adverse events.

The rereview, including rehab versus lumbar disc replacement, which was the Hellum study, is basically an inappropriate study for this venue. It's an out-of-the-United-States study. It involved 30% of people with two-level disease, and it involved the rehab component that is unavailable in the United States of America. Despite that, it still showed improvement in efficacy with a reduction in pain and cost-effectiveness compared.

The safety data, which has been ignored, is that there are five studies encompassing now 1500 patients with a complication rate of lumbar disc replacement of under 6% compared to an almost 11% complication in fusion, a 5% reoperation rate in lumbar disc replacement versus a 6% reoperation rate in fusion.

In conclusion, cervical disc replacement clearly offers advantages over ACDF for both one and two levels with two levels even being greater statistically significant. Lumbar disc evidence, overall, is unchanged, since 2008, and continues to demonstrate equivalence to lumbar fusion, and the only study that has been referenced is a study that really should be discounted in terms of the study inclusion and the criteria does not exist in the United States.

Jens Chapman: Thank you, again, ladies and gentleman. A couple of followup points. I'm speaking here as the surgeon who put the first disc replacement that I know of in the state of

Washington into a patient and to the present date, these are some of my happiest patients that I see. I have strong methodological concerns about what you're about to hear from Ms. Andrea Skelly from the contracted organization, and I warn you and hope that you will side with me in avoiding a pick and choose approach towards evidence based, which your committee chair, Dr. Standaert, asks you to do. First of all, for some reason, specialty society guidelines were ignored. That includes the Spine Society, Arthroplasty Society, and it includes also North American Spine Society, an interdisciplinary large body with many opinion very similar to Dr. Standaert who serves on the NAS board. It ignored substantial level one North American evidence, and that is despite their own inclusion criteria, which basically states comparison to nonoperative fusion or other spine surgeries. I don't get it. That's level one U.S. evidence. A lot of emphasis was also possible to five-year followup data from our own country, from our own shores. It was ignored. I don't know why. A lot of emphasis was placed on this article here, British Medical Journal, a Norwegian study, an ethnically homogeneous population, which is oil rich, and which, for reasons that we don't understand, chose to have surgeons put in disc arthroplasties in a third of patients in two levels, which we can't and don't do in our country, and they don't use access surgeons. We are obliged by hospital standards to use access surgeons, a general or vascular surgeon. That may explain the 3 to 6000 cc's blood loss, and the loss of a limb, and a significant ischemic episode in another patient. I don't know how else to explain that. I am in charge of spine research in the Providence health group. I have surveyed our data. I have not seen anything close to this in 183 lumbar disc replacements in the Providence Health System. Maybe this is a different shore and different climates. Same concerns applied to the overemphasize on Scandinavian and British spine fusion data, which, again, was used for your previous coverage decision, but which chose to ignore lumbar disc fusion data, which showed way better results on our own shores. So, I ask you to avoid overemphasizing this study with 60 hours of intensive cognitive behavioral therapy, which, by the way, I'm lucky to get my patients to get six quality hours of PT certified. The methodological approach of doing rehab or fusion is a very important one. I would argue, I never do surgery on a patient who has not

had appropriate well-performed nonoperative care. I summarize, I ask you to avoid circular logic. I ask you to avoid overemphasizing data, for instance the Charite disc, with outdated implants that have been removed from the marketplace and which have been refuted, since then, with much better quality data. Thank you.

Chris Standaert: Just one clarification. You said... I did serve on the NAS board several years ago. I have not served on the NAS board for several years. So, I am not currently on the NAS board. Dr. Channard? Oh, wait. No, wait. We have... you donated your time, right?

Female: Yes. Yes.

Chris Standaert: OK. So, we'll have Dr. Channard then, anybody else in the room who wants to talk.

Dr. Channard: Thank you, everyone, for letting me speak. I'm the director of Spine Scope, which is a surgical care outcome assessment program that tracks the outcomes of spine surgery.

Chris Standaert: Can you get close to the mic so it can be recorded?

Dr. Channard: Tracks the outcome of spine surgeries in residents of the State of Washington.

Chris Standaert: Statement on conflicts quickly.

Dr. Channard: None.

Chris Standaert: Thank you.

Dr. Channard: Let me see which one of these is going to work. Spine Scope started granularly and grew as an organic entity. We're now across the entire state. The thing I want to speak to you about is, as you can see when you look at the numbers, there are 33,400 patients in Spine Scope. We have extensive experience with tracking the outcomes of surgical care for quality, for safety, for efficacy, in individual groups of types of surgery, such as what you are now looking at. In individual groups, there are 3,000 and 4,000 patients. In the data that you will be looking at today, you will not see such numbers. My point to you all is, is this is something

that is available for your decision making, and I am recommending that you consider extending this decision to next year when you can look at the data from Spine Scope and answer these questions. What I will show you is the data is strong, trend, powerfully impactful data, but it's incomplete because we don't have a thing called universal enrollment. You need every patient, every surgery, every time in order to make statements about what works and what doesn't work. We link our surgical care, medical record data, to CHARS data, which is billing data, so that we can discern the cost of that care. With universal enrollment, it's a 1:1 match. These are the criteria. You know it well. I will pass on it, except to say the very thing you are studying is the very thing we do well. When you look at disc replacement, we have 230 cervical and we have 124 lumbar. Those are not every operation. With universal enrollment, we'd be able to speak about every operation, but let me show you what the data shows. There is not a safety issue here. The cervical is safe. Those adverse events are hoarseness and swallowing difficulties. The lumbar is safe. Those adverse events are urinary retention and one unplanned ICU admit. The adverse events in the long-term for lumbar were one wound dehiscence, one person who fell, but none of these patients went back to the operating room, and none of these patients died. These patients were appropriately indicated. Sorry I have to stop.

Chris Standaert: OK. So, Dr. Channard's slides are submitted and will be available in the meeting materials after the meeting. So, are there other people in the audience who want to make a comment? Can we open up the phone line? So, for people on the phone, this is the January 20th meeting of the Washington State Health Technology Clinical Committee. We are currently discussing artificial disc replacement and this is the time for public comment. So, if there is somebody on the phone who would like to address the committee, please identify yourself so that we can have you do so.

Gregory Brown: This is Gregory Brown. I have no comment. I just want to remind you that I am on the phone.

Chris Standaert: Mm-hmm. Thank you. So, nobody else?

- Seth Schwartz: If we wanted to hear the rest of that Scope data, can we request to hear the rest of that Scope data?
- Chris Standaert: How much more data do you have?
- Dr. Channard: [inaudible]
- Chris Standaert: How many slides do you have left? So, you have one more slide, roughly? And you would like to hear it?
- Seth Schwartz: I'd like to hear the rest of it.
- Chris Standaert: OK. Go ahead. Can you pull up Dr. Channard's talk?
- Dr. Channard: The thing I wanted to reiterate, these are the outcomes of residents and citizens of this state. So, you're looking at the outcomes of your neighbors, your family. So, what you see here in the indication section of cervical and lumbar, they are appropriately indicated. They have the appropriate severity of disease, disability, and pain presentation. If all patients were enrolled, this data would be profoundly insightful. What you are seeing are trends, that's different. If with universal enrollment we would have statistically valid answers to every one of these questions and then let me look at the safety issue. So, no person was harmed. No person went back to the operating room. No person died in either the lumbar or cervical groups. The adverse events were minor. The same wound healing problem you have with a simple hernia operation, no one got a deep infection. No one got an artery injury. No one got a spinal cord injury. So, the cervical and the lumbar have comparable safety parameters, and the operations are safe based on these trends. Statistically valid answers for safety would come from universal enrollment. I recommend that this body recommend to the Health Technology Assessment that we ask for universal enrollment, all patients, all procedures across our state, and I would be glad, if invited, to come back and present that data to you each year.
- Chris Standaert: Dr. Channard, I have a couple of quick questions about our data acquisition. So, we get our data from the vendor. So, is this data publicly available currently?

Dr. Channard: Yes. This is Spine Scope data, and it is quarterly presented and at the annual forum, each year, this data is presented.

Chris Standaert: Is it published in a searchable, accessible way in peer reviewed literature? So, if someone did a peer reviewed search for this, would they find it?

Dr. Channard: There are research papers published on the data set they are.

Chris Standaert: OK.

Dr. Channard: There is no research on this data set, because it's not mature.

Chris Standaert: Right.

Dr. Channard: It doesn't have universal enrollment.

Chris Standaert: And it wasn't submitted to the evidence vendor as part of their evidence search? Did you tell them about the data or send the data to them?

Dr. Channard: My apologies.

Chris Standaert: OK. I'm just curious. So, just whether they would have found it and it would have been vetted.

Dr. Channard: No one has actually asked us to do that.

Chris Standaert: OK.

Dr. Channard: And I have been before this committee before...

Chris Standaert: Yeah.

Dr. Channard: ...offering that we would gladly engage.

Chris Standaert: OK. Thank you. Alright. No other public comment? So, we move on. So, who is presenting? Dr. Skelly? So, to our evidence vendor.

Andrea Skelly: Thank you. I would like to take a moment to thank my colleagues who contributed to this report. As has already

been stated, this is an update to a 2008 report that was done. Since that report, there are new studies on the cervical spine, as you have heard, and some new studies in the lumbar spine. There are some new devices, and there are some new indications.

With regard to background, as you all know, low back pain and neck pain are important causes of disability in the United States. They can be expensive to evaluate and to treat, and degenerative disc disease, as you know, is a potential cause of that pain. Surgery may be considered in cases that are refractory to conservative treatment, and that is maybe 10 to 20% of patients with lumbar disc disease, or up to 30% in cervical disc disease may be unresponsive to conservative treatment.

As we age, our spines lose moisture and elasticity, and that potentially increases the stress, then, on the articular cartilage of the vertebrae and the endplates, and that may result in on osteophytic spurs, as well as maybe some annular degeneration, leading to disc protrusion or herniation. The spinal canal can be compromised and narrowed from any of these or from posterior longitudinal ligament ossification and that, as you know, can result in either compression of the spinal cord or myelopathy, or compression of the peripheral nerve root, resulting in radiculopathy.

Over the last 50 years, there has been a lot of research into artificial disc replacement, one of the surgical options, potentially, for treating degenerative disc disease. It was developed as a potential alternative to fusion. When you have a fused segment, the movement in the spine is, of course, no longer there, and that may increase the stress and mobility of other areas around the fused segment. So, the purpose of the artificial disc would be to preserve the motion of the target area and hypothetically that decreases the stress on the adjacent segments.

There are a variety of different devices that have been evaluated, different designs over the years, and it's interesting, a study in some historical things, but we really don't have time for that.

There are three FDA approved lumbar disc disease lumbar artificial discs that are pictured here. Then, there are many more artificial discs for the cervical spine, which are listed here.

In terms of indications, in general, the indications for cervical artificial disc replacement or cervical arthroplasty are single-level symptomatic disc disease or two consecutive levels for the Mobi-C, as you know this is a newer device newly approved for two-level disease. Patients should have for indications radiculopathy and/or myelopathy with radiographic evidence and have failed six weeks of nonsurgical care or may have progressive symptoms despite nonoperative care. The contraindications are listed here.

There are similar indications for the lumbar disc, in terms of it being confined to a single level for degenerative disc disease and patients should have failed a six-month trial of nonsurgical care. These are detailed in more detail in your report.

The key questions have already been described. In terms of the scope, the scope was consistent with the scope in the 2008 report. In other words, we were looking for patients with degenerative disc disease in the lumbar spine or the cervical spine. In the cervical spine, the population was the population of those who had radiculopathy and/or myelopathy. In either population, we attempted to look at only new index level instrumentation and did not include studies who had significant populations with prior surgery.

In terms of intervention, we looked at FDA approved devices. We did exclude devices that were no longer FDA approved or generally not available in the United States and then the comparators were nonoperative care, fusion, or other spine surgery. The focus is on the highest quality of studies available with concurrent controls and full economic studies.

In terms of outcomes, as was the case in the 2008 report, we focused on the primary outcomes of clinical success, as defined by the FDA looking at function and disability, pain reduction, and then device failure, which we took to be

reoperation at the index level, including revision or reoperation or removal. Then, secondary outcomes included quality of life and other things.

In terms of the appraisal of the studies, just as a very quick reminder, the studies are appraised individually. All included studies are appraised individually, and they are based... the appraisal is based on commonly accepted criteria for risk of bias. While study design plays a role, the areas for risk of bias are included in that evaluation. It's a two-step process. So, that's the first step is to evaluate risk of bias. The second step is to incorporate that determination of risk of bias and consider the consistency of information across studies for a specific outcome, the directness, the precision, and whether or not there is the possibility of publication or reporting bias, and this is across studies for any given primary outcome. One way to think about it is that we individually appraise the studies, combine that information on risk of bias with those other domains, and for each primary outcome, we come to a determination of whether the strength of evidence is high, moderate, low, or insufficient, reflecting our general confidence that the effect estimates are true to what would actually be possible if you were to have an infinite sample size. So, our high strength of evidence means that we are very confident that the estimated effect is true, moderate, of course, moderate confidence, and it goes down from there. We screened over 1800 citations and ended up with 84 citations in the final published report. We did take a look at anything that was submitted for public comment, in terms of publications which we may have missed, and there were very few, if none, reported. We also did take a look at the bibliographies of all included studies and did a PubMed search on the most recent 20 that were available to attempt to account for all possible studies that were includable, based on our criteria.

Noninferiority studies have special characteristics, and the FDA IDE trials, most of them, used a noninferiority design. The intention of a noninferiority is to determine whether a new treatment is the same or is not worse than an active control by a specific margin. Superiority can be identified using this design, and the interpretation of a noninferiority study depends on where the confidence interval for the

treatment effect lies relative to both the margin of inferiority, that delta, or the null effect. I'll have a graphic example here in a moment. One of the assumptions of noninferiority designs, however, is that the reference treatment must have an established efficacy or is in widespread use.

If we take a look at the graphic, we can see that on the farthest left margin here, let's see. Do I have a pointer here? No. OK. I lost my slide. So, on the farthest left margin, if you see on the horizontal axis, there is a little delta. That's our noninferiority margin. You can see that if a point estimate and confidence interval was to the left of the null effect, the zero line, excuse me, to the right of the null effect, to the zero line, superiority could be demonstrated. The confidence interval does not cross zero, and the point estimate clearly is in favor of that treatment that is to the right hand side of the zero. Noninferiority is demonstrated in points B and C because the line of identity, the zero line, is crossed, but it's not to the right side of the noninferiority margin. So, we say that the technology is not inferior to the comparator. H is very obvious, as well. It's outside of the noninferiority margin. It's clearly inferior, and it does not cross the zero line. The others are potentially inconclusive.

The analysis that we attempted was complex. I won't go into a lot of detail here. Suffice it to say that we checked for superiority using both intention to treat and completers analysis, and then we also did, in the case where there was not congruence between the intention to treat and completer's analysis, we did check for noninferiority and due sensitivity analysis. That is all detailed in your report.

We focused for our strength of evidence on the completers analyses, because that's the more conservative approach. For cervical artificial disc arthroplasty, the majority of the new evidence is in cervical artificial disc replacement. Again, there were some new devices approved. There were additional trials for one level, and a new indication of two-level artificial disc replacement. In my presentation, there are a lot of slides. There is a lot of data. I intend to focus primarily on the overall clinical success and the NDI success, the neurological success, as those are generally the more

conservative, and that's what the FDA has used. We will also talk about adverse events, as well.

You've already been reminded of the National Coverage Decision. We did attempt to identify clinical guidelines through the National Guideline Clearinghouse, and there were limited guidelines that we found. These are the ones that we did find.

In terms of the evidence, this is a very busy slide, and as you know, there are now new RCTs and longer-term followup, as well as information on two-level arthroplasty, as well as some new cost-effectiveness studies.

Again, what we did is, we looked at the overall clinical success based on the FDA composite, and this was for both one and two level interventions, which included a composite looking at NDI of improvement of 15 points or greater from baseline, neurological success, no secondary surgery as a result of device failure related adverse events, and for the Mobi-C no intraoperative treatment changes. This is the focus of our outcomes that we will be sharing. We will also look at NDI success, neurological success, and where appropriate, pain.

At 24 months, the evidence was moderate that cervical artificial disc arthroplasty was superior to ACDF for achieving clinical success at 24 months. You see that in the forest plot here. It clearly is to the right hand side of the line of identity, the zero line.

At 48 to 60 months, again, it appears that cervical artificial disc arthroplasty is superior to ACDF for achieving clinical success, and the evidence was again considered moderate, but by 84 months, there was only one trial available and limited information from that one trial, and it still showed superiority, but it was downgraded for risk of bias and lack of precision.

In terms of NDI success, again, cervical arthroplasty appears to be comparable or slightly better than ACDF for achieving NDI success, in other words, a greater than 15-point improvement, greater than equal to 15-point improvement in NDI; however, by months, the level of evidence was less,

again, because... oh, excuse me. I went back. That was at 24 months. By 48 to 60 months, the evidence was considered low again based on lack of precision. We have fewer studies, more variability in the data, and at 84 months, it looks like the cervical artificial disc replacement is comparable to ACDF for achieving NDI success.

The NDI scores, I do have slides and appendix if you're interested. In the interest of time, most of them were... at 24 months, they give some evidence that the NDI scores on a 100-point scale, statistically, were different. It's unclear that this represents a clinically meaningful change. At 48 to 60 months, there was moderate evidence, again, but this was driven in large part by four moderately high risk of bias studies, which contributed substantially to the pooled estimate, and by 84 months, again, there was only one moderately high risk of bias trial available.

If we look at neurological success, again, arthroplasty may be slightly better than ACDF in terms of neurological success at 24 months. If we look at 48 to 60 months, again, we conclude that it's slightly better than ACDF, but again, by 84 months, we have limited information and low confidence in the evidence that artificial disc arthroplasty is comparable to ACDF.

In terms of arm pain success, the authors defined, in these two studies, defined it as at least a 20-point improvement in arm pain, and we felt the evidence was low. Again, downgrading for risk of bias, as well as imprecision. It appeared that artificial disc arthroplasty and ACDF were comparable. Again, the pain score suggests that artificial disc replacement may be comparable or slightly better than ACDF, but statistical differences may not translate into clinically meaningful change.

Neck pain success, it appears that cervical artificial disc replacement is comparable to ACDF at 24 months and if we look at neck pain scores, it appears that if you look at the high quality studies, the higher quality studies, those that are moderately low risk of bias and the top of the forest plot, they indicate that the two treatments are comparable. The moderately high risk of bias trials, however, suggest that artificial disc replacement may be slightly better. There

is substantial heterogeneity when we combine the trials. The weighted mean difference of 5.1.11 points on a 100-point scale may not be clinically meaningful.

If we take a look, again, at neck pain scores, again, a similar trend is seen. Artificial disc replacement may be comparable or slightly better than ACDF. Again, statistical differences are not likely to be clinically meaningful. Again, I have appendix slides for these other time periods.

If we take now a look at two-level artificial disc replacement, all of the previous slides were related to single level arthroplasty. There was one study on the Mobi-C, which looked at overall clinical success and there was moderate evidence, again, that artificial discs were superior to ACDF, when you looked at overall success, in terms of both clinical success, as well as NDI success. It was considered to be comparable looking at neurological success, and both of those were components of the overall success.

Again, looking at pain scores, artificial disc replacement may be as good or slightly better. The differences, again, may not be clinically meaningful.

If we look at the study that included patients who had one, two, or three-level disc replacement, again, we don't have clinical success or neurological success. All we have are scores. It appeared that artificial disc replacement was comparable in patients with radiculopathy at 24 months in one study, and for the other time periods, it appears that artificial disc was as good or slightly better in patients with myelopathy. Again, clinical significance is not clear. If we take a look at the safety of artificial disc replacement in the cervical spine versus ACDF from a viewpoint of secondary surgery, bearing in mind that secondary surgery was defined differently across studies in many instances, and this may not just be indexed level surgery. It could be index level or both index level or adjacent level surgeries, but there was moderate evidence that fewer patients required secondary surgery in the artificial disc group compared with ACDF.

In terms of secondary surgery then at a later timeframe, so the previous slide was in 24 months. This seems to persist between 48 and 60 months across these trials, and the evidence was considered of low quality. Fewer patients in the artificial disc replacement group did undergo secondary surgery in this time period, as well. By the time we get to 84 months, we have low quality evidence, because we have fewer trials and more dispersion of the data, and still fewer patients in the artificial disc replacement group underwent secondary surgeries, but there were only two RCTs.

Looking at serious or major adverse events, again, these are as classified by the trials, and they were very heterogeneous in how they classified serious or major adverse events, but again, fewer artificial disc replacement recipients compared with fusion patients had serious adverse events. The overall quality of evidence was considered low.

Again, at one level, at other timeframes we have very sparse information from the RCT data available, and it appeared that artificial disc replacement was comparable to ACDF at these other timeframes, but that's based on single studies.

In terms of device related adverse events, again, artificial disc replacement appears to be superior from the standpoint that device-related events were less common with cervical artificial disc replacement than with ACDF. This was at 24 months. At 60 months, it appears that they are comparable. We don't have data, except for one trial of the ProDisc-C at 84 months, and it also appeared that there were no differences between the two treatments.

Any adverse event is sort of a hodgepodge, again, variably defined across trials, and the data were not well reported for any of the adverse events, in terms of accounting. In your appendices, you have a long laundry list of anything that was reported in any of the trials. It was very difficult to summarize the data across them and as a result, we don't have a lot of confidence in this particular result, that there was insufficient evidence that the two treatments were comparable with regard to "any" adverse event.

Looking, again, now at the two-level intervention, secondary surgery and adverse events, again, as defined in the trials, there was low quality evidence to suggest that fewer patients in the artificial disc replacement group underwent secondary surgery. The serious and adverse events were also less common in the artificial disc replacement group. The device related adverse events were also less common in the artificial disc replacement group.

If we look at that study that had one, two, or three level intervention, it appeared that there were no statistical differences between ACDF and artificial disc replacement for secondary surgery at the index level. Again, reporting of major adverse events and device related events was not very well done. None were reported in either trial in terms of serious adverse events. With regard to device related events, only dysphagia was singled out as being different between the two groups, and it was less common in the artificial disc replacement group. Our confidence in the estimates, however, is low.

There were no studies that specifically evaluated differential efficacy or safety in artificial disc replacement at the cervical level.

In terms of cost-effectiveness, there were four cost-effectiveness studies that were based in the United States, all of which suggest that single-level artificial disc replacement may be more effective and less costly at a willingness to pay \$50,000. There were a number of study limitations, however, one of which only incorporates a 60-month time horizon and, as Dr. Franklin pointed out, these discs need to be operative in a patient for their lifetime, which may be a 30 or 40-year proposition. The analyses were not well done in terms of their evaluation of their assumptions and looking at sensitivity analyses, it's a very complex way to try and do some of the modeling that they suggested. Nonetheless, their bottom line was that they suggest that it is more cost-effective.

In the two-level intervention, there was one randomized control trial, as you know, and the two economic studies looked at things at two different timepoints and those two

different timepoints, at both timepoints it suggested that artificial disc replacement is cost-effective versus ACDF at all the timeframes that they evaluated, which is actually, again, only up to 60 months. Again, there are some limitations. They did not do a lot of accounting for some of their costing data, and the hospital length of stay was not well captured.

In summary, for the cervical artificial disc replacement, we found that there was moderate evidence to suggest that artificial disc replacement at the cervical spine was superior to ACDF based on clinical success up to 60 months at one level, up to 24 months at two levels, and NDI success at two levels at 24 months. The evidence and our confidence in the evidence, in terms of superiority of ACDF is less at longer timeframes, as you see here. It was considered comparable for the arm pain scores, the neck pain scores, at both timeframes.

In terms of safety, here was moderate evidence to conclude that secondary surgery and device related adverse events were less common with artificial disc replacement at 24 months in the single level interventions. There was low evidence to suggest that that would continue then between 48 and 84 months for the one level or 24 months at the two levels. Again, device related adverse events were less common in the artificial disc replacement group, but again, our confidence in that evidence is lower. Same with serious adverse events. We felt that the artificial disc and ACDF were comparable with regard to serious adverse events at one level, up to 84 months based on single RCTs, and comparable in the two studies that mixed one or two level artificial disc replacement. Again, no information on differential efficacy or safety, and single level artificial disc replacement and two-level artificial disc replacement do appear to be cost-effective at a willingness to pay threshold of \$50,000. That wraps up cervical artificial disc replacement. I'm going to go fairly quickly over the lumbar disk arthroplasty data, because of time, but also it's a lot easier to go through.

At 60-month followup, basically the same RCTs that were included in the 2008 report of one-level artificial disc replacement versus fusion basically were available. There

were two new RCTs at multiple levels, and then the efficacy findings were basically similar to the other report. There was low evidence that lumbar artificial disc replacement was comparable to fusion for overall clinical success, ODI success, neurological success at a single level or two-level intervention, and pain success or pain relief at 24 months and 60 months in all studies. So, in other words, artificial disc replacement was basically comparable to fusion in these studies. All but one study was artificial disc replacement versus fusion. It's already been mentioned that there was one study of artificial disc replacement versus multidisciplinary rehabilitation.

Again, the national coverage decision has been described, and the guidelines that we did identify are reported in section 2.4 and for lumbar arthroplasty, for patients with nonradicular low back pain, the American Pain Society recommended that clinicians consider offering an intervention, that there was no real difference between artificial disc replacement and fusion up to two years, but they felt that the data were insufficient beyond that. Artificial disc replacement was recommended by the Colorado Department of Labor and ACEOM did not recommend for chronic nonspecific low back pain.

In terms of outcomes for efficacy, again, the focus is on the overall clinical success based on the FDA composite of ODI improvement, no device failure, no neurological deterioration, and then one of the studies, Blumenthal, added no major complications. Zigler also added improvement in health related quality of life related to SF-36, which made this a more conservative measure. ODI success, neurological success, were also part of this, and we will talk about those, again, with a focus on the success outcomes.

Because the artificial disc replacement versus multidisciplinary rehab is the outlier in terms of comparators, I will present those data first. The study was at moderately high risk of bias. It was a poor quality randomized control trial with only 24 month followup. The only success parameter they report is ODI success and they report that more people who got the artificial disc replacement were successful than those who had

multidisciplinary rehab. They also reported that the VAS pain scores were greater; however, they did not adjust for baseline differences between the two treatment groups, but it is unclear whether an eight-point difference is going to be clinically meaningful. The confidence intervals are wide. So, there is not a lot of precision in these estimates.

If we look at the other outcomes, these were... we did not do strength of evidence on these, but for completeness and for transparency, the authors report that the ODI scores were significantly better in the artificial disc replacement group, as were the SF-36 physical component scores. In terms of work status, there were no differences between the two groups, either at baseline or at 24 months, and the same with medication use that were statistically equivalent at 24 months.

In terms of safety, there are very limited data on the safety of artificial disc replacement or multidisciplinary rehab in this study. All of the adverse events were defined based on artificial disc replacement related type of adverse events, and they were defined very differently than any of the other studies in the lumbar spine comparing it to fusion. So, there's not really a lot we can say, other than to provide what the range was for secondary surgery and complications.

There was one cost-effectiveness study based on this randomized control trial, and it suggests that in the short-term time horizon, at a willingness to pay of at least \$49,000, lumbar artificial disc replacement may be cost-effective compared with multidisciplinary rehab, but there were a number of shortcomings to this evaluation. One of the primary ones is, they really did not adequately describe or evaluate the impact of potential adverse events of lumbar artificial disc replacement, and they mention no information on any adverse events or the consequences of the rehab.

Moving now then to the artificial disc replacement versus fusion, I'm going to go very quickly through this. At 24 months, the data... this is what we had for the previous report. It showed that artificial disc replacement was comparable to fusion. This persisted to 60 months when

we added those data that were available. It's important to note in these two studies, the Blumenthal and Zigler studies, the IDE studies, with the additional 60-month data, there was substantial loss to followup. There was only 69% of patients available for the ProDisc trial at 60 months and only 43% of the original participants in the Charite trial were available. So, the conclusions for 60 months, we're not very confident in those, but it does appear that disk replacement is comparable to fusion at 60 and 24 months in terms of overall clinical success.

Similarly, for ODI success, the quality of evidence is low, and the treatments are comparable at 24 and 60 months.

In terms of neurological success, again, we see a very similar pattern; however, we felt that the data were insufficient. We didn't have any confidence in the data at 24 months, because the two trials are on opposite sides of the line of identity. At 60 months, we felt that there was comparability between the treatments.

Looking at pain scores, again, our focus is on the success information. There was some suggestion that artificial disc replacement was comparable or slightly better in terms of pain relative to fusion, but that's based on the scores, themselves, and again, it's not clear if it's a clinically meaningful difference.

One study, which was basically in addition to the IDE trial by Zigler looked at two-level fusion and completed analysis at 24 months suggests that there was no difference between the two treatments at 24 months, either in overall clinical success or neurological success, and again, the scores may show ODI as maybe slightly better following artificial disc replacement, but again, it's unclear that it's clinically meaningful. If we take a look at the one study, additional study that looked at one or two-level fusion, there were no differences between groups. We concluded that there was low evidence that artificial disc replacement was as good as fusion for achieving clinical success. They define clinical success not by the FDA standard; however, they looked at patients who were totally pain free or much better at that time period.

In terms of back pain scores, again, there were no differences between groups, and if we looked at subsequent surgery, there was low evidence that artificial disc replacement was comparable to fusion at all timeframes, and in terms of timeframes, and in terms of device related events, again, artificial disc replacement looked to be comparable to fusion at 24 months, and there was low evidence, again, for any adverse event at 24 months, that the two treatments were comparable, and at 60 months, as well. There was insufficient evidence from the studies to conclude anything about serious adverse events, including death. So, for all adverse events and complications, again, they appeared to be comparable. If we look at two-level fusion and safety, there was low evidence that additional surgery and surgery-related adverse events, complications, were less common in the artificial disc replacement group. When we looked at device related complications, such as subsidence or migration, there were no statistical differences between groups, but there was insufficient confidence in that finding.

Continuing with safety, it appears that artificial disc replacement was associated with significantly fewer secondary surgeries and most of them were device related. So, therefore, the device related findings are similar, but the quality of evidence was considered low.

When we look at major complications, there were fewer complications following artificial disc replacement, but statistical significance was not reached across one trial, again, in Sweden, possibly due to sample size, and for any complication, the two treatments were considered comparable, but the confidence in our estimates is low. There were no studies that looked at differential effectiveness or safety.

In terms of cost-effectiveness, with regard to lumbar disc arthroplasty, across the two studies, results are inconclusive. Fusion may be more costly from a healthcare perspective when reoperation is included. In the other study, they found that it was potentially cost saving compared with fusion; however, it depended on what outcome you were looking at. Neither study did real robust

evaluation for sensitivity analyses. So, in the short-term, adverse events don't seem to be well described in these, and they did limited sensitivity analysis in these two studies. So, we felt that it was unclear that disc arthroplasty was better than fusion from a cost-effectiveness standpoint.

So, in summary, with regard to the lumbar arthroplasty, there was low evidence that artificial disc replacement may be superior to multidisciplinary rehabilitation. Again, as you know, there are a number of issues with the study. So, the evidence was considered to be low, our confidence in the estimate was low. With regard to ODI success, and we discussed the issue that pain, it is unclear if the results were adjusted for baseline or clinically meaningful. With regard to fusion, again, basically it appears that there is comparability between the two treatments, and again, as a reminder for noninferiority trials, the assumption is that the referenced treatment must have an established efficacy or that it's widely used, and in the case of lumbar fusion for degenerative disc disease, that remains uncertain, especially when compared with nonoperative care.

With regard to safety, little can be said about the multidisciplinary rehab, except for the ranges of complications that they identified for artificial disc replacement only. With regard to fusion, again, it appears that artificial disc replacement and fusion are comparable, both at the single level and at two-level intervention. For subsequent surgeries and device-related adverse events, the evidence is insufficient that fusion is comparable regarding any major serious adverse events. With regard to the two-level study, major surgery-related complications were less common, but statistical significance was not reached, and there was insufficient evidence to make a conclusion regarding the comparability for device-related complications. Sample sizes were small, possibly contributing to that finding. Again, no differential efficacy or safety information is available, and there is lack of clarity with regard to whether or not artificial disc replacement may be more cost-effective than fusion. One study in artificial disc replacement versus multidisciplinary rehab suggests that it could be cost-effective, but again, given the limitations of the study, it is unclear.

So, that in a nutshell, is our evidence report. I could go through the rest of the... what, 64 studies if you'd like.

Chris Standaert: Yeah. We're OK for now. Questions for Dr. Skelly? Yes, Seth.

Seth Schwartz: Thank you. That was obviously a complex assessment. So, I just had one question about an outcome we haven't really talked about, which is... one of the things that's always brought up is that the long-term risk of fusion is that there may be issues in the levels above and below the fused level. Just empirically, it seems that if you're not actually fusing, but you're replacing the disc, that there might be less of an instance of that. Do we see any evidence at all that there was any differential effectiveness, in terms of effects on the above and below levels of fusion versus disc replacement?

Andrea Skelly: We did look at that, as a secondary outcome, but we had limited information. We did not look at radiographic evidence for adjacent segment disease or motion differences. Our understanding from our clinical expert was that it's really difficult to equate radiographic ASD with symptomatic ASD. We did attempt to capture information on symptomatic ASD that resulted in subsequent surgery. I don't have that at the tip of my fingers, but we can look that up and give that information to you. Certainly, the idea behind the artificial disc is that it does preserve motion and does not put stress on those other segments.

Chris Standaert: So, you went looking for studies that talked about treatment of symptomatic adjacent segment disease, or in the studies where you looked at longer-term followup, did they bring up issues of a treatment. So, you didn't even go specifically looking for adjacent segment disease as a different topic.

Andrea Skelly: No. We did not.

Chris Standaert: OK. So, you would have found it in the course of looking at the followup studies where they talked about it, which are, what, 60 months maybe.

Andrea Skelly: Right. And we did exclude studies that looked only at radiographic aspect or motion aspects.

- Chris Standaert: OK.
- Andrea Skelly: Again, that was based on the advice of our clinical expert, as well.
- Chris Standaert: OK. Carson?
- Carson Odegard: Yeah, in regards to cervical artificial disc replacement, you mentioned in the safety section about how it was difficult to compare studies, and you kind of breezed through that. So, I just kind of, if you could elaborate on why it was difficult for secondary surgeries. What were the differences there? Was it criteria for surgery or was it methodology or what were the differences between them?
- Andrea Skelly: Well, and I'll let Erica chime in if she has some additional input, but across the trials, it was very difficult to discern by the way that they were reported whether it was a surgery at the index level, at an adjacent level, or both. So, it was difficult to segregate. By study, we do have that information that can call up for you. It's also in the appendix, but part of it is in the way they define secondary surgery.
- Carson Odegard: Oh, I see. So, it's more anatomical than.
- Andrea Skelly: There were some anatomical differences, but it was primarily in how they accounted for the patient and how they accounted for, was it index level or was it adjacent level or both.
- Carson Odegard: OK.
- Andrea Skelly: So, the data on the complications in these trials, we went to the FDA reports, as well. It is very difficult to follow and come up with a single [inaudible] descriptor, but we did try to do our due diligence, and in our report, it is detailed who accounted for what, how.
- Carson Odegard: Thank you.
- Andrea Skelly: Mm-hmm. Is that fair, Erica? Does that... because she did the safety stuff, a lot of it.

Chris Standaert: I had a question. In the Hellum study, that study has always bothered me in one particular way. That's the study of rehab versus disk replacement in the lumbar spine. One of the subjects who had a disk replacement, the prosthesis dislodged after three months. They went back in to operate. There was an arterial injury, and the person had their leg amputated.

Andrea Skelly: Yep.

Chris Standaert: That wasn't in your slide. It wasn't in Dr. Franklin's slide. That's a wildly severe complication in my own estimation. I can't say I've ever seen that from PT, right? So, I gather it's rare. We don't have 20,000 patients with this to know the incidence of it. We've got examples of studies of 180 or 300 or 500 patients, but that's going to be a rare complication, but it's real. It happened in a published study, which is uncommon. Then, the authors, when they even talk about this study, they say... they talk about the significance of the difference in the ODI between the two groups, and they said it didn't meet our A-priority criteria for significance, and they said that both groups, really, got a lot better. They recommended, considering how well people do with rehab and the complications of surgery, it's, you know, you should consider that. The cost-effectiveness data, you said a couple times it suggests it may be more cost-effective. You could also suggest that it isn't cost-effective. With the [inaudible] it wasn't.

Andrea Skelly: That's right.

Chris Standaert: Right? So, it equally suggests effectiveness and lack of effectiveness, which is different than saying it suggests effectiveness. I'm not sure how, in a study, they calculated the cost of the amputation in the cost of the surgery. I mean, that's... how do you factor that into a quality of life factor. You know, it's catastrophic.

Andrea Skelly: It is.

Chris Standaert: So, I didn't quite get that in there, and that piece of those studies just sort of lingers with me, because it's so dramatic, and this issue of you don't get into the data other than the

studies, but the problems with revision of a lumbar disc prosthesis, right? It's a complicated surgery when you go back in.

Rod Oskouian: Most people don't go back in and take it out. So, you know, and part of that, I'm glad you're mentioning that Norwegian study. I think a lot of this stuff, and just telling you from my experience as a practicing neurosurgeon that does a lot of spine, you don't go back in and fish out an artificial disc. You just fuse it, and in the U.S., again, I think the problems with... even when you look at the Norwegian study is that it just doesn't really apply to what we do in the United States. I don't go, you failed physical therapy. You're going to get an artificial disc, you know? So, I think the standard in the U.S. isn't, and I think you can see some of the issues that, in fact, Seth brought up, is that it's not... you can't, like, compare... in fact even comparing some of the... when you look at the different comparisons, it's a different procedure and in my practice, I don't go, OK. This patient is going to get... they failed everything, so they're going to get an artificial disc. It's not... it's a very selective procedure in patients who have really gone through the gamut of... they have kind of failed everything, and it's, as you pointed out, it's a very select population. That's why it's hard to... that's why you can't really compare it to say, OK. It's superior to fusion or superior to nonoperative treatment. That's just... it's a very few number of patients who get this. Even in the Norwegian study, we don't do our own approaches to place the discs. In the U.S., we have an access surgeon, and we just don't see... I mean, I've never had... I've never seen some of these complications, but they can happen. We don't go and fish them out. We usually do a fusion if the disc fails, so.

John Bramhall: This is not literature. This is your personal experience. The implication is that you would identify, in your practice, what [inaudible] of patients who require an intervention. Then, you're going to fractionate those, if I understand right, you're going to fractionate those into those that are appropriate for fusion and those that are much more appropriate for disk replacement?

Rod Oskouian: That's correct, and again, most people that practice spine surgery, most people don't get surgery. Most people... my

practice is everyone doesn't get surgery, and in this state, we're all part of Scope. We see the data every quarter. In fact, I wish we could have a chance. I wish you guys used some of NEAL's data. This is relevant to what's going on here. What you guys... what she just presented is not relevant to what's done in my practice. It's not relevant to the United States. I think... I would encourage this committee in the future to use NEAL's data, it's the leading national database for spine surgeons, and situated across hospitals. In my practice, that's exactly what I do. I don't... it's very few patients in my practice that get artificial discs, and especially lumbar, but in the select population that... and even in our state, there are very few surgeons that put them in, but in the right patient, done appropriately, these patients do well.

Laurie Mischley: In terms of us sorting through the potential conditions, can you help us think through who that right patient might be in your experience?

Rod Oskouian: Yeah. So, I do agree with the... it is cervical and lumbar are totally different. I think that the perfect arthroplasty patient is someone who is, again, isn't necessarily a... it's not, like, OK, they're... most of them don't, in my experience... for example, back pain. A lot of them have leg pain. So, we don't, as a surgeon, I don't see someone say, OK. You're a great candidate for an artificial disc, and we're going to do this procedure, put it in. It's not like that at all. Usually, it's someone who has done injections. Most of the time, their disc is compressed, and their neural foramen where the nerves go out are compressed, and you don't necessarily want to do a laminectomy, which is the posterior procedure, and they have compression, and they have a lot of... on the MRI, there's what's called Modic changes. So, there's a lot of inflammation at that disc. And again, it's a very select population, and they've failed everything. I mean, these are, like, normal people. It's not workman's comp. It's not people that aren't wanting to go back to work. They do great. There's a handful of guys in my practice that I would send them to do the artificial disc, and these patients do phenomenal, but again, it's a really small... I'd say in my practice... and that's why the numbers are so low, is I think surgeons in the U.S. are extremely, especially, I think, in the State of Washington, very

selective. We try to put them in the appropriate patients, and when selected appropriately, done with the right surgeon and everything, they do fantastic.

Seth Schwartz: I think what I'm struggling with here is that, we have these... so, I think for the cervical data, I think we have pretty good information that it's as good as ACDF if not better than ACDF and then pretty compelling that it's probably better, and we have pretty clear cut indications for when a spinal fusion patient would be a candidate for surgery, and it seems reasonable that this is the approach you would take, rather than ACDF. I think lumbar is a second issue, and that's what I want to talk about. I think what I'm struggling with is, that you have patients with chronic DJD in their back who have pain. We're not talking about radiculopathy. We're talking about pain, and we looked at this before, and there really are not great indications for surgery in these patients. So, probably rehab, whatever that looks like, is the best option for these patients, as far as you can go. Then you have the small group of patients who fail everything else and they still have pain, and it's still not clear to us that surgery is going to be better for those patients than not doing anything else, but we're being asked to say, should you then do a disk replacement in these patients. So, I'm struggling with why should we do a disk replacement in someone who we really shouldn't even necessarily be doing a fusion in, and I'm hearing, OK. Well, maybe in a select group of patients, this is a good operation, but I didn't see in any of the papers, and I'm still, with all due respect, I'm still not understanding how we could operationalize who that small group of patients is that we actually think this would be useful in.

Rod Oskouian: But it's not fair to compare them... so, this is why...

Chris Standaert: Wait, wait, wait. Hold on one second. So, one, we're drifting a bit. We've got to stick with Dr. Skelly said. I want to back this up just one second. You made a comment that the data we just heard isn't relevant to what we're doing. The data is what we're doing, right? So, if there's other data that is something else that tells us something else that didn't make into their search, this is a whole different question, but if what she presented is the published data on disk replacement, this is what we have, right? So, it's not

that there's... and I appreciate the work of Scope, but until it is published in a peer-reviewed, searchable form where people can find it and your data is mature, it's very hard to use it, and we as a committee don't go seeking data. The data is sought in a very systematic, prospective way, with lots of public input and expert clinical advice by Dr. Skelly and her colleagues to collect data for us to consider, and that's where the data comes from. So, the comment that it's not relevant I don't quite get, because that is... of course, it's relevant. That is what we're doing. This issue of are there... we talk about this a lot. How do you define people who might work, and we'll get into this discussion about whether we actually see them in our data or not. That's a good discussion to have. It's not a discussion for Dr. Skelly at the moment, but yeah, Andrea.

Andrea Skelly: As a point of information, the bulk of the studies, the bulk of the information that is presented in my presentation, is from FDA IDE trials. I assume, those are... although they are multicentered trials that may have included places outside the U.S., that still is a U.S. based data set. We always do the best that we can to evaluate and make sure that we are not missing data from a variety of sources in the databases that we search, in looking at the bibliographies of included studies, and also paying attention to public comment. The only studies that were brought to our attention during public comment did not meet our inclusion criteria for a variety of reasons, no matter where they from. There are 84 studies in here and a lot of detail that we just don't have the opportunity to present, but I am happy to look up whatever you feel is missing in here. We're more than happy to help clarify.

Chris Standaert: I appreciate the point. That directs our discussion, but it's probably better in a second when we're done with Dr. Skelly. Do we have other questions on her presentation or the data that she gave us? No? OK.

Seth Schwartz: The other question I would have is, regarding the patients in the lumbar trials, just in terms of the entry criteria, the patient said that in the rehab trials, they're comparing rehab to fusion. Had the fusion patients all had previous rehab? Like, had they failed all conservative therapy before they went on to have surgery?

Andrea Skelly: Are you talking about the Hellum Trial? All of them had failed at least six months of what they said physical therapy or chiropractic care. All of them had back pain for at least one year. Those were the inclusion criteria for that study.

Seth Schwartz: So, they're basically comparing the... and both groups had that. So, then, the nonoperative group just had more of it, and the other group went on to have fusion? Is that the division point?

Chris Standaert: Now, the Hellum study follows the Brock studies for design for the lumbar spine fusion data, and in the Brox, Fairbanks, the Brox and Fairbanks studies for the lumbar fusion that we had discussed previously, it's... all these people had failed sort of routine care in the community, essentially, be it PT or chiropracty, and very nonstandardized ways. Then, they developed a separate rehab program that was cognitive behavioral informed physical therapy or a very structured exercise program, was fairly intensive, a lot of hours, and as I would point out, is not routinely available here, but that's what they did. They built a rehab program for these people that was fairly intensive. The Hellum study used the exact same protocol that they had used for Brox. So, these people had been through, essentially, community-based rehab of whatever sort, and then brought into a study and then bifurcated into this fusion versus rehab or disc versus rehab in that same way.

Andrea Skelly: Yeah, it was 60 hours, three to five times per week, including the cognitive-behavioral exercise.

Chris Standaert: Not 60 hours three times a week, but 60 hours...

Andrea Skelly: 60 hours, oh, yeah.

Chris Standaert: That doesn't work.

Andrea Skelly: Thank you.

Rod Oskouian: Chris, can I just make one comment? Seth asked me about... I don't think... and I think this is the hard... it's a difficult clinical question, and I think this is what Seth was referring to. To me, it's not... OK, if someone fails, it's not

they get fusion or a disk replacement. That's not, you know, you have to have certain, as someone who practices this and... it's a very few people. Again, it's not... I think the correct... the incorrect way to think about this is that, we're trying to cure back pain in someone, and my only alternative is to fuse or do a disk replacement, and that's not how we approach it. In fact, most of the people don't end up getting anything. You know, fusion, in my practice, isn't for back pain. No one does that. It's for someone who has a spondylolisthesis. They failed surgery, you know, it just... they're not comparable. It's like saying you're going to put a stent in versus open heart surgery. It's not the same... and that's the trouble, I think, when you look at this. There are very few segments, in my practice, that get this, and it's not just anybody. It's not A or B.

John Bramhall: It does seem that there ought to be an objective way of describing that. I get it. There's a pool of patients that you don't want to fuse that are going to do well with the replacement, but it does seem to me that there ought to be, maybe in an ideal world, some objectivity that we could grasp as a committee here, for example, to define that population.

Rod Oskouian: So, there is. There... there...

John Bramhall: Is it foraminal stenosis or something like that?

Rod Oskouian: ...there's guidelines by, so NASS has guidelines. The surgical societies have guidelines, and we have those, and again, it's... the hardest thing, as a surgeon to do, and I think you can see this by the numbers, is that these are patients who have absolutely failed everything. They're not just... there's guidelines to when these are placed and it's actually formed by NASS. It's multidisciplinary. It's PT. It's chiropractors. So, we have those guidelines. We go by those guidelines. And the patients that are selected for lumbar arthroplasty in the United States, in my opinion, do well. I mean, they do. Again, it's not a fusion patient. It's not a... usually it's not someone who is a chronic pain patient. They haven't... they have certain radiographic features that I look at. It's usually they have some foraminal stenosis. They have a lot of Modic changes on their MRI, and in somebody like that

who is... I wouldn't fuse and... they do well with artificial discs, I mean, it's just... that's just how we kind of look at it.

Seth Schwartz: If there are guidelines, did you guys see those guidelines? Do we have those guidelines? Is it objectively spelled out in the guidelines?

Andrea Skelly: We may not have captured all the guidelines. I would like to know which guidelines they are. The ones that we did capture are in the... on the report in section 2.2, I believe.

Chris Standaert: OK. They captured a few of them.

Andrea Skelly: But we may not have captured them all. If they were not listed in the National Guideline Clearinghouse, which is sort of the repository of quality evidence-based guidelines, we may not have identified them.

Chris Standaert: Again, our charge will have to be to see what the evidence tells us. That's what we have to use to a large degree. Why don't we take a break until 2:00, by that clock is the one I'm using, but 2:30. Then, we will go through our deliberative process. Thank you, Dr. Skelly.

Andrea Skelly: Thank you.

Chris Standaert: OK. We're going to get going. So, in a second, I'm going to have them pull up slides of our existing coverage decisions for arthroplasties and fusions, because we're not starting nowhere here, right? We have preexisting coverage determinations that we're now addressing. Do we keep them the same? Do we alter them, and they are intimately related to our fusion decisions, I think, personally. So, we're going to pull those up in a second. First, um, Dr. Brown, who is on the phone, had a question, and we never unmuted. So, he never got to say anything. So, Dr. Brown, are you on the phone? Are you unmuted?

Gregory Brown: Hello?

Chris Standaert: Hello? You're unmuted now. I forgot to unmute you. I apologize.

Gregory Brown: I'm not on mute if you can hear me.

Chris Standaert: We can hear you. Would you like to ask... you would like to...

Gregory Brown: OK. Thank you.

Chris Standaert: ...ask a question?

Gregory Brown: Yes. I'm sorry. I'm just trying to clarify the indication, if I may. If I heard correctly, what I heard the indication may be is that you have disc height loss with foraminal stenosis, and you don't want to do a laminotomy, so you do a disk replacement to restore height and open up the foramen, but you're doing it for leg radicular symptoms, not for mechanical back pain. So, if we looked at an indication for that, that would be consistent with our degenerative disc disease fusion decision. Is that correct?

Chris Standaert: So, is that a question about our decision, or a question for Dr. Oskouian about whether that's what he was saying or do you have two questions?

Gregory Brown: Correct. And so, I didn't hear a clear indication. So, he made the comment that we don't do spine fusions for disc disease, you know, degenerative disc disease and back pain. So, would this be an indication that, you know, basically radicular pain would be the indication with loss of disc height or something?

Chris Standaert: So, I guess the question is then, are you saying for Dr. Oskouian, are you saying that one of your indications for using a lumbar disk replacement would be foraminal collapse with radiculopathy, absent spondylolisthesis. So, you're really just trying to expand the disc space with the device, I gather. Did you get his question in there?

Rod Oskouian: Yeah. I think that's what he's trying to ask. I think most people that do artificial disk replacement, especially in the lumbar spine, is... it's not... again, in my practice, I don't ... you don't just see someone and say, OK. You have low back pain. You have one disc that looks funny. We're going to do an artificial disc. There are certain things we look at, like, the facet joints. Is there... usually these people have some lateral recess stenosis. Oftentimes, they have Modic

changes. They have certain things we look at on... and again, they get thorough workups, plain x-rays, flexion extension, CT, MRI, and there are just certain... and with the lumbar artificial disc, you do get indirect decompression of the neural foramen, and most of these people don't just come in and say, doc, you know, it's... I have total back pain here and there. Usually, in my experience and in my practice, most of these people come in with axial low back pain, but then when you examine them and you talk to them, they have radicular symptoms. They have some other clinical symptoms. It's not just for axial low back pain. Usually, there's... but, you also have patients who have axial low back pain, but usually there's something on the MRI that kind of moves you in that direction.

Chris Standaert: Does that help, Dr. Brown?

Gregory Brown: Absolutely. I guess what I'm trying to get at is, if we approve lumbar disc replacements and spinal fusion is not approved for degenerative disc disease, isolated degenerative disc disease, then an L&I patient with degenerative disc disease, the only option would be a disk replacement, because you couldn't do fusion based on our earlier decision.

Chris Standaert: If we did that, and we left the language open like that, yes. That would be what would happen.

Gregory Brown: OK.

Chris Standaert: If that's where... so, as we get to our language, we have to be cognizant of what our existing coverage determinations are, because we're talking about very similar patient populations, and we don't want to conflict with ourselves or cause unintended consequences.

Gregory Brown: OK. Thank you.

Chris Standaert: No. Thank you. Do we have the slides, do you think?

Joann Elmore: Yeah. I think it will be helpful to review the prior coverage decisions, because back in 2008, the artificial discs were approve for both lumbar and cervical, but then follow up with fusion.

Chris Standaert: No. That's what we're going to do. I'm totally with you. I'm not cutting you off. I'm totally with you. That's all I'm doing, so, yeah. So, I will... so this is our determination for lumbar disk replacement. This is our existing coverage policy. So, it is approved with conditions, and the condition is that somebody must essentially fail a structured intensive multidisciplinary program for management of pain, if covered, must be 60 years or under, largely due to the FDA thing, I suspect, and then FDA criteria, as follows. So, you can read them there. OK, next slide. OK, and now does everybody get lumbar? OK. Wait. Go back. Cervical disc, so this is cervical disk replacement. Basically, it said you had to follow the FDA indications, which really included the issue of intractable radiculopathy, myelopathy type symptoms or findings, right? That's sort of what they're after. The symptomatic cervical disc disease is not necessarily... I don't know if I would equate that with radiculopathy or myelopathy, because you could just get neck pain you think is from a bad disc, but that's not what they're talking about. So, that's what's existing now. So, that's the existing coverage. I think this goes to some of your earlier questions. Do we have data that people who go through... you take the treatment arm of one of these trials and put them through an intensive rehab program, they don't do that well. Can you then fuse them or do a disk replacement and have them get better. I didn't know anybody did that, but that's what this says. So, this is our starting point, essentially. Next slide, again. These are not... so, there's an existing National Coverage Determination under Medicare that these are not approved for people over 60, because every study of artificial disc was on younger populations. Everybody over 60 was excluded from every study that's been done for the FDA IDE, which is why the Medicare, when they did the National Coverage Determination said they will not pay for people over 60. So, this is... I was not on the committee at this time. My assumption is, this is to be consistent with the Medicare coverage determination, that they had determined there was no data on efficacy in people over 60. So, Medicare has an existing National Coverage Determination that we have to really be compliant with, unless we feel strongly otherwise. I don't know. I wasn't on the committee at this time. Don't look at me. I don't think any of us... well Carson was. So, it's all his fault.

John Bramhall: [inaudible] It just seems surprising that you've got an arbitrary cutoff and [inaudible] an argument for having the cutoff is, well, no one ever looked [inaudible].

Chris Standaert: No. It's not arbitrary, because that's an exclusion criteria in the studies. It's not arbitrary.

John Bramhall: Well, it's been arbitrarily selected by somebody.

Chris Standaert: By the people who designed the studies.

John Bramhall: People who designed the studies.

Chris Standaert: Right, but that informs what we can do.

Carson Odegard: We've had this discussion before on other age-related contraindications or indications, and as I recall back then, we had a similar discussion about that. Where is your cutoff point, and I remember spending minutes on that subject? So, [inaudible] can relate to that, too. I'm the cutoff point on age at that last meeting. It was because of the studies. It was a cutoff point in the studies. We had no evidence to say at 62 you could.

Rod Oskouian: Number one, it was really part of the original fusion decision, and this decision was based on the fusion decision.

Chris Standaert: Yes.

Rod Oskouian: That if you could get a fusion and if you decided not to do a fusion at a single level, you could do an artificial disc, instead, and that's why number one is in there, because it was part of the original fusion decision. When we revisited fusion with much longer followup and much more compelling evidence of lack of efficacy compared to multidisciplinary care, for degenerative disc disease, uncomplicated degenerative disc disease, that's what this is about, and that's what this discussion is about. It's uncomplicated degenerative disc disease. It's not about neurologic impairment or anything else. One was not put in here de novo for artificial disc replacement. It was put in here because that was the fusion decision.

Chris Standaert: Mm-hmm. So, we have existing already, the conundrum that Greg brought up, that we have somewhat non-consistent coverage determinations, but that's up to us to figure out what to do with it. No, 60... I don't believe 60 is arbitrary if that's where the Medicare came down. So, I would... I don't know, but knowing the committee well, I assume they went looking for a reason for that.

John Bramhall: [inaudible]

Rod Oskouian: I think we kind of didn't really address it at that time. Ostensibly, we would have said, not covered over 60 because of the Medicare decision, and this program must sort of follow recent National Coverage Decisions. So, I'm not sure it was adequately addressed, honestly.

Kevin Walsh: So, nobody's ever done a subpopulation analysis of patients over 60 to demonstrate efficacy or lack of efficacy. So, there's no basis for making a decision.

Chris Standaert: Yes, and that's essentially what Medicare deemed... based their decision on, as I recall, going through that decision process, yeah.

Laurie Mischley: Nor is there any evidence that a 61-year-old is notably different than a 60-year-old.

Chris Standaert: Well, they are different than 40-year-olds.

Laurie Mischley: Right. I, I get it.

Chris Standaert: We do this all the time. There are ranges where things are covered or not covered. We do it all the time and risk...

John Bramhall: And the fact the decision is made on the basis of no evidence, the decision is made not to cover. So, there's a decision made on the basis of no evidence.

Chris Standaert: Turn on your mic. OK. Let's go to the next slide. That's lumbar. That's where we are now, cervical. That's where we are now. Basically, whatever the FDA said essentially, skeletally mature reconstruction of a disc space following discectomy for radiculopathy or myelopathy. Pull up the

next slide, please. This is our coverage for cervical fusion, which we did in 2013. So, cervical fusion is covered when patients with signs and symptoms of radiculopathy and advanced imaging corresponding nerve root compression and failure of conservative nonoperative care. Why didn't we put... why isn't myelopathy in there? It should be radiculopathy and myelopathy, I would think. I wonder how we left that out. What do we do about that? Too late now. Anyway, so it was meant for... the cervical fusion was meant as a way to treat radiculopathy and myelopathy with corresponding nerve root or spinal cord compression in failure of nonoperative care. That's our current cervical fusion. Go one more to lumbar. Myelopathy at the bottom. Lumbar fusion, we said it's not covered for degenerative disc disease uncomplicated by other things. OK. So, we basically have two different topics, and we can talk about these collectively or separately. I suspect we're going to separate them out, lumbar and cervical. It seems like we should do them separately when we get to that point. Well, let's get to our discussion a bit. So, anybody have a perspective they want to offer? Someone comfortable with this [inaudible], uncomfortable with this [inaudible]? Do we think we can move forward? Sad about the Seahawks?

Tony Yen: I do wonder why we have a lower bar for lumbar, artificial disc replacement versus cervical artificial disc replacement?

Chris Standaert: What do you mean a lower bar?

Tony Yen: Well, with the lumbar artificial disc replacement, at least the existing language, I think, is from 2008. It doesn't mention anything about cervical, sorry, anything about myelopathy or radiculopathy or please let me know if I missed that language, but it seems that... I'm sorry?

Chris Standaert: He's using what the FDA said, and it's not a primary... treatment for degenerative disc disease as opposed to treatment for myelopathy or radiculopathy, typically based on the difference in the surgical procedures you have to do to treat that problem.

Joann Elmore: You may also be asking why was it approved in 2008, the committee was early, learning how to evaluate evidence.

Tony Yen: It's more that it seems like in 2008, lumbar artificial disc replacement was approved for indications of degenerative disc disease without myelopathy or radiculopathy. Then, last year, I believe the committee stated that fusion versus intensive rehab was equivalent.

Chris Standaert: So, this is... well, like Gary said, the original fusion decision said the same thing. So, we read... we rereviewed lumbar fusion last year. The original fusion decision was made before the disc arthroplasty decision. The original fusion decision was, lumbar fusion was covered after failure of an intensive rehab program, right? And we changed that decision last time based on a rereview of the evidence. So, we flipped lumbar fusion and said, it's not covered, because we didn't feel there was evidence to support it from the standpoint of efficacy, safety, and cost. That had been a change from the prior decision. The lumbar disc decision you just saw came out subsequent to the lumbar fusion decision and really is concordant with the language of the lumbar fusion... that the initial lumbar fusion decision had. That's what Gary was saying, Dr. Franklin was saying. The language in there was meant to match the language in the fusion decision. That was the same criteria, essentially. Providing the age 60 thing and a couple other things. So, but we've changed the decision upon which that language was determined. So, we can keep that language if we like it, or we can change it if we think that isn't what we should be doing.

Gregory Brown: Chris, can you hear me? This is Greg again.

Chris Standaert: Yes, Greg.

Gregory Brown: So, does the FDA have an indication for lumbar disc replacement for radiculopathy, or is it only for degenerative disc disease?

Chris Standaert: Dr. Skelly?

Andrea Skelly: I was just checking that actually, and all the FDA SSED's under the contraindications, they list isolated radicular compression syndromes, especially due to disc herniation, and that's for all three FDA approved, the ProDisc, the

activL, which is the new one, and the Charite, now called In Motion.

Chris Standaert: And those are contraindications?

Andrea Skelly: Contraindications, correct.

Gregory Brown: For isolated radiculopathy.

Chris Standaert: What's the, what's the indication for?

Andrea Skelly: The indications?

Chris Standaert: Mm-hmm.

Andrea Skelly: Skeletally-mature patients, single level degenerative disc disease from L3 through S1 or L4 through S1, depending on the discs. It has to be... the degenerative disc disease has to be confirmed by patient history, radiographic studies, or physical examination. If they have spondylolisthesis, it can't be more than Grade 1 for the ProDisc or the activeL or more than 3 mm for the In Motion, and failure of at least six months of nonoperative treatment.

Rod Oskouian: So, can I make a quick comment? So, I think that the reason why... so, the initial studies that were done for... the reason it was... the leg pain was excluded is that during the initial IDE's, they didn't want to have people who had, like, disc extrusions getting lumbar disk replacement. So, that's why, if you see in all the literature and everything, that's where I think, again, just... having... I think Dr. Brown pointed this out. Having foraminal narrowing in a disc, you still have leg pain. It's the same symptoms, but neurologically or clinically, it's being compressed. One is in the central canal, and the other one is out in the neural foramen. Going back to, I think, Tony's question, why do you have this definition. It goes back to the fact that they did these studies with the FDA that they would not have patients who have leg pain, because they didn't want those patients who have disc extrusions to get a lumbar disc replacement.

Chris Standaert: That is where our evidence yes. That's the way they set up the studies.

- Kevin Walsh: I need some help. There seems to be a logic discordance, as I track through the decisions over time. So, fusion was essentially... was initially covered. Then, artificial disc replacement was covered. Then, lumbar fusion was rereviewed with longer-term followup data, and it was denied. Now we're back.
- Chris Standaert: Lumbar disk replacement, yes.
- Kevin Walsh: So, if I'm stuck in logic, I'm wondering if lumbar fusion is denied because of the followup data, on what basis would we approve lumbar artificial disc replacement. I understand there might not be evidence to the contrary that says we shouldn't, but I'm still stuck with that discordance.
- Joann Elmore: Well, then your comparator should be nonsurgical, because any comparison with fusion with the artificial disc is not helpful. So, our comparison that we should be looking at is with nonsurgical approaches.
- Chris Standaert: No, the comparison of fusion to disk replacement would be helpful if it showed that one was wildly superior over the other.
- Joann Elmore: Sure.
- Chris Standaert: They were designed as noninferiority studies, but they have the potential to show superiority, if it was there, and they didn't, right? So...
- Kevin Walsh: So, my read is that artificial disc replacement is about equivalent as fusion...
- Chris Standaert: A equals B and therefore...
- Kevin Walsh: ...in lumbar.
- Chris Standaert: ...and B equals C, so A equals C.
- Kevin Walsh: So, if fusion is denied, how are we... how can we approve artificial disc replacement.

Chris Standaert: OK. So, I think that is a fair question for the committee, and I think...

Kevin Walsh: So, we're all in the same rabbit hole? OK.

Chris Standaert: Yeah. I think that's a fair question. I think the issue of, is there a circumstance where it is superior, and did someone see it. So, if it is superior to use a disc replacement over fusion versus our... again, what we've already said for fusion, where does that take us?

John Bramhall: And we suspect that there are these two populations.

Chris Standaert: What two populations?

John Bramhall: The population of people that would, on a surgical decision tree, be appropriate for fusion and a population that would be appropriate for [crosstalk].

Chris Standaert: Based on... did you see that in the data?

Kevin Walsh: Based on what?

Joann Elmore: Fusion is not approved.

Chris Standaert: Can you help me?

Joann Elmore: Because fusion is not thought to be evidence based. Fusion is not thought to be helpful. So, fusion is no longer supported and approved in the State of Washington.

John Bramhall: Right, so again, it's a logic issue that there's a... there's a pool of people that could get fused, and they're not going to get fused, because it's not approved, because they'd be better off with rehab. Have we identified that group of people that shouldn't get fusion, they should get disk replacement.

Chris Standaert: I don't know. Did you identify them in what you heard?

John Bramhall: Well, that's what we were struggling with, and it seems like there is a population in the mind of the surgeon.

Chris Standaert: But in the mind of the data. I mean, that's our...

- John Bramhall: Well, we have an expert here who says that this is what he does.
- Chris Standaert: I understand. This is evidence based medicine. So, we have to weigh that against the data.
- Kevin Walsh: We try to make our decision based on evidence. Otherwise, there wouldn't be any need for us to be here.
- John Bramhall: I'm looking... I'm looking for that evidence. I mean, do we have...
- Kevin Walsh: Well, an expert opinion is no evidence, with all due respect.
- John Bramhall: No, I understand that, but is the, yeah. OK. I mean, the... it's just that the studies haven't been done. OK.
- Joann Elmore: Well, there was one study, I guess it was in Norway, it published in BMJ. It had artificial disc in the lumbar compared with very good rehab. There were 86 people in the artificial disc, and remember that's the one where one person had a terrible outcome and lost a limb. So, out of 86 people, you had, I think, five or six people that had long-term permanent outcomes that were concerning. So, that's... I think what we've been presented, the only evidence that compares lumbar artificial disc with rehab nonsurgical approach. So, that's what our... to me, our comparator should be if we don't see superiority.
- Chris Standaert: Right.
- Joann Elmore: Compared to fusion.
- Chris Standaert: And that study did not show clinically relevant difference. They found a statistical difference of eight points on their ODI, but they didn't think that was clinically relevant by their [crosstalk].
- John Bramhall: [crosstalk] study, the one about... the testimony was that this study...
- Chris Standaert: We shouldn't pay attention to it anyway.

- John Bramhall: It was a bad study.
- Chris Standaert: But if you take that away, that's all we... that's that whole pool of data. There's one study on that. It's essentially a version of the Brox study we looked at for low back pain for lumbar fusion, essentially a similar concept, similar group. Yeah, Brox and Fritzel are two of the authors of the original fusion studies are on that research group. So, lumbar fusion, did we see... the data is tricky. So, evidence of superiority is somewhere. Hard to find? Safety concerns? Let's talk about cervical for a second, and then we'll go to our tool, but the cervical is different for people, or cervical is the same for people? So, we don't have the same discordance between our cervical... there's some artificial disc decision and the fusion decision, but it's not wild. It's not quite like the lumbar. So, what do people think about the cervical?
- Seth Schwartz: I've been sitting on this committee for a long time, and rarely do we see data as good as we saw for a cervical disk replacement with meta-analyses of decently done randomized trials. I mean, it's pretty compelling that it's at least as good, if not better than, the current standard, and there's not a lot of controversy that that current standard is the right thing to do. So, I have very little trouble with that, as well as the safety data shows that it's at least as safe, if not safer, with fewer events. So, I think that cervical is pretty compelling.
- Chris Standaert: Well, the cervical studies are all IDE studies, as well, largely? So, mostly largely, like one ubiquitous thing on your slide was risk of bias in every column where you could put that. Risk of bias was in every single one, as I recall. So, although it is better data than we usually get, it's not totally clean data. It's not exactly what you'd ideally like to have, but it's, yeah.
- Rod Oskouian: But I think one of the things, just getting back to it. I mean, you guys were talking about evidence, um, the Spectrum Group did a good job of looking at some of the evidence, not all of it. Again, the article that you guys keep referencing in the British Medical Journal, I mean, I don't view that as evidence, you know?

Chris Standaert: How can you not view it as evidence? It's a published non-industry funded randomized control trial, and the only one covering that topic.

Rod Oskouian: Because for me, Chris, I don't... it's not what we do in the United States. It's not relevant to... we don't... it's just not. It's like saying that... going back to the discussion again, I don't think you're... the FDA studies that you do for these things to get them on the market is to prove that they're safe. They're just as effective, and there is no harm being done, which is the safety thing, but for me, again... you're in spine. A disc, artificial disc patient is not the same as doing a fusion. They're completely different populations, and you guys have to understand that. I mean, it's just... that's just how it is.

Kevin Walsh: I'm sorry. I respect what you're saying and I will accept that what you're saying is true, but as a group of specialists, you haven't done due diligence to demonstrate that in the literature.

Rod Oskouian: It actually has been demonstrated. So, again, for me, there are randomized clinical trials that have shown in the United States that lumbar disk replacement is effective. It's safe, and it works.

Chris Standaert: That aren't the ones we heard?

Rod Oskouian: They were presented. Go ahead and comment. They were presented by I think the previous group of surgeons.

Chris Standaert: So, ones... so, you're talking about... so, what we need... we're looking for evidence, right? So, if the IDE trials we saw, which are, since they show noninferiority, we understand what that data means. And in terms of what else we're viewing. Is there... are there additional studies you're thinking should have been included that aren't, that weren't brought to their attention that they haven't...

Andrea Skelly: OK. I'm unclear what studies you're speaking of that are not included in the full report.

Rod Oskouian: So, again, for me, as a practicing surgeon who does this every day, I... this is not... this is... you don't compare...

comparing artificial disc to not having surgery versus a fusion is not how I decide whether patients are going to get treatment or not. I mean, it just doesn't work that way. So, for me, that's not a way... and again, even your coverage decisions... that's just... I mean, we don't... I don't say, OK. Well, this patient is going to get a fusion based on this study that was published in the British Medical Journal. I mean, that's not how we practice.

Chris Standaert: Well, I guarantee you there are people who say you should get a fusion based on the Fritzel study and that went on for years, and that was done in Europe, was a different setup too. It had a different conclusion than the other ones, but I heard that for years. I guess it's not a question of whether it's... I guess what you're... the point that you would view the relevance of the study differently is different than saying it isn't data, because that is the only data we have, and if we don't have data, then we have nothing to go on at all. So, we use the data that's available, and if there's a study that calls out the criteria you're trying to define for where you would find the intervention helpful, that would be really useful. I didn't see it in what they presented.

Rod Oskouian: Again, so for me in the way they even got the FDA studies, I think one of the things I have a problem with, even with the coverage decision with fusions is, no one does fusions for back pain anymore. I mean, it's just not a... so you guys are saying, OK. So, we didn't cover it for fusions. Now, we don't want to cover for artificial disc, and that's the reasoning that I think you guys are trying to use. I would say that for the group, the reasoning should be, and this is how in my... this is how clinicians practice, is that a cervical disk replacement is not the same as a cervical fusion. I usually do cervical fusions on someone who has severe stenosis. They've got myelopathy, which wasn't mentioned there in your coverage... and disk replacement, Seth and I were talking about it, I would do in a younger patient who has let's say foraminal stenosis. It's anterior. They're both effective. I could probably do the cervical fusion on that same patient, but in our experience and the data, those treatments are equivalent. Yes, they're equivalent, they're both safe, but they're different problems and they're different patients. So, there's different treatments. Now, is one superior to the other, I think it's going to be hard to

prove that, and I think the same thing goes with lumbar. No one in my experience today, and that's why I think it's relevant and there is evidence, is that most people that do artificial discs in the lumbar spine don't do it just for axial low back pain. There's other things going on, in addition to having low back pain.

Kevin Walsh: And we're not excluding them from doing that surgery for those other reasons. All we're making a decision about is degenerative disc disease, is isolated degenerative disc disease, and you're saying nobody does surgery for that reason, but historically...

Rod Oskouian: No, I'm just saying not just for that.

Kevin Walsh: ...the surgeons... but historically, there were fusions done for that reason, and when we followed those people out for protracted periods of time, there is no benefit compared to no surgery. So, don't mix things. I mean, I understand what you're saying, but we're not trying to make a decision about radiculopathy in lumbar disease. We're only talking about degenerative disc disease.

Chris Standaert: We're talking about degenerative disc disease, and we're excluded from talking about isolated radicular syndromes, given the exclusion by the FDA.

Kevin Walsh: Right. So, the patient who comes in with lumbar back pain but has radiculopathy is not going to be excluded from having a disc replacement based on this decision.

Rod Oskouian: But see, this is what I'm trying to say is that, the way they did the studies is that it's not approved for patients with leg pain.

Chris Standaert: Right.

Rod Oskouian: So, when you do them... when I do it in my practice, it's off-label. A lot of this stuff we do is off-label. So, you're going based on what they... this is based on what they did the clinical study on with the FDA.

Chris Standaert: Anyway, we're going to go back to our discussion on our data. We're getting locked in here, and there is an issue

that, you know, there's an FDA approval, and it would be sort of unusual for us to deny the FDA cover part and leave open people to go off label for something. That would be sort of bizarre. So, I'm just looking to see whether Andrea, was this limited purely in scope to uncomplicated degenerative disc disease literature, or was this a broader search that included degenerative disc disease as a more encompassing thing?

Andrea Skelly: One of the reports... and in the inclusion criteria, we... let me... we're looking at our search criteria right now. Our search criteria, in general, are fairly broad so that we have the opportunity to capture whatever may be most appropriate, and that's in the appendix. We did not exclude based on whether they had radiculopathy or not or had any specific kind of leg pain or not. It was a very general search.

Chris Standaert: OK.

Andrea Skelly: In terms of the inclusion/exclusion criteria, I'll have to go to my book and find the inclusion/exclusion criteria in the full report, which may take me a moment.

Chris Standaert: That's OK.

Andrea Skelly: Yeah, PICO, and in terms of the lumbar studies, some of them did include patients with or without leg pain, but they do not specify radicular pain. They do not specify anything with regards to nerve compression, etc., but they may have included patients with leg pain.

Chris Standaert: Yeah. Some say leg pain. Some say some leg pain, but predominantly low back pain. They're a bit variable in that regard.

Andrea Skelly: Exactly.

Chris Standaert: But they are all fundamentally treating degenerative disc disease in the spine.

Andrea Skelly: Correct. There is one study, the Charite did specify back or leg pain without nerve root compression.

Chris Standaert: OK.

- Andrea Skelly: I don't know if that's helpful at all.
- Chris Standaert: That's helpful.
- Andrea Skelly: But yeah, a lot of them... they almost all include yeah, back or leg pain.
- Chris Standaert: So, I think we're going to go to our tool just to make sure we stay focused here, because that may help us. Steal Joann's pen. So, this is page five of your book. So, we're going to do this twice, because we're going to do lumbar and then cervical, at least this part of it. We'll get to the... we'll do this, both columns twice, and then we'll do the votes twice. So, we're talking about lumbar disc, so safety. They listed several for us, revision, device, serious major adverse events, and our comparators are really rehab or fusion, essentially, right? So, which of these are particularly outcomes, probably essentially all of them, yeah? They're all relatively high. We see data of concern in our evidence about these? Are there safety concerns from the data on lumbar fusion, or lumbar disk replacement, sorry? So, revision secondary surgery, there is some data, which is relatively short-term. We don't have 10, 20 years here. We got six, roughly. So, somebody help me, concerns in safety.
- Kevin Walsh: If one of the comparators is rehab...
- Chris Standaert: Mm-hmm, it is.
- Kevin Walsh: Then, there are safety concerns with disk replacement.
- Chris Standaert: Yes.
- Kevin Walsh: There's not, I don't think I see significant safety concerns with disk replacement compared to lumbar fusion at the lumbar, yeah.
- Chris Standaert: Similar equivalency to fusion, but compared to nonsurgical approaches, significantly more concerns and data for that of high importance. Other safety outcomes, and all the operative stuff, perioperative things, DVTs and stuff, I suspect, happen that don't happen in rehab, they're there. They're high, but not quite as high as the ones we saw.

Blood loss, other issues with surgery, all safety outcomes, too, and there is definitely an issue there with access surgeon point brought up earlier. So, effectiveness? We have global clinical success. We have neck disability index, which is really a neck version of the Oswestry Disability Index, which is the low back form. Neurologic success, pain reduction, functional disability, not all of these are relevant for lumbar. So, we're really looking at ODI not NDI for lumbar. We're not talking, so much, about neurologic success. So, which of these are important to people?

Kevin Walsh: The last two.

Chris Standaert: The last two, pain and function.

Kevin Walsh: Yeah.

Chris Standaert: And for lumbar disc, did we find evidence of equivalency, inferiority, superiority? We have a decent amount of data, a decent number of studies in people.

Joann Elmore: Not compared to rehab and not strikingly superior to fusion.

Chris Standaert: OK. Well, the data we have are just for equivalency moreso than superiority or inferiority in terms of outcome.

Joann Elmore: Well, equivalency to something that is not evidence based as being effective.

Chris Standaert: Right. Gotcha. Equivalency, yes.

Gregory Brown: Chris, this is Greg.

Chris Standaert: Yes, Greg.

Gregory Brown: So, I'm confused. I'm not sure how to proceed, because I actually found the presentation during the public comment compelling for disc replacement versus fusion; however, based on our earlier decision, we decided fusion was not effective for simple degenerative disc disease.

Chris Standaert: Mm-hmm.

Gregory Brown: So, to me, we need to specify one or the other to proceed. I don't know how to...

Chris Standaert: Meaning specify whether it is purely isolated degenerative disc disease without radiculopathy or without leg pain? I mean, the problem is, our studies did not do that. Our studies included leg pain of varying degrees. They all focused on treatment of degenerative disc disease. Some had leg pain. Some had no neurologic compression, but some leg pain, slightly different. I mean, even the fusion studies, the Fritzel study, had more complicated people than just back pain also. So, I suspect our disk replacement decision and the FDA approval isn't for radiculopathy, right? It's for back pain with degenerative disc disease, maybe with some other things. So, we're discussing in the context of our IDE studies, which are designed to get the FDA approval that was obtained, because that's what we have. Does that help?

Gregory Brown: So, I... correct. So, I guess what I think I agree with you. My point then is that basically, since, based on our earlier determination, lumbar fusion is an ineffective treatment for degenerative disc disease, then doing the comparator with that is irrelevant, because it's an ineffective comparison, which is what our evidence report says, that the decision that we're making should be... the comparator should be rehab or nonoperative treatment.

Chris Standaert: We have that also as a... we do have that as a comparator. So, the... in your own deliberation, right... this isn't just we have to compare it to surgery, right?

Gregory Brown: OK.

Chris Standaert: So, whether you think the study is relevant or not is different, as Dr. Oskouian pointed out, but we have one study on rehab, and frankly the absence of data is a factor, as well, when you start thinking about these things, and you have to weigh in your head, does it need to prove superiority in some way, or is there some philosophical superiority you can grant it without that, but that's... we have varied on that, depending on some circumstances, but that's what you have to weigh.

Gregory Brown: OK. So, if, I guess this is the question for Dr. Franklin. So, if we vote to not cover lumbar disk replacement, and there is a patient with radiculopathy that a surgeon thinks could be appropriately treated with a disk replacement, they are allowed to decide whether that's acceptable or not. Is that correct?

Gary Franklin: We have separate criteria for, like, a single nerve root compression, and the standard of care for a single nerve root compression is discectomy or a laminectomy if surgery is going to be done. In general, fusion, and artificial disc replacement, has been done for low back pain. It has not been done for radiculopathy. The standard of care for clearcut radiculopathy is a decompressive procedure. It is not fusion, and it is not artificial disc replacement. We're not reviewing radiculopathy here. We actually are proposing to possibly look at the treatments for radiculopathy at some other point in the future, but what we're talking about here, and I would say that the vast majority of injured workers that receive these procedures are getting them for low back pain and degenerative disc disease.

Chris Standaert: And again, these procedures are contraindicated for the treatment of radiculopathy by the FDA. So, I don't think we should remotely go there, myself. So, we're talking about degenerative disc disease and do you want to... I guess you could get into somebody who has failed a disk and had a reherniation, and they... you did a microdiscectomy. They reherniated. You do a microdiscectomy and they reherniate. You're going to go do a fusion, could you do a disk replacement? That is not the FDA approval criteria. That is not what our data shows. So, you can get into this, how many different scenarios you can think of... there are lots, but you have to still stick with what our data is and where it was set, and what the FDA approved these for, because that's what the data shows.

Kevin Walsh: Let's limit ourselves to the sandbox we were given.

Chris Standaert: Yes.

Gregory Brown: No. I agree with you. What I'm trying to ask or understand is that the FDA looks at something for radiculopathy. The

FDA looks at someone with degenerative disc disease and mechanical back pain, what if a patient has both, and the surgeon thinks that this is an appropriate option? All I'm asking is if that would not be covered by this decision. Is that correct?

Chris Standaert: No. If you think there's evidence to say that they should be able to do that, then we should allow that. The topic determination and the PICO tables are not limited to isolated degenerative disc disease with only axial low back pain. That is not what these studies are on, but they're also not studies on primary treatment of radiculopathy. So, if you're thinking the treatment of the radiculopathy is to jack open the disc space, that's not in the studies, because that's not what they're treating it... that's not what they were doing.

Rod Oskouian: See, I think that thing that Dr. Brown and Chris, and this is what I've pointed out, is that these studies, they do include people with leg pain.

Chris Standaert: They do.

Rod Oskouian: And so, it's not just degenerative disc disease. So, it's a mixed bag. So, that's where I think you're looking at evidence that these patients got... and it's not contraindicated to do it, but it's not what this study was... that's not how the studies were designed.

Chris Standaert: No, but the design of the studies has to dictate what we do, because that's our only data.

Rod Oskouian: But the data they presented, Spectrum, right, the vendor, Spectrum, your data includes patients with leg pain, as well as low back pain.

Andrea Skelly: There we go. The inclusion criteria for the studies, some of them did say the patient may or may not have leg pain. Only one of them, the ProDisc-L said that maybe they had radiculopathy. That's the best that we have, in terms of what they have set for their inclusion criteria. We don't have other information. It is available in appendix tables.

- Rod Oskouian: So, my view of the data and my concern, and the way you guys are going about this is that, you're saying, OK. We have this data and then this is the coverage decision we made for lumbar spine fusions, but that doesn't necessarily relate to... so, what if someone has low back pain and leg pain? Is that the same thing or not?
- Chris Standaert: What are you treating them, for? So, this gets tricky, right? So, we go by where the studies are. We go by where our data is. The preponderance of data is meant to treat the degenerative disc. They all imply degenerative disc disease of some sort with back pain with some degree of leg pain. Some studies say don't specify. Some say back pain more than leg pain. Some say no compressive radiculopathy. There's... personally, there's no data of superiority of a disk replacement in any of these circumstances, so.
- Carson Odegard: But the inclusion criteria was... they could have had both. They could have had both.
- Chris Standaert: They could have had both.
- Carson Odegard: Yeah. So, we have to consider that.
- Andrea Skelly: And there was no stratification in the studies by patients who did not have leg pain, and if you're interested, Appendix G, the tables explicitly lay out the inclusion criteria for all of the studies, including those that we did not present fully.
- Rod Oskouian: I guess the thing for me, as the clinical expert is, if you look at Dr. Franklin's data, these are very few people that are getting these procedures. Now, again, L&I is a whole different bag. Most of those patients have other extenuating circumstances. These are very difficult patients to have them get back to work and do all the other things, but this isn't... and I think this is my point about what this decision is. So, first of all, it's... very few people get this, and being a surgeon and taking care of patients who have... like, I'll see in a year five patients that need to have artificial discs. We should offer... it's a safe... I mean, I recommend people have artificial disc replacements, because it's safe. It's effective. It works. I would not prescribe it if I didn't

believe that it worked. It's not this 500 patients in my clinic getting it.

Chris Standaert: So, there are lots of people who do things that they believe works for their patients, and there is innumerable evidence in medicine where we all did that and then found out that we did didn't work. So, the belief is not what drives our process. Evidence is what drives our process. So, the belief part is really hard to wrap your head around here, but...

Rod Oskouian: But the belief is based on evidence that was presented today, maybe not necessarily by the vendor, but by the public commentary. I just think, again... I think that there... it shouldn't be that based on one decision we're going to make another decision, and not to have an available treatment for people.

Chris Standaert: So, I would argue we're not basing one decision on another decision. We're using data that informed the decision about fusion to inform our decision, but they're not entirely one versus the other.

Rod Oskouian: But those patients...

Chris Standaert: Wait. Wait. I need... we need to hear from other people on the committee here. So, we need to decentralize this a little bit, right? So, Tony, we're trying to get at efficacy here. So, Tony, tell me what you think here, lumbar.

Tony Yen: And what I'm trying to also get is that efficacy comparing artificial disc replacement against fusion head to head for the lumbar spine. So, the vendor actually quoted this study, Wey, 2013. It's on page 100 of the full report towards the bottom. Sorry. I'm looking at a PDF. It's actually on page 89 of the full report. So, and that wasn't... I didn't see that study being discussed very much, in terms of, like, a vendor presentation. So, that's a meta-analysis. I know that we all understand kind of the limits of meta-analyses that maybe it's not the best possible studies, but it does show a difference in terms of a superiority lumbar artificial disc replacement versus lumbar fusion for degenerative disc disease with the meta-analysis that takes six randomized control studies, lumps them all together, and that's probably the only piece of data that I can find. This is in kind

of relationship with all the other studies that we look at, individual studies that look at head to head lumbar artificial disk replacement versus lumbar fusion where there's really no clinical difference in terms of, like, overall clinical outcomes, neurologic outcomes, or other pain scores.

Chris Standaert: Andrea, you had a comment on that.

Andrea Skelly: Yeah, for information, we do not formally include systematic reviews. We do provide summaries, as you have noted. This particular meta-analysis, we do have hard copy, one hard copy if anyone is interested, but if you look closely at that, they are basing their decisions based on not the overall clinical success, as we have done, and they're basing their decision primarily on pain scores and other things that, again, it is unclear whether there is clinical significance associated with it. Furthermore, if you take a look at their forest plots, you'll see that they tend to be closer to the knoll that one might have expected from the previous presentation. I'm very happy to share this meta-analysis with anyone. They also did include a randomized control trial that we excluded, because the device is no longer available and not FDA approved. So, there are a variety of differences between that meta-analysis and what we have provided to you, and I'm happy to discuss it further.

Chris Standaert: And you did prepare a number of forest plots, which are essentially summations of multiple studies that you presented for us, which all essentially sit on that line, meaning no difference.

Andrea Skelly: Yeah, and there were also non-randomized studies included in the report, if anybody's interested, but that's not the highest quality data that we can provide for you.

Tony Yen: Thank you.

Chris Standaert: Chris, what do you think, lumbar efficacy?

Chris Hearne: The argument that I hear you making, and correct me if I don't understand you correctly, is that it doesn't make sense to necessarily compare these two populations of people, people getting a fusion and people getting an artificial disc replacement because these are, in some

sense, two different populations of people that would not benefit from the same procedure. Do I understand you saying that correctly?

Rod Oskouian: That's correct, yeah.

Chris Hearne: OK. So, you, in clinical practice would see someone with low back pain or maybe radiculopathy, and say you look like somebody who would benefit from disk replacement or fusion, and these are two separate groups in some sense?

Rod Oskouian: Yeah. I mean, most the people that we see, like I was saying, we don't even offer surgery. I mean, fusion, for, for low back pain is not even on the table, and they are completely different populations. That's correct.

Chris Hearne: So, the question I have, then, and that sounds like a very... I mean, that may be a very reasonable way to practice, but why would the authors of these studies randomize these people to receive one or the other? I mean, it seems like there must be some sort of... they must be, in some senses, comparable if they were going to do these studies at all. Like, why would you randomize somebody to something that would not fit in with the surgical society guidelines. It doesn't make a... do you understand what I'm asking?

Rod Oskouian: Yeah. So, that's what I'm trying to say is that we don't do that in the U.S. We don't... I don't see someone in my clinic... and that's why for me, Chris, it's not relevant. I'm not in Norway or Sweden. We don't say, you're going to get an artificial disc or 60 hours of rehab. We just don't. So, that's, for me, I guess... I don't look at those studies that are done in the Sweden studies or the Norwegian studies. That's just... we don't... you don't say surgery or rehab. Based on that randomized clinical trial, then that's not how we practice.

Chris Hearne: But as far the RCTs comparing, I realize the one comparing rehab and disk replacement, but comparing fusion and disk replacement, it seems like, at least, some people out here who are doing these surgeries think that that's an appropriate way to practice. Otherwise, we wouldn't even have these studies, it seems to me. I don't know if that makes sense, but, and so when we're making a

determination, we have to bear that in mind that some people may be practicing that way.

Chris Standaert: Other comments on efficacy? So, we went through safety, and there are safety concerns compared to nonsurgical approaches, in particular, that are high. There's relative equivalency in the studies we have, in terms of what we think are important outcomes without anywhere there being an overt benefit for disk replacement. What do we know about cost? Was the cost data compelling to anybody?

Joann Elmore: No.

John Bramhall: Well, the cost data is a bit confusion, because there seem to be procedures that are done for \$3000 and \$22,000 in the same bucket, so.

Chris Standaert: Right.

John Bramhall: I don't know that that's very helpful.

Chris Standaert: Right. Again, a data black hole for us.

John Bramhall: There's the cost of not doing it, but we don't have that information.

Chris Standaert: We don't know that either. Yes. Are there special populations we should be thinking about, whether or not they were called out isn't the issue? If they were called out, we should note that. If they weren't called out, we should think about it. So, does gender matter, age? There's an age issue. Our studies all had an age cutoff. I didn't see much on gender. I didn't see much on body habitus, BMI. All of these things are probably relevant, I would bet. No data on that. Nobody broke them down by some demographic variable that's useful for us.

Andrea Skelly: It's not preferential, effectiveness or safety, there were no interactions that were reported or evaluated.

Chris Standaert: These were mixed race, ethnicity, mixed gender studies?

Andrea Skelly: I'd have to go back and look at that appendix, but I think most of them were Caucasian. A large percentage of them, if I remember correctly, and before I go... actually, we just got it up. Most of them are Caucasian, usually more men than women. The average age, I did look up, is around anywhere between 40 and 50 years old, even though the criteria were generally patients who were less than 60 or 70 years old.

Chris Standaert: Well, one issue, oh, go ahead, Kevin.

Kevin Walsh: No, that's... I'm looking at the study now. It's a little bit more male than female, age 40 +/- 8, 92% Caucasian, 4% African-American, 4% other.

Chris Standaert: Limited demographic representation. We do have an issue of time. I didn't bring it up under safety, but long-term safety is a question, because we don't know. We don't know long-term benefit. We don't really understand adjacent segment disease. Does it really change that? We just don't know. We don't have... our data isn't far enough out. Do these things last 30 years? Are they better than... maybe they're better than a fusion after 30 years. I don't know. I don't think... we just don't know. Our studies aren't nearly long enough to get us out of that zone. Yes.

Joann Elmore: I'd like to share my thoughts on lumbar artificial disc replacement. We're only doing ten a year in the State of Washington, according to the numbers, and I would like to summarize that the data we have seen to my review, I would suggest that we not cover. The data shows that it is comparable to fusion. We voted last year that fusion is not efficacious. The data showed that it is not superior to fusion. The data showed that there are harms. And the data that have compared it with rehab, which is a good comparator, although it's the idealized rehab that I wish was available to everyone, it was not clinically superior. So, my summary is that, I suggest that we not cover lumbar.

Gregory Brown: This is Greg. Can you hear me?

Chris Standaert: Yes.

- Gregory Brown: So, I agree with that statement. I would also add that we do not [inaudible].
- Chris Standaert: We lost him at the critical moment. Finish your sentence, Greg.
- Joann Elmore: We couldn't hear you.
- Gregory Brown: We don't cover with degenerative disc disease.
- Chris Standaert: So, we say don't cover for degenerative disc disease. OK. Let's get... we'll get there in a second. OK. So, our next step is to vote on... a nonbinding vote on the evidence. So, we start with safety. The first vote, is there sufficient evidence that technology is safe for the indications considered? So, this is really, do you think... which of these is it? Is the safety unproven, is it less, equivalent, more in some, or more in all? We're doing lumbar. We're going to finish lumbar. We're going to move this and put the conversation over there. Then, we can come back to cervical.
- Carson Odegard: Just one question. So, the safety concerns that you're talking about are what?
- Chris Standaert: Our comparators. Our comparators are fusion and nonfusion. Those are both of our comparators. No. We have nonfusion data also.
- Carson Odegard: OK.
- Chris Standaert: Again, what you do with the data is up to you. Whether you think that's big enough to sway your vote is up to you, but...
- Carson Odegard: OK.
- Chris Standaert: ...yeah. We had nonfusion... we have... it's fusion or non... compared to other treatments.
- Joann Elmore: But if fusion is not efficacious, a good comparator for harm is, do you do surgery where 6% of people have permanent outcomes that are pretty bad, including amputations.
- Carson Odegard: I understand that, if you're including the nonfusion.

- Chris Standaert: No. You're comparing nonoperative care or not operating with this or operating. You could work with either circumstance, if you wanted to. So, in the ecosphere of caring for these patients with degenerative disc disease, compared to other thing you can do for them, is this a safer alternative than your other options?
- John Bramhall: [inaudible]
- Kevin Walsh: I would disagree.
- Chris Standaert: I would disagree.
- Kevin Walsh: I would say you've got... we've got two groups on one side. We've got therapy, and we've got fusion, and we're asked to compare artificial disc replacement to that. That's how I'm reading it, to both nonoperative therapy and fusion. So, that's the comparator.
- Chris Standaert: You have to make a bit of a judgment call what you think is stronger, right? So, if you really think it's really a lot safer in some circumstances and that outweighs the places where it isn't, you would vote more. If you really think there are safety concerns here that outweigh everything else, you vote less.
- Kevin Walsh: I thought the language was, if it was less safe in any circumstance you vote less.
- Carson Odegard: Not safe in any circumstance. Right.
- Kevin Walsh: That's how we used to be asked to answer these questions.
- Joann Elmore: It was worded in a card for us, and we were always, like...
- Chris Standaert: This was always vague. I mean, it's not...
- Joann Elmore: ...we tried to fix it.
- Chris Standaert: ...it's not purely binary, depending how we look at it, but I guess compared... it's just compared to your other alternatives. Do you view this... how does the evidence strike you compared to your other alternatives?

- John Bramhall: We don't have an alternative, because no, because fusion isn't covered.
- Joann Elmore: Yeah. I think our comparator should be PT.
- John Bramhall: We don't deal with fusion here. You guys said we're not...
- Carson Odegard: No, but that's what the study is...
- Kevin Walsh: No, that... we're coming to a... so...
- John Bramhall: It's irrational to compare the disk replacement with something that we've already decided is irrational therapy.
- Chris Standaert: So, what the...
- John Bramhall: [inaudible].
- Chris Standaert: ...what the sentence used to say is, any or all circumstances, which is vague. So, we tried to make it less vague, but apparently not. So...
- John Bramhall: I don't want to be... I'm not trying to be dogmatic or awkward or anything. I just... I'm going to have to hold up a card, and in my mind...
- Chris Standaert: No. That's a good question.
- John Bramhall: ...I've got to make a decision, which I think is binary for me, is it safe or not safe, less safe, more safe? I'm genuinely confused as to whether I'm comparing it with this huge pool of people who get no surgery and some surgery with this specific surgery or no surgery and the...
- Kevin Walsh: I think this is an innate argument. Why don't we have two votes? Is it safer than PT? Is it safer than fusion?
- Chris Standaert: Alright. So, is it safer than nonoperative treatment?
- John Bramhall: OK. That [crosstalk].
- Chris Standaert: Is it safer than nonoperative treatment?

Josh Morse: OK. I see it as, you're a less? Ten less and let's check with Dr. Brown, or nine less, sorry. Is Dr. Brown on the phone? Is the phone still muted?

Chris Standaert: Dr. Brown, are you still there? We don't have your vote.

Josh Morse: OK. So, we don't have his vote right now.

Chris Standaert: So, our other comparator is fusion, but our expert is saying these aren't necessarily apples to apples. So, it isn't a question of whether you fuse. Our data says that, but he is saying that isn't what he does in practice. So, we're going to leave this as operative care, OK?

Josh Morse: Five equivalent, one, two, three, four unproven.

Chris Standaert: So, this one, I don't think we need two votes on this one, I don't think, unless I'm not seeing it yet. Is there... this is efficacy and safety. Is there sufficient evidence the technology has a meaningful impact on patients and patient care? That's our vote. This is all circumstances.

Josh Morse: I see eight unproven, one equivalent.

Chris Standaert: Cost-effectiveness. Is there sufficient evidence the technology is cost-effective for the indications considered?

Josh Morse: Nine unproven.

Chris Standaert: Alright. So, now our options... we're going to vote on this one and just be done. So, the... not to just be done, but just because we're in the discussion, and we should finish it. So, our vote choices are several. There is not covered. So, we're not going to cover lumbar, this is lumbar disc. We're not talking about cervical. We will cover unconditionally, or we will cover under certain conditions, which we will spell out. I anticipate in this one, there are very few who are saying cover unconditionally, although maybe somebody is. Then, the debate will come down to the not cover versus cover with conditions. If there are conditions, could someone define those? That's sort of it.

Laurie Mischley: And just to clarify, it is always allowable to petition on behalf of an individual in extreme circumstance. I mean,

this is not... we are not saying... I'm seeing yes's and no's in terms of head shaking.

Josh Morse: I can answer that question. If you vote to not cover something or cover something with conditions, and somebody appeals the... wishes to have that procedure, it is not true that it can be... an exception can be made in all programs. So, if it's not covered, it's not covered.

Female: However, in Medicaid, if something is not covered, if something is an uncovered benefit, you can be considered for an exception to rule, which is different than the Public Employee Benefit.

Chris Standaert: I wonder if there's somebody... I don't know if there's anybody here who... I don't know how people feel. We haven't done a straw vote thing, but I'd be curious what... does somebody, in their head, have an idea of conditions?

Kevin Walsh: I think we should vote, and if conditions carry, then we parse it.

Chris Standaert: OK. I'm just... I'm curious to see if somebody has a thing they want to articulate. That's all. No? In people's head?

Seth Schwartz: I'm struggling with, I'm struggling with this. I think... so we're voting for degenerative joint disease. We're not talking about decompressive procedures or anything else? We're talking about...

Chris Standaert: No. It's not indicated.

Seth Schwartz: ...not radiculopathy, not myelopathy? OK. Just the degenerative disc disease.

Chris Standaert: Yes.

John Bramhall: And it's a treatment for... the symptom is back pain, not radicular pain. The symptom is back pain. Is that true?

Chris Standaert: It could be... well, it's treatment of symptomatic degenerative disc disease.

John Bramhall: The symptom is core back pain. The symptom isn't tingling in my foot.

Chris Standaert: No. The symptom is not tingling, no.

John Bramhall: Alright. OK.

Chris Standaert: It's not, yeah, but that's where, again, the FDA approval gets us. It's... the intent is to treat a radiculopathy, that's not, yeah, outside FDA approval. OK. So, our choices are not cover, cover unconditionally, or cover under certain conditions.

Josh Morse: Nine not cover.

Chris Standaert: So, our charge now is, are we consistent with the Medicare guidelines and expert guidelines... Medicare decision and expert guidelines. The only Medicare decision we have, we are consistent with. They're over 60 anyway. They don't have one. They don't say that they will cover under 60. They just don't say. Is that correct? Is that what the Medicare decision was?

Josh Morse: The Medicare decision is in your decision tool.

Andrea Skelly: I think all we have is what you have in your packet for the Medicare decision. So, for... let's see, for services performed on or after the 2007 of August, CMS found that LADR is not reasonable and necessary for the Medicare population over 60 years of age. Therefore, LADR is not covered for Medicare beneficiaries over 60 years of age. For Medicare beneficiaries 60 years and younger, there is no NCD for LADR.

Chris Standaert: It'd be inconsistent with it, because it doesn't exist. Our guidelines, American College of Occupational and Environmental Medicine says it's not recommended for nonspecific low back pain, radicular pain, including sciatica or spinal stenosis. The American Pain Society says it is recommended. Strength of evidence was fair, and the Colorado one just seems to summarize things and not actually say anything, as I read that. So, there's good evidence. It's not inferior, but I don't know what that means. We don't seem inconsistent with those. So,

[inaudible] published. The community had a chance to respond to that and send us letters of questions or other interpretations of it. Other ways we should be thinking about it, and if there's literature that we should be thinking about, they can do that, as well. All that is open game. We'll discuss that again when we come back in a couple of months, what March, two months?

Josh Morse: March.

Chris Standaert: OK. We're going to back up and do the same thing for cervical. Dr. Brown, are you there, still? No. OK. People want to keep moving, or are our brains fried? Finish it. Let's go. Alright.

Joann Elmore: I suspect a lot of people here will say cover with conditions.

Chris Standaert: We have to go through...

Joann Elmore: OK. Let's go through it.

Chris Standaert: So, I understand. Just so everyone on the committee knows, right? So, for us, what we have to do, it has to be clear, from our record, from the record of our conversation, that we went through this process, and we considered all these factors. That's why I keep making us do this and dragging these things out saying, can we respond? It has to be clear that we've done this, that we've considered all the relevant cost factors, all the relevant safety factors, all the relevant... we just have to say that we did it, and we have to go through our process. Our process is what maintains the validity of our decisions, right? So, if we skip things in our process, and once our decisions are made, they are finalized by the agency director, assuming that we have gone through our process. If we don't go through our process, then there's a potential to invalidate them.

Seth Schwartz: I move to get on with the process.

Chris Standaert: OK. Just being clear. Safety. So, cervical disk replacement. Let's spin people back a bit. Are there safety concerns for this? I mean, there are. You're certainly putting something in the neck. Are they... in this case, you really have to compare them to a fusion, I would think, if you're thinking

safety. This isn't... Dr. Oskouian, you can help me with this. So, this isn't... usually this isn't usually a decision of you're going to do a disk replacement or you're not going to operate. That usually isn't what you're thinking.

Rod Oskouian: Well, I think, um, I don't think you can compare it to PT. I think you have to compare it to another procedure. I didn't want to say anything, but you can't compare a surgery to PT for safety.

Joann Elmore: That's fine, and the studies show that it might even be safer than fusion.

Chris Standaert: Right. We're concerned about the same things, as far as device-related events. We're worried about dislodgment. We'd be worried about these sorts of things that could happen. We don't see a lot of evidence that happens in the cervical spine in the studies we have, and there is some evidence on the whole that perhaps it is safer than fusing people, right? So, this... these are all high concerns, again. We have some evidence that maybe shows a small magnitude of benefit in favor of the disc.

Effectiveness. So, now, we have NDI, neurologic success, clinical assessed pain. We don't have ODI. Cervical discs are somewhat different. We have neurologic stuff now, not just pain. What do people see in the data?

Seth Schwartz: I'm confused. I thought we've already discussed this, and we're doing the voting now? I mean...

Chris Standaert: No. We haven't discussed this for cervical. We just went through lumbar.

Joann Elmore: He wants us to go through the table...

Seth Schwartz: Oh. I thought we already went through the table for both at the same time?

Chris Standaert: No. We didn't.

Joann Elmore: Just lumbar.

- Chris Standaert: So, we excluded NDI. We excluded neurologic issues. So, there is data on neurologic issues and NDI.
- Joann Elmore: Disk replacement seems to have slightly higher effectiveness than fusion in some of the... especially short-term outcomes, to summarize the data.
- Chris Standaert: So, pain... all of them essentially, pain, function, neurologic success, all potentially are better. NDI and neck function better, as well, NDI? It's about the same, slightly...
- Joann Elmore: Slightly better.
- Chris Standaert: ...about the same. Again, these are important outcomes. Neurologic is certainly important. It's important it didn't get worse, and it got better. Again, safety, we didn't bring it up, but the same issue of durability. We don't know. There's lot of experience with 30-year-old fusions. There isn't lots of experiences with 30-year-old cervical discs.
- Seth Schwartz: Erica showed some... we were looking at some of the evidence about what happens at the upper and lower levels, and there is some indication that patients who have fusion have higher reoperation rates for this... reoperation rates for the above and below levels than you see for the disk replacement. Is that accurate?
- Chris Standaert: So, that's adjacent segment change...
- Seth Schwartz: Adjacent segment changes seem less in this group, as it does in fusion group.
- Chris Standaert: ...as an outcome. OK. I don't know if that's a safety issue or an outcome, but it could be either one, but it's better and slightly better perhaps. OK? Cost?
- Joann Elmore: The usual.
- Chris Standaert: The usual.
- Joann Elmore: Too many assumptions, low quality studies.
- Chris Standaert: Again, no, I think, convincing...

- Seth Schwartz: Better than some of... not great, but better than what we've seen for some other things.
- Joann Elmore: True.
- Seth Schwartz: I mean, there's... I mean, they...
- Chris Standaert: Is it worse? Is it more costly, or?
- Seth Schwartz: No. I think they said it was equivalent or better at the \$50,000 cutoff, and we're going with reasonably good outcomes data. So, you can always make the criticisms about cost assumptions, but relative to what we see, it's pretty good.
- Chris Standaert: OK. Special populations, which, again, would be nice. Do we have one? Do we have age cutoffs? Do we have other things in our studies that we need to pay attention to?
- Andrea Skelly: In the cervical artificial disc replacement, the average ages were anywhere between about 45 years old and 47 years old.
- Chris Standaert: Is there a consistent age cutoff for one in the FDA approval, an age cutoff that would be relevant for us?
- Andrea Skelly: For the FDA IDE studies, most of them say 18 to 60 years old, we're in cervical, though.
- Chris Standaert: Yeah. We're in cervical.
- Andrea Skelly: So, for cervical, at least 21 years old. That's the Brian IDE, again about 40 years old. Range was up to 78 years old. Again, range up to 72 years old in the Prestige.
- Chris Standaert: So, the FDA indications and precautions of these vary, is what I gather. The different discs have different exclusion criteria.
- Andrea Skelly: Well, in the studies, the IDE trials, there is some difference in inclusion/exclusion criteria.
- Chris Standaert: But under the FDA criteria, there were differences. They weren't all... they didn't all have the identical approval or...

- Andrea Skelly: You mean, in terms of indications?
- Chris Standaert: ...mm-hmm, and contraindications, right.
- Andrea Skelly: Yeah, although they're fairly consistent. If we look at the FDA indications, we've got a table that we have copies of, if you are interested.
- Chris Standaert: I'm only interested if they're variable. It gives us an option of saying, you can use them per FDA... we can use what the FDA has already decided for that individual disc, rather than trying to dig into each individual disc.
- Andrea Skelly: Yeah. We don't have... the criteria do not specify age.
- Chris Standaert: OK.
- Andrea Skelly: It just says skeletally mature, so that leaves it open.
- Chris Standaert: So, I guess my other question is, if they're variable we can then use FDA criteria as one of our conditions, if that's where we're going so that we don't have to deal with relative use of something. They're slightly different in when they're used and when they're not used and what they're approved for.
- Andrea Skelly: I think they're fairly consistent. Most all of them say radiculopathy and/or myelopathy, and they want some sort of radiographic evidence, and failure of nonoperative care of at least six weeks.
- Chris Standaert: No, I guess it's the contraindications I'm after.
- Andrea Skelly: Hmm?
- Chris Standaert: There are different contraindications.
- Andrea Skelly: Contraindications, yes. So, on page 65 of the report are a list of the contraindications that are by disc.
- Chris Standaert: That's all I want. That's all I'm after.

- Andrea Skelly: Some of them are a little bit different, like, cervical instability applies to all of them, except for three.
- Chris Standaert: That's all I'm after.
- Andrea Skelly: OK.
- Chris Standaert: Just that they're different, that's all.
- Andrea Skelly: A little bit.
- Chris Standaert: That's all I need.
- Andrea Skelly: OK. Alright.
- Chris Standaert: Thank you. Alright, and we'll move to our nonbinding vote. For safety, is there sufficient evidence that technology is safe for the indications considered?
- Josh Morse: Six some, three equivalent.
- Chris Standaert: Is there evidence the technology has a meaningful impact on patients and patient care when compared to its comparator, which, in this, another surgical comparator.
- Josh Morse: Seven some and two equivalent.
- Chris Standaert: Cost-effectiveness? Same thing, sufficient evidence the technology is cost-effective for the indications considered.
- Josh Morse: Two some and seven unproven.
- Chris Standaert: Alright. So, unless somebody says otherwise, the way everybody just voted would lead me to thinking we were talking about coverage with conditions. So, we need to start working on conditions, unless somebody raises a flag and says don't do that. So, maybe pull up what Dr. Franklin put up as a way to start.
- Josh Morse: You also have an existing decision.
- Seth Schwartz: Why don't we start with the existing decision?

- Chris Standaert: Can we pull them both up? It makes me want to go back to our... so the fusion decision really doesn't say myelopathy on it?
- Josh Morse: It does actually say myelopathy on that decision, but it doesn't say it in the... I will pull it back up. It says noncovered conditions, and it says conditions and situations where there's not evidence of radiculopathy or myelopathy.
- Chris Standaert: I was looking to see if it's in our stuff somewhere, but it's not. OK. So, our decision says, the existing one... oh, that's spinal fusion.
- Josh Morse: Is that what you're asking about or?
- Chris Standaert: Signs and symptoms of radiculopathy, I guess we'd have to put in myelopathy, advanced imaging with corresponding nerve root compression, failure of conservative nonoperative care. So, do you have the disc one? Do you guys have that, the first few slides you pulled up when you started talking, is that disc?
- Joann Elmore: If we could look at the agency medical director recommendation slide 19 and 20.
- Chris Standaert: Let's bring that up.
- Joann Elmore: Slide 19, agency medical director recommendations.
- Chris Standaert: So, what Dr. Franklin wrote was, artificial disc replacement is covered for treatment of degenerative disc disease resulting in cervical radiculopathy or myelopathy when the patient meets 2013 HTCC criteria for ACDF. That's the fusion. It is not covered for chronic neck pain without evidence of radiculopathy or myelopathy. It's covered for two level of FDA approved device when radiculopathy is demonstrated, but you have to have objective evidence of radiculopathy or myelopathy at both levels. This is all somewhat tricky. It depends on how you define degenerative disc disease. So, if you had... this is a bit different, because you could have just a relatively healthy-looking disc with a huge central disc herniation that you have to go get, right? So, you wouldn't classify that as

degenerative, but you still might want to do a disk replacement, yeah?

Rod Oskouian: Yeah, that's correct.

Chris Standaert: So, I don't know that I would want the degenerative disc disease language in there, because there are times you're actually after a relatively healthy disc that herniated. So, then the two-fold one, there are times when you're doing... you think the myelopathy is because the cord is crunched at one point with cord signal change, and there is not cord signal change above it, but it's still pretty crunched. So, it wouldn't... you're still going to decompress that level, even though you think the level below is the one really causing the myelopathy. So, seeing you have myelopathy from two levels is different than sort of meeting indication for two-level decompression, yeah? I'm just finding the language more restrictive than you all might use in practice.

Rod Oskouian: Yeah, no. I think it's restrictive. I think the cervical is... because of the cord.

Chris Standaert: Yeah. Can we get something up on the screen? Can somebody on their computer pull up our existing cervical disk replacement coverage determination? Could one of you all with a laptop pull that up? Not the fusion, the disk replacement. What did we say? Yeah, I want the decision. So, we said, patients must meet FDA approved indications for use and not have any contraindications. FDA approval is device specific but includes skeletally mature patient reconstruction of disc following a single-level discectomy for intractable symptomatic cervical disc disease, radiculopathy, or myelopathy confirmed by patient findings and imaging. Contraindications, acute systemic infection or infection localized at the site of implantation. I would hope people won't argue with that. Allergy or sensitivity to implant materials and certain bone and spine diseases, marked instability, that sort of thing. So, I mean, if we just took the first... I mean, do we have to change that a lot? Does that function now? I don't know if we need to change the cervical part, other than adding two levels covered for... if you meet indications for the two-level device.

Rod Oskouian: That's what I would...

- Chris Standaert: Right.
- Rod Oskouian: ...two levels.
- Chris Standaert: Because there is a disc with FDA approval for two levels, and it's the same studies.
- Seth Schwartz: We saw evidence that two levels seems to work better than in fusions.
- Chris Standaert: Right, with the FDA approved device. Do we need the second half of it, the contra... the general contraindications, active systemic infection and all that sort of stuff, because it always says not have any contraindications for the FDA device.
- Carson Odegard: Where did we get that?
- Chris Standaert: I don't know.
- Josh Morse: It says FDA general contraindications.
- Chris Standaert: Yeah. I don't care if they're there or not.
- Joann Elmore: So, we all have in front of us slide 19.
- Chris Standaert: Well, we need to see it. Yeah. People need to see it.
- Josh Morse: Does your machine work, Christine?
- Chris Standaert: Your machine works?
- Christine Masters: My machine works.
- Chris Standaert: We just need a Word document. Patients must meet FDA approved indications for use and not have any contraindications, and that's, I think, because the approval and disapprovals of these are device specific. FDA approval is device specific but includes... we can go correct it later. Approval is device specific, but includes colon, next line, skeletally mature patient, skeletally mature patient. The next line, reconstruction of a disc following single-level discectomy. Was that Dr. Brown?

- Josh Morse: I think he's back on the line, yeah.
- Gregory Brown: Yes. I'm back. I also texted all my votes if Christina and Josh got them.
- Chris Standaert: Oh, you did? For intractable symptomatic radiculopathy or myelopathy. Forget the cervical disc thing. Radiculopathy or myelopathy, confirmed by patient findings and imaging. Confirmed by patient findings and imaging. And the next line, two-level cervical disc arthroplasty is covered for FDA approved devices when the patient meets criteria for two-level decompression? What word?
- Rod Oskouian: See, that's where I think... I mean, the cervical spine, when you go anterior you're taking the disc out.
- Chris Standaert: Two-level what? Two-level discectomy?
- Rod Oskouian: Yeah. I mean, it's...
- Joann Elmore: Objective evidence of radiculopathy or myelopathy at both levels.
- Chris Standaert: For two-level discectomy.
- Seth Schwartz: Why do you have to specify? Why can't you just have it be... the whole thing be for one or two level?
- Rod Oskouian: One or two level, I think.
- Seth Schwartz: Why do you need to specify.
- Joann Elmore: Then they'll have disease at one level and they'll put in two.
- Rod Oskouian: I think Seth has got... just say one or two level. I mean, that's right.
- Chris Standaert: The trouble with saying they have to have a myelopathy or radiculopathy... I mean, you wouldn't normally... if you had a really stenotic level that you thought wasn't necessarily symptomatic, but the one below really was, you wouldn't do this and leave the one above it. You'd do them both.

- Rod Oskouian: Chris? I'm sorry. I think you're right on myelopathy. It's, you know, it's going to be kind of maybe a long kind of a compression. So, maybe you don't specify it so much on myelopathy, but on radiculopathy, when we implemented the ACDF decision, we went through a lot of stuff about... and it's in our guideline from here, you had to radiculopathy or radicular findings at two levels to get the two-level disc thing. So, that's why I put that in there, but I agree it may not be for myelopathy. It gets too complicated.
- Chris Standaert: So, objective evidence of radiculopathy at both levels or cord compromise at both levels, or cord compression, or spinal stenosis or?
- Rod Oskouian: I think the myelopathy piece is sort of not that common. It's mostly the radiculopathy piece. So, I'd leave it up to the surgeon for the most part on myelopathy. I mean, you're talking about usually pretty severe situations, but definitely radiculopathy, because there's a lot of movement around that, as you know.
- Chris Standaert: Right. Covered for FDA approved devices. Yeah. I guess you could just start off by saying one or two level cervical disc arthroplasty is covered when patients meet FDA approval, yeah, because then it says FDA device specific, and then we kind of cover it. So, go, yeah. Start there and say one or two-level. Oh, OK. So, the disc following a single or two-level discectomy. Yeah. OK. So, go to the sentence that starts reconstruction, third sentence down. That one. Single or two-level... no, no, no. Move over to where it says single and put or two-level. Then, you can get rid of that stuff at the end.
- Josh Morse: Shouldn't it read one or two level?
- Chris Standaert: Yes. Change the word single to one. Get rid of all that. All the stuff you highlighted, just delete. Change single to one. Gary, does that work?
- Gary Franklin: That whole sentence is all three lines.
- Chris Standaert: The whole sentence. There is one sentence. So, the four should not be capitalized.

- Gary Franklin: So, reconstruction of disc following one or two-levels for intractable symptomatic... confirmed by patient findings and imaging. Is that... so, that's the whole thing?
- Chris Standaert: That's the whole thing.
- Gary Franklin: I think that's fine.
- Chris Standaert: Unless that doesn't work.
- Seth Schwartz: It says reconstruction of a disc, but it may be two discs, if it's two levels. So, should it be reconstruction of discs?
- Joann Elmore: Reconstruction following.
- Seth Schwartz: Disc parenthesis S-.
- Joann Elmore: Yeah, parenthesis.
- Chris Standaert: Shouldn't it say arthroplasty following, yeah? So, get rid of reconstruction of... I guess that works or just put the words...
- Rod Oskouian: Yeah, because you can't take a disc out [inaudible].
- Chris Standaert: Yeah. Is it really reconstruction of a disc or do you just want the word arthroplasty? Yeah, just take out reconstruction of a disc and put disk replacement following one or two that includes... where'd you go?
- Christine Masters: I'm trying to print and save it so I don't lose it.
- Chris Standaert: Yeah. I suppose they want you to define... that's sort of what that says, intractable symptomatic radiculopathy or myelopathy confirmed by imaging findings. [inaudible]. Then the third one, failure of conservative care.
- Joann Elmore: I'm just asking Chris to look at slide 20 of the medical director recommendations. It basically states the criteria for the cover with conditions. They have to have signs and symptoms of radiculopathy or myelopathy, advanced imaging evidence of nerve root compression, and failure of conservative, nonoperative care. I just want to make certain we have the failure of conservative nonoperative

care. So, Chris, would it be OK to draft those three bullets to put in here?

Chris Standaert: Yeah. We could just change that last sentence to include the two of them. Patients must have advanced... we're getting redundant but you want that part about this? Must have advanced imaging evidence of corresponding nerve root or spinal cord compression who have failed nonoperative care, or have progressive neurologic... failed or be inappropriate for nonoperative care. Again, acute myelopathy, that's not appropriate to [inaudible]. Make that inappropriate. I'm not sure non-appropriate's a word. For nonoperative care.

Rod Oskouian: But I think if they have myelopathy then you're not going to be concerned with [crosstalk].

Chris Standaert: That's why it's inappropriate, yeah.

Rod Oskouian: Oh, OK.

Chris Standaert: I'm trying to figure out a way to say that, because I didn't want to say you have to, like, if you have a progressive C5 palsy or you have a progressive myelopathy, like, I shouldn't... I send them to you guys. I don't send them to PT.

Rod Oskouian: Well, I wouldn't say imaging evidence, clinical... I mean it seems like you would say advanced imaging or clinical evidence at both levels, one or both levels.

Chris Standaert: Advanced imaging or clinical evidence.

Gary Franklin: Yeah. I mean, you're doing a neurologic exam in somebody that has myelopathy, and you're going to see spread. You're going to see stuff that's not exactly at that level. I'd hate to tie their hands for a decompression on that one, but the key is, on the radiculopathy, because some surgeons want to do two levels, even though there's a single level radiculopathy, and we just need to make sure there's radicular stuff objectively at both levels.

Chris Standaert: [inaudible] at treated levels... at treated levels, yeah?

- Rod Oskouian: Well, that's what corresponding nerve root... it says that.
- Gary Franklin: I think the way it was before was good.
- Chris Standaert: You don't like that treated levels?
- Gary Franklin: No.
- Chris Standaert: OK.
- Gary Franklin: I don't know what that means.
- Chris Standaert: It means the levels you're on... it means it's corresponding to the levels you're going to operate on.
- Gary Franklin: The thing is, it's strong enough... clinical or advanced imaging evidence of corresponding neurologic problem at one or both levels. The main thing is on the two-level new disc, because there's going to be a lot more two-level discs that are going to be marketed. So, we just need to be careful about what does it mean to have two levels of neurologic stuff going on.
- Chris Standaert: Well, that's what I'm saying. So, sometimes saying at the levels you're going to treat, right? I mean, you don't want to be treating uncompressed levels. You don't want to turn every disc for a one-level myelopathy into one-level [inaudible] two-level thing.
- Gary Franklin: Well, if they're asking for a C5 and C6 two-level Mobb, we're going to ask... we're going to look for objective evidence in the record of radiculopathy at both levels.
- Laurie Mischley: OK, so something like patients must have evidence of...
- Joann Elmore: If they want to get a two-level procedure. I don't think we're saying it clear enough you guys.
- Chris Standaert: So, put up... finish that sentence. Put a period at the end of that sentence. Then put for two-level procedures, objective evidence or what do you want to say?
- Joann Elmore: Of radiculopathy at both levels must be noted.

- Gary Franklin: There should be objective evidence of radiculopathy at both levels.
- Laurie Mischley: And adjacent.
- Gary Franklin: Well, it's only adjacent right now.
- Chris Standaert: Of radiculopathy or cord compromise.
- Gary Franklin: At the two adjacent levels, because right now it's just adjacent. We're not allowing an artificial disc at one level and then two levels away we... we have gotten some requests for that.
- Chris Standaert: Right, but objective evidence at... get rid of that... objective evidence of...
- Joann Elmore: Radiculopathy.
- Chris Standaert: ...of radiculopathy or cord compromise.
- Christine Masters: What compromise?
- Chris Standaert: Cord... spinal cord compromise at two consecutive levels.
- Tony Yen: When you say objective evidence, are you just really meaning imaging?
- Chris Standaert: Meaning imaging, but that's where the cord compromise would be imaging and the radiculopathy could be multilevel weakness.
- Rod Oskouian: It's clinical and advanced imaging.
- Chris Standaert: Yeah. It's sort of both.
- Rod Oskouian: We kind of look at all of it.
- Chris Standaert: Yeah. That's why I said objective. It could be loss of reflexes. It could be weakness. It could be cord compromise on the MRI.
- Tony Yen: If you just have weakness, is that sufficient?

- Chris Standaert: Objective weakness in two consecutive myotomes, you can clearly separate with corresponding findings, yeah.
- Gary Franklin: Yeah, or there might be an EMG in those patients that demonstrates that.
- Chris Standaert: Right.
- Joann Elmore: And that last sentence, compromised, should it be compromised, add spinal before the word cord. Then, we need an ending at the ... consecutive levels is required or should we use...
- Chris Standaert: What I'm trying to do is get rid of the need for saying you have a two-level myelopathy versus saying you have two-level cord compromise, and I also know this is something that...
- Joann Elmore: Is required.
- Chris Standaert: ...again, you're not going to be uncomfortable not decompressing the level, but where you're thinking myelopathy [inaudible].
- Gary Franklin: I think it's fine.
- Joann Elmore: Consecutive levels is required?
- Chris Standaert: Questions?
- Rod Oskouian: Neuropathy, stenosis, or myelopathy.
- Chris Standaert: Radiculopathy, spinal stenosis, or myelopathy. OK. So, go to radiculopathy, spinal stenosis, or myelopathy. Then, get rid of or spinal cord compromise.
- Gary Franklin: Well, wait. I'm sorry. It's not spinal stenosis. The indication is radiculopathy or myelopathy. That's what the FDA...
- Joann Elmore: Can't we just have radiculopathy or myelopathy at the [crosstalk].

- Gary Franklin: I mean, what is causing that radiculopathy or myelopathy, that's not... I don't think you have to go into all that detail, because it's a lot of different stuff that does that.
- Joann Elmore: Yeah. Can't we get rid of or spinal cord compromise?
- Chris Standaert: So, are you then going to say to somebody who has C5-6 compression with a very tight C4-5 canal with cord signal change at C5-6 that they can't operate... they can't decompress C4-5?
- Gary Franklin: No. I said before that I thought you could make it a little looser on myelopathy.
- Chris Standaert: Yeah. That's why I'm... yeah. That's why I don't like the word myelopathy, but that's the... I guess... do you like spinal cord compression instead of spinal stenosis?
- Gary Franklin: OK.
- Chris Standaert: Spinal cord compression or myelopathy.
- Gary Franklin: Again, we're not as concerned about that myelopathy situation, as we are about the radiculopathy.
- Chris Standaert: No. That actually works. That works. Patients must meet FDA approved indications for use and not have any contraindications. FDA approved device [inaudible] that includes skeletally mature patient, disk replacement following one or two-level discectomy for intractable symptomatic radiculopathy or myelopathy confirmed by patient findings and imaging. This is our criteria, not the FDA criteria. Patients must have advanced imaging or clinical evidence of corresponding nerve root or spinal cord compression and have failed or be inappropriate for nonoperative care. For two-level procedures, objective evidence of radiculopathy, myelopathy, or spinal cord compression at two consecutive levels is required.
- Josh Morse: So, those first two, could you bullet it and sub?
- Chris Standaert: The first two are bulleted and subbed.
- Joann Elmore: Skeletally [inaudible].

- Chris Standaert: Indent before skeletally mature patients, yeah, just tab, whatever, bullet, whatever you want to do, and then the same thing there. Then that's it. Then, yeah, not that one. Not that one. That includes. Are we all grammatically good? OK. We still have to vote. So, we're going to vote. As we're voting, this is our condition. So, you can vote not cover. You can vote cover without conditions, which means that you don't care about this at all, just cover, or if you vote cover with conditions, you're voting for that. If you don't like any of those choices, speak up now. Alright. So, for cervical total disc arthroplasty. Does Greg have a vote?
- Josh Morse: I see nine cover with conditions. Is Dr. Brown on the phone?
- Chris Standaert: He said he texted you things, or one of you things.
- Josh Morse: He did text me. His vote for cervical artificial disc replacement is cover with conditions.
- Chris Standaert: OK.
- Josh Morse: So, that's ten cover with conditions.
- Chris Standaert: So, are we compliant with our... we're relatively compliant with our cervical fusion one, but somehow we have to fix the language on it, because I don't know where myelopathy went. I bet it was there, but it went somewhere. We don't have a National Coverage Determination on cervical discs, I don't think.
- Josh Morse: We will look on the next page.
- Chris Standaert: And our guidelines and other things. So, we're compliant with ACOEM, because they said the same thing. NASA, they're comparable, doesn't actually have a recommendation. We're roughly in line with Colorado. So, I think we're consistent with the National Guidelines and Coverage Determinations that we are aware of, and we are done. Thank you, all.