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Health Technology Clinical Committee Public Meeting

May 18, 2018

- Gregory Brown: Okay. Welcome to our meeting for the Health Technology Clinical Committee. I'm Greg Brown. I'm an orthopedic surgeon with Franciscan Health in Tacoma and Federal Way. Again, welcome. Today, we have two topics. If we could start by letting everybody introduce themselves. And we have Christoph Hofstetter who is a neurosurgeon at the University of Washington. I'll let him introduce himself for our expert for the first topic this morning. Dr. Rege.
- Sheila Rege: I'm Sheila Rege. I'm from Tri-Cities, southeast Washington. I'm a radiation oncologist there.
- Mika Sinanan: Hi, Mika Sinanan. I am a general surgeon at the University.
- Laurie Mischley: My name is Laurie Mischley. I'm a naturopathic physician and a neuro-epidemiologist.
- John Bramhall: I'm John Bramhall. I'm an anesthesiologist. I work at the University system at Harborview Medical Center.
- Tony Yen: I'm Tony Yen. I'm a hospitalist at Evergreen in Kirkland.
- Josh Morse: I'm Josh Morse, the program director for the Health Technology Assessment program.
- Christoph Hofstetter: I'm Christoph Hofstetter. I'm a neurosurgeon at the University of Washington. Background wise, I trained at Cornell. Fellowship is at the Mayo Clinic at the University of Miami. I treat patients with spinal ailments and also with cranial ailments, if necessary. So, my expertise includes traditional surgery, minimally invasive surgery and I'm an expert in endoscopic spine surgery, too. So, I really do, I think, all facets of spine surgery at the University of Washington.

- Kevin Walsh: I'm Kevin Walsh. I'm a family medicine physician in Ellensburg.
- Carson Odegard: I'm Carson Odegard. I'm a chiropractor. I practice in Kirkland, Washington.
- Gregory Brown: Wonderful. Thanks, everybody. We have eight of our nine members. So, we have our quorum, and Josh, if we can proceed with the Health Technology Assessment program updates.
- Josh Morse: Okay. Thank you. Welcome to the meeting today. Today's topics on today's agenda in the morning is the topic of surgery for symptoms of lumbar radiculopathy, and/or sciatica. Following that topic, the committee will look at pharmacogenetic testing for patients being treated with anticoagulants.

A few meeting reminders. So, this meeting is being recorded. The microphones are quite sensitive. So, please be aware that the things you say are being recorded. When you do wish to give comment, please try to remember to state your name for the transcriptionist.

So, anyone who wishes to provide public comment at today's meeting can do so and sign up on the table, which is right outside the door towards the back of the room.

So, a little background about the Health Technology Assessment program. This program is administered by the Washington State Health Care Authority. It was created in 2006 through legislation. They designed this program to use evidence reports and this panel of clinicians to make coverage decisions for selected medical procedures and tests, based on the evidence related to their safety, efficacy, and cost-effectiveness. Multiple state agencies participate to identify topics and ultimately implement the determinations that come from this program, and they include the Health Care Authority programs, which are the Uniform Medical Plan and Medicaid, the Department of Labor and Industries, the Department of Corrections, and as I said, the agencies implement these determinations within their existing statutory frameworks following the completion of the process to make these decisions final.

So, the purpose of the Health Technology Assessment program is to ensure that the medical treatments, devices, and services that are paid for with state healthcare dollars are safe and proven to work. This program provides a resource for the state agencies that purchase healthcare. The program aims to develop scientific evidence based reports on the medical devices and procedures or tests that are selected. And we provide staff

support to this clinical committee who are a group of individuals from across the states in active practice.

This is a high-level view of how this process works. Topics are nominated. Anyone may nominate a topic. There are public comment periods related to the topic selection phase. Ultimately, the director of the Health Care Authority, Sue Birch, who will be here later today, has the authority to select topics for review through this process. We then develop key questions, work plans, drafts, put these out for public comment. And then our contracted technology assessment centers produce evidence reports. Those are then published for public comment. They're made final prior to the public meeting when they're brought here before this committee. Again, following the completion of the determinations, the agencies implement the decisions.

A brief look at our calendar, as we schedule for the next year. The next meeting of this group is scheduled for July 13th. This is a phone webinar meeting to finalize decisions from today's meeting. The next meeting is scheduled for September. Traditionally, the committee's retreat. November, we have scheduled a re-review of Optune or Novocure, and a rereview of the Positron Emission Tomography, or PET scans, for lymphoma.

Looking into 2019, we currently have scheduled for January a review of sacroiliac joint fusion and peripheral nerve ablation procedures for knee pain. In March, we will be looking at wearable defibrillators. In May, a rereview of the Proton Beam Therapy previous decision.

Anyone may participate in this program. We have all of our information on the Health Care Authority webpages under the Health Technology Assessment program. A person can sign up to receive program updates via email, and that information is on that webpage. Anyone, again, may provide comment at today's meeting or on proposed topics when we go through that selection phase on key questions when they're published, and on draft and final reports, and on the draft decisions. Thank you very much.

Gregory Brown: Thank you, Josh. Next order of business is review of our meetings from December. We have those in the binder here. Any comments or questions. There have been a couple of proposed changes to the minutes regarding our bylaws. We voted to approve them. There is a suggestion just to revise this to under the... basically why they were revised and to change that. The bylaws were revised in order to first bullet point align with updates to Washington Administrative Code and Revised Code of

Washington changes in 2016, improve readability, and guarantee consistency between topic areas and the new laws. So, any other comments or suggested changes to the minutes?

Sheila Rege: I move for approval.

Mika Sinanan: Second.

Gregory Brown: Second. Question?

Sheila Rege: Alright, I'm Sheila.

Mika Sinanan: And Mika Sinanan for the second.

Gregory Brown: Okay. Then vote to approve the March minutes with the changes just in describing why we did the bylaw changes. All in favor, aye.

Group: Aye.

Gregory Brown: Any opposed? Passed unanimously.

Josh Morse: Okay. All approved. Thank you.

Gregory Brown: So, next we had one topic for our last meeting, and that was gene expression profile testing for cancer tissue. We had our draft findings and decisions. There was a comment received from Myriad Genetic Laboratories, and under prostate cancer, they suggested changing early stage disease to low-risk or favorable intermediate risk disease. I'm not sure if the...

Sheila Rege: This is Sheila Rege. It is clearer. So, I like that language.

Gregory Brown: As our radiation oncologist, a topic that's more close to your specialty than certainly mine.

Mika Sinanan: Mika Sinanan, I agree. That sounds clearer.

Josh Morse: I think you have two copies, you should have two copies of this draft decision in your binder.

Gregory Brown: Well, it's actually just before lumbar radiculopathy sciatica tab in our book.

Sheila Rege: I'd like to read it. I'm having trouble finding it.

Josh Morse: This is one copy, and if you turn the page again, and then behind that. I apologize. You have the correct copy in your... we can show you the previous version. So, the version that you have in here has not been subject to really change, but the one that we published was formatted a bit differently.

Gregory Brown: Okay.

Josh Morse: And what you're not seeing is the comparison of what was published to what we then reformatted for clarity. So, you're seeing what we recommend be used, and it aligns with your previous intent.

Gregory Brown: So, the Health Technology Clinical Committee coverage determination, gene expression profile testing, is a covered benefit with conditions for breast cancer or prostate cancer. Gene expression profile testing is not a covered benefit for multiple myeloma or colon cancer. Then, the limitation of coverages, as listed here. So, under additional conditions by test towards the bottom of the page, prostate cancer tests, Oncotype DX and Prolaris are covered only for early-stage disease, and that would be where we would substitute low-risk or favorable intermediate risk disease.

Josh Morse: Okay. Thank you.

Gregory Brown: Yep. So, we have two members supporting that change for clarity. Any other discussion or comments? Okay. Are we ready to vote on that? Then all in favor of adapting that change and approving our decision?

Group: Aye.

Gregory Brown: Any opposed?

Josh Morse: All approved.

Gregory Brown: Unanimous decision. Okay. Thank you. And so, we are ready to move forward for our first topic of today, surgery for lumbar radiculopathy/sciatica.

Gary Franklin: Can you pull that up on here, too?

Female: I don't have the ability to do that.

Gary Franklin: You can't do that?

Female: No.

Gary Franklin: Okay. Alright. Hi, I'm Gary Franklin. I'm the medical director at Labor and Industries, and the co-chair of the agency medical directors' group. I'm also a neuro-epidemiologist. Thank you. So, I think the report was great. We did have a few things to comment on there, but we're talking about today is trying to unroof a nerve that has been pinched by either an extruded disc or stenotic bones. And the report really... most of the evidence is on decompressive discectomies and laminectomies, but another topic in here is minimally invasive surgery through any manner of devices, and there are nine different devices, I believe, 14 studies or so. Our main concern is on the minimally invasive surgery, not on the regular procedures for unroofing a nerve. Those are pretty much standard of practice, and the only question there is, are you going to get better quicker or not. That's really a patient decision with her physician on that. So, we don't really have any issues at all with the routine procedures, but we do have issues with the minimally invasive procedures, which we actually think are a problem. Most of the open procedures are done by surgeons, but a lot of the minimally invasive procedures are done by all manner of people, pain people, rehabilitation people. I know a neurologist in Eugene, Oregon, who does a lot of these at a spine center, and a laser center was on the spine of the Seattle yellow pages. That guy did a lot of these minimally invasive procedures. So, one of the problems is how these things are regulated and who does them, but our main concern, and the purposes of this discussion is the evidence on minimally invasive is not strong, and there's a potential adverse effect.

I can't really see this. So, I'm not going to go into a lumbar radiculopathy. This is all pretty clear stuff. I mentioned there were nine different techniques for minimally invasive, about 14 RCTs represented here. One of my spine surgery friends in the state said one of the main problems here is there's no direct visualization. It's only indirect visualization for most of these procedures.

Gregory Brown: Dr. Franklin, would you like to borrow my paper copy so you can...

Gary Franklin: Sorry?

Gregory Brown: Would you like to borrow my paper copy, and then you can be on the other... then you have it in front of you on paper, or is that?

Gary Franklin: Yeah. I, I have a paper copy.

Gregory Brown: Oh, okay. My neck's getting sore watching you, sorry.

Gary Franklin: Sorry. So, this is a slide that I've used for a long time. It summarizes federal oversight of all of our medical interventions, and the Food and Drug Administration approves drugs based on two randomized trials, and then they approve a drug for the indications from the studies that were done, but then once the drug is approved, any doctor can write a prescription for any off-label use. So, the off-label use of these drugs is not regulated, for the most part. So, that leaves it up to states to try to make decisions about whether that's working or not. One example of that was when gabapentin was shown to be effective for zoster and neuropathy pain, we started getting a lot of prescriptions in Labor and Industries for gabapentin, but the vast majority was being written for back pain, not for neuropathy or radiculopathy. So, that's just an example of, you know, the best oversight of the federal government is on drugs, but there's a lot of off-label use.

Then, medical devices have way lower standards of approval. The invasive procedures that include devices have what's called PMA studies. You can get a hold of these studies, and they're usually published, both by the FDA and also in peer review journals, but the vast majority of devices that are approved are approved under what's called 510K equivalence, which means that the device, and that's true for, I think, all of the minimally-invasive devices that we're looking at here today, are approved based on that they're similar to some other device that was around before 1976. I'll come back to that in a minute. Then, most surgical procedures have no federal oversight at all. So, you know, this kind of framework of regulation of healthcare, you can see how it leaves a lot of holes in regard to what a payer has to, you know, what kind of information does the payer have to use to make decisions about whether it's safe and effective and worthwhile.

So, on one of the minimally-invasive devices that was mentioned in the report, the disk effect system, I found the actual FDA letter that approved that procedure under the 510K regulation. Again, it's approved... it's not... when the FDA approves these things, it's not approved... when they approve it, it's not, like, they're saying this work. They approve it for marketing, in that it is substantially equivalent to something before 1976. So, the language on this one was, we have reviewed your section 510K premarket notification of attempt to market the device and have determined the device is substantially equivalent for the indication for use, blah, blah, blah. So, I just wanted to point out that none of these... all of the procedures related to the minimally invasive stuff that we're looking at here were based on this 510K approval, in terms of the devices that are used.

The agency medical directors' group have... these are the concerns that we have had all along, safety medium concerns, efficacy medium to high concerns, again primarily for the minimally-invasive stuff, and the cost is high.

There are a few things in here that are covered with prior authorization, like endoscopic decompression, but again, these were not looked at formally, and this decision was not made based on any formal technology assessment by the agencies.

The costs have been moderate across the agencies. I don't really need to go into gory detail here. So, a lot of those that are being done.

So, there are open surgical procedures, as you could tell from the report. There are seven RCTs that compared surgery to conservative management. I feel like these are probably the most valid comparators for validity, and again, we don't really have much question short-term if patients are better off, and longer term, say at one year, things are pretty much equivalent. So, it sort of comes down to what does the patient want and how much radiculopathy do they have, and do they have any motor findings, etc. So, we're not really, again, too concerned about that.

The effectiveness of the open 'micro' discectomy procedures is also decent, and we don't have much concern on that, although the evidence is not as strong.

The effectiveness of minimally-invasive procedures compared to standard procedures, I don't believe there was any study that compared them to good conservative management. So, things in some of these studies, pain reduction, function improvement, quality of life, are similar in the short-term for the standard versus minimally-invasive. Then, there is... some of the studies that comment on return to work, which is said to be improved in some of these studies, but I have some issues with those studies and how important those outcomes were. None of those studies had return to work as a primary outcome. It was always a secondary outcome, and that's an issue. The quality of evidence on most of these studies is very low or moderate. The procedures were all quite different. We took some issue with the evidence-based folks who are going to do the presentation in a minute, as to why these were lumped together in the report, and we felt like they should not have been lumped together, because they were all different technologies.

So, the way I came at this was to look at some of the individual studies and to look at some of the more detail, but since the RTI's use the grade

methodology, grade kind of implores groups to lump things together, but that is, to me, a flaw in the analysis here on the minimally-invasive surgery.

So, just some examples of problems, for example, reference 36, I'm not sure it's still reference 36, maybe it changed with the redo of the... update of the report, but the Chatterjee study and Spine, this was automated percutaneous lumbar discectomy versus microdiscectomy, and they specified it had to be only for small contained disks. A lot of people think that if you have radiculopathy, you need to have an extruded disk to be able to tell anything. These were small contained disks. So, you can imagine, lots of people with small contained disks with symptoms that are a little bit like radiculopathy are doing these kinds of procedures would be a problem. This trial was done in the U.K., and they found that the automated group had much less satisfactory outcome, 29%, compared to the microdiscectomy, 80%. This was funded publically in the U.K., and this trial was stopped early, due to poor outcomes. So, this is probably one of the stronger studies, even though I don't love the controls. So, that's kind of a problem.

Reference 37, Brouwer and the Spine Journal in 2015, this was percutaneous laser disc decompression versus microdiscectomy. It was a non-inferiority design. Again, public health funding. They used the Roland-Morris, and they did find speedier recovery compared to conventional surgery, but reoperations in the percutaneous group was 38% versus 16% in the conventional operation. So, this is a recurrent theme in this literature, even though the literature is weak, there is a substantial underlying question, because you can't really directly visualize things, and because it's not an open procedure. I know a certain friend who came today may disagree with me here, but if you've got a rehab specialist and a pain guy in Edmonds doing these procedures, and you can't really see things very well, and you have a higher reoperation rate, you've got a problem.

There was a Cochrane review, and most of the studies in the Cochrane Review were included in the RTI review. So, that's great. Cochrane concluded that minimally-invasive surgery had a higher risk of rehospitalization due to recurrent disc herniation, increased dural tear, and slightly worse pain outcomes.

Then, there was a... one of the best studies that was cited was Arts in the report. Arts did a follow-up five-year study. So, this was one of the best studies that was included here, and this was a five-year follow-up, which was not originally included in the RTI study, because it wasn't in their reference year range that they looked at. It was published after that. One

of the things in this study was, reoperation rate was 18% in tubular discectomy and 13% in microdiscectomy. That was not significant, but six patients in the tubular group ended up with instrumented fusion versus none in the conventional microdiscectomy group. So, again, can you really see what you're doing? Depending on who is doing it, I presume that some great neurosurgeons could do this extremely well and maybe not have these outcomes, and I presume we'll hear a little bit about that from our guests.

Then, one of the conclusions in the RTI report was that a number of these studies reported on a better return to work outcome. I had a problem with that, as well. So, the Thome study, reference 26 from 2005, for example, that used an outcome, which they called a Prolo-score, which was a combination of pain interference with function and capacity for return to work. Those are two different things. So, that was a combined score. You couldn't tell from the fact that the score was somewhat better at the end, which part of that combined score was actually better, but it wasn't specifically on return to work. It was just combination. Then, the Hermantin study, 1999 video-assisted arthroscopic microdiscectomy versus open discectomy, this study was conducted in a surgeon's office. I don't know if you remember one of the studies that we looked at previously for treatment of plantar fasciitis with the blasting machine, what's that called?

Gregory Brown: Lithotripsy?

Gary Franklin: Yeah, it's like lithotripsy. This is not a... this was just done in somebody's office. It looked... the study had all the I's dotted and the T's crossed for a randomized trial, but there were some issues with how it was conducted.

Then, reference 29, the Ruetten study, 2008. This was a German study. There was no conflict of interest stated. This was a randomized trial to endoscopic versus conventional microsurgical discectomy, and they used these instruments. There were three reoperations and three fusions, and these were not included in the follow-up. The reoperation rates were 6.6% and 5.7%. So, they weren't so different. Then, the mean postop work disability was less in the endoscopic group, 25 days versus 49 days, but you can't tell what proportion of patients had preoperative or postoperative disability. There were no methods presented. No details presented, as to what all that meant that they reported.

You have to look at the gory detail in these studies before you conclude overall that yes, there's a little bit of the hint that maybe return to work is better, but when you get into the weeds here, it doesn't look so good.

Then reference 32, Mayer, these are all pretty old studies, by the way, 1993. The title of this study said preliminary results. So, I don't think I need to go into a lot more detail there.

On repeat surgery, and we'll get back to this in a little bit when we get to our recommendations, there's almost nothing on this. This is a real problem, because you're going to be left with a decision, and you have the regulatory authority to make a decision, even with no evidence, because the burden is really on the manufacturers to study these things, not on state agencies to prove that it doesn't work. So, there's nothing here, and you'll have to figure out for yourself, whether you can make a decision on that.

So, I wanted to mention one study that actually is not completely in the wheel house of this topic. This is the Spine scope group in Washington State that has been getting information from hospitals with a consortium of spine surgeons. This is a great consortium of [inaudible], and most of this is looking at things like reoperation rate, blood loss, and stuff like that, that you can get from hospital records, but they also tried to talk to patients at baseline and in follow-up to see if they could figure out what functional outcomes were. They weren't able to get a hold of a large proportion of people, but the people they were able to get a hold of, they could report the outcomes. One of the things that they found was that lumbar spine discectomy was... I'm sorry, lumbar fusion outcomes and workers compensation is way worse, and this is consistent with all the other studies that have been published, over a hundred studies probably, that have looked at various procedures comparing worker's comp outcomes to non-worker's comp outcomes, and the outcomes in worker's comp are usually three to four times worse in regard to any function or return to work.

I'm not going to get into the safety of the surgery. I think that the report from the vendors will adequately cover that, but one issue is the reoperation rate. I believe that the reoperation rate that was reported from the randomized trials are actually quite a bit lower than the reoperation rate that has been seen in population based observational studies. Martin, I think, is one of the people that has looked at this. This is from 2012, using Washington State hospital discharge data. The hospital reoperation rates at four years was 13.8%, and that is a high variation in the reop... much higher... the variation based on surgeon was much higher than the variation based on hospital. So, the surgeon base variation was more important. We already talked about the questions in minimally-invasive about higher reop rates and the quality of the evidence. I'm not

going to say much about cost-effectiveness here. You'll hear a lot more about that in a minute.

Private payers typically have not covered most of the minimally-invasive procedures. There are probably examples where some of it is covered.

Then, this is the Spine SCOAP study that I mentioned earlier. This is mostly lumbar fusion, and one of the great things about this study, so 20% of it was decompressive procedures, but you can't really sort it out, you can't say this was related to that, is that they included in their paper, which I think was published in JAMA Surgery, that they actually included a tool that any patient who might be having a fusion can put in their own data and figure out what their risk of not getting better is at one or two years. The odds of functional improvement, if you're a worker's comp patient, was 20%. So, this is a little hard to believe that that is going on. So, I think that supports your earlier decision on lumbar fusion.

So, our state agency recommendations are for the open procedures, it should be covered with conditions. Adult patients with lumbar radiculopathy, and I think it's important to define what's subjective and objective neurologic findings that are corroborated with an advanced imaging test, and failure to improve with a minimum of four weeks of nonsurgical care, unless there is progressive motor weakness. Then, for the minimally-invasive procedures, we think that they should be noncovered and that the concerns about reoperation rates, low quality data, and in some cases, higher cost.

Then, you're going to have to grope with, you know, figure out the reoperation decision. So, we took a shot at this. If you do decide to make a decision, this is just an example of a way to think about it. So, this is reoperation from the open procedures. By the way, a lot of those patients that have reoperations go into lumbar fusion. So, reoperation only for recurrent symptoms that occur after a period of clinically meaningful improvement in pain and function lasting at least six months, and clear-cut evidence of a recurrent disk herniation. If a recurrent or residual or herniated nucleus polyposis seen on a postoperative MRI is equal in size or larger than the original HNP, earlier surgical intervention may be required for reoperation. Then, absence of comorbidities that could explain lack of improvement, such as smoker's, opioids, worker's comp, and I had another thing in here, but my surgeon friend said that there's not enough evidence on it, but I'm pretty sure that it's important, which is scarring after these operations. We have seen many patients at L&I, and the only way you can find the scarring is by doing a gadolinium MRI. It's the only thing where the scarring lights up, and I have seen many requests for reoperations in

patients that have substantial epidural scarring. I did not include it here, because it is not an evidence-based opinion. So, I think that's it, and thank you.

Gregory Brown: Thank you, Dr. Franklin. So, next is our, actually, any questions for Dr. Franklin? Yeah, sure.

Kevin Walsh: This is Kevin Walsh. At the end, looking at your reoperation conditions, so is the last condition, you're saying that to be considered for reoperation, the person would have to not smoke, not be taking opioids, and not be on worker's comp? Am I interpreting that correctly?

Gary Franklin: Well, yeah. I mean, I know that would be a tough sell, you know, and hard to employ.

Kevin Walsh: It would greatly reduce the number of candidates.

Gary Franklin: Well, I'm more concerned about how people are doing. I actually don't care. I, I'll pay for anything that works, but, we see a lot of reoperations that the outcome, again, there's almost no data in this whole literature on the effectiveness and the safety of reoperations, but we see a lot of it at L&I. So, I'm just offering some ideas here. I'm not saying they're all solid. This is ... there are worse outcomes with those things.

Christoph Hofstetter: Dr. Hofstetter, University of Washington. So, thank you for putting this talk together. I think it's always humbling, kind of, to see what the evidence is. I think you give a very, very nice summary. I think there's a couple issues, I think, that everybody should be very much aware of. First of all, let's start with the title of this meeting. Here we go. We're talking about lumbar radiculopathy. Okay. So, your talk was about one little aspect of lumbar radiculopathy. Additional reasons for lumbar radiculopathy, I don't have to go into, but it ranges from cancer, patients have, you know, like, cancer in the pedicles and the spine compression, cauda equina, lateral recess stenosis, central stenosis, spondylolisthesis, spondylolysis, [inaudible] lysis, chronic disk herniations, acute disk herniations, plus/minus neurological deficits, and so on. I think I could go on forever here right now. So, I think the title of this meeting is interesting, but it does not define what we are talking about right now. Number one, so I think we don't have a topic defined we're talking right now, and I think it was represented very nice in your talk where you talked about fusion surgeries. You talked about this and that and this and that, useless. Number two...

Gary Franklin: Can I just say one thing about that. So, so the group could, when they come to the decision, include in their decision, well this decision does not apply to, you know, these other conditions or to cancer or, I understand your point. I think it's a great point, and I think it should be addressed.

Christoph Hofstetter: ...and actually, so, I'll just keep, you guys can stop me. So, the other thing is, you know, I think I'm shocked being here and, you know, who is paying for all of us here, being here? Who is paying for this? It's Washington State. It's the people that live in this country, the people that come to my office, all of our offices that we take care of. There's not a single representative here for a patient who had surgery, not had surgery. I mean, I think it's embarrassing here that we are discussing this, and we don't include our customers. I mean, they pay for this. They pay for you. They pay for me, and we are just making this decision. It is a shame.

Kevin Walsh: I mean, I could, I disagree with you.

Christoph Hofstetter: Yeah. No. I think they should be here, and I think we should have patients that have different treatments.

Kevin Walsh: I appreciate your opinion, but that's not the opinion of the other...

Christoph Hofstetter: I think I'm done with my...

Gregory Brown: Yeah. I was going to say. I think we can, we can bring this up in the discussion later on. Certainly, in answer to that, we have open comment and public and patients and surgeons and industry are all free to make comment during that public comment period, which is actually our next scheduled section. So, do we have a list of...

Josh Morse: We have one scheduled...

Sheila Rege: So, just as a response, this is Sheila Rege. People can even call in, so they don't have to come here, and that's what this public comment is about. So, any patient who wants to can call in, and give us their story. They are also welcome to come in person, and we've had that in previous meetings. So, this is an open meeting. Let's go to the public now.

Josh Morse: We have one scheduled public comment, and then we'll go to the signups from today. Dr. Leveque, and we have... so you have three minutes, sir.

Dr. Leveque: Okay. Thank you. Can I make one small editorial comment before my three minutes?

Josh Morse: Go for it.

Dr. Leveque: First off, I just wanna say I'm here representing these organizations today. I'm current president of the Washington State Association but have signed off on this presentation from the Association. It's listed here, which represents most, I would say many spine surgeons, including orthopedic surgeons and neurosurgeons across the United States. My editorial comment is that I agree with Dr. Hofstetter's point that I think that some of our definitions here are a little bit vague. And I believe that many of us interpreted this as a question on operative procedures for likelihood ratio in toto. Gary, as you stood up, I think one of your first statements was, we're not debating that open procedures can work. Well, I think that's what we felt was open for debate. And I think that you, overall, I think many surgeons would agree with you that there may be some novel procedures that have been left along the highway of various treatments that probably should have been left along the side of the highway. There may be providers who provide substandard care, either through lack of training or other nefarious reasons. I think that as surgeons we would agree that we want the best for our patients. I'm not sure that the manner in which this is structured actually tries to get to that answer, because I believe that in trying to address many of these edge cases, you've thrown the whole thing into question, as a means of trying to get to these edge cases, and I don't believe that that's actually really an intelligent way to go about it. So, most of this presentation is focused on the defense of any sort of surgical treatment for likelihood ratio, which again, I think you opened by saying, I don't have any issue with that. So, there we go. So, I think that... and I'm sorry to just be reading slides, but unfortunately in three minutes, that's about all I have time to do.

The cited literature does not warrant a policy change. We do not believe that there has been a substantial change in evidence on this topic, and to be clear, this topic is surgical treatment of likelihood ratio from disc herniation via discectomy. We do not support a change of the current coverage policy and do have some issues with some of the specific elements of the report.

I think there were... the majority of the studies were non-U.S. based, and we felt that the non-U.S. studies evaluated impact in other healthcare systems that have different socioeconomics and demographics, i.e. many of these Netherlands or U.K. studies. They may be vulnerable to error when applied to the U.S. and limiting the analysis to the studies from the U.S. alone may have been more appropriate in making this coverage decision. The conclusion on long-term outcomes is inaccurate. The draft evidence report concludes that compared to non-surgical treatment,

surgery reduces pain and improves function up to 26 weeks of follow-up, but the difference does not persist at one year or longer. There is a fair amount of data that contradicts this, including the SPORT trial, and I don't... I think all of you have this presentation available. So, I'm not gonna read every single part of this, but we did see that there was, in this SPORT trial, an improvement in sciatica and saw great improvement at one and four years in favor of surgery, as-treated analysis in favor of surgery for all primary and secondary outcome measures, at every time point, and demonstrated persistence at eight years, and also demonstrated benefits to patients who cross-over surgery. In terms of minimally-invasive surgery, outcomes for minimally-invasive approaches were comparable to more traditional open discectomy and microdiscectomy in the draft evidence report. I will add the editorial comment that I think that the terminology minimally-invasive surgery is very vague and perhaps in defining these types of coverage decisions, needs to be broken down, because if you just tell me percutaneous, I don't really know what that is. If you tell me minimally-invasive surgery, there's about eight different things that would apply to that. And I think that a blanket decision has been made for something that is much more detailed than that.

So, overall, I think that minimally-invasive techniques, and again, that may be a subset then, may have distinct patient advantages and choice based on patient factors. We support the continued use of, I would add, specific minimally-invasive approaches for appropriately selected patients. In terms of meta-analysis, patients from different studies often represent distinct patient populations and grouping these patients together may be inappropriate, and there may be biases introduced when defining inclusion and exclusion criteria.

So, in conclusion, we believe that surgery remains a cornerstone treatment option for patients with likelihood ratio when considering both therapeutic value and cost-effectiveness, and the cited literature, as aggregated together, we believe does not warrant a policy change, and here are the references. Thank you.

Gregory Brown: Excuse me. Can I make question. I know it's not normal. I struggle the same thing with terminology for our discussion last night. If we said direct visualization versus indirect, would that distinction help?

Dr. Leveque: So, what's interesting was, in Gary's presentation, indirect visualization included view with a microscope or view with loops. I mean, I would argue that given my aging eyes, a microscope may give me more direct visualization than actually just looking down through a wound. So, I guess I would... and, you know, Dr. Hofstetter is very experienced in endoscopic

surgery. Again, he could make a very strong argument that putting a camera a millimeter or two away from a nerve is probably going to give a better visualization of what's actually anatomically going on there on a screen than a view a foot and a half away. I think our laparoscopic colleagues in general surgery would agree. I think that the concept may be sound in thinking that way about it. I'm not sure that just stating it as direct visualization or indirect, as it was subdivided in Gary's presentation, necessarily gets us there.

Gregory Brown: Maybe I'll rephrase it. Maybe visualization versus no visualization of the herniation. I mean, so the percutaneous techniques without visualization, laser, disc ablation, thermographic disc ablation where you're removing the nucleus but not directly visualizing the herniation. Is visualization versus non-visualization a better?

Dr. Leveque: Christoph any thoughts?

Christoph Hofstetter: Again, I came back from Singapore a couple of days ago, and the head of the MI taskforce for the AO Spine Society. So, it's a worldwide organization, and I think if we could, at some point, I would like to slap up one slide again. I didn't know what to expect here right now, but I like that, and I think when I talk to my colleagues in South Korea and Germany, what they typically do in these procedures, is they document what they've done, right? So, you just look at the pathology. You look at the goal of surgery. For example, disc herniation, for example a lateral recess and we are fairly experienced now with what we have to accomplish. In Germany, for example, one of the 29 references that Gary had of Dr. [inaudible] when I was there, and I do the same thing at the University. When you've got accomplished and done what you want to do, you take your picture and you document it. I think visualization is key as a surgeon. For me, I want to see what I'm doing. And for me, I agree with that.

Gregory Brown: Okay. Thank you.

Dr. Leveque: So, I will just end my thing. I think that the concept may be sound. The devil is in the details on this.

Gregory Brown: Sure. Thank you. For people that signed up today.

Josh Morse: So, yes. We have one other signup, Dr. Tredway, and then we'll check the phone.

Trent Tredway: Thanks. I'm Trent Tredway. I'm a neurosurgeon here in the State of Washington. I was at the University of Washington for nine years one

month and 11 days. So, I know some of the folks that are here. I am actually in private practice right now, one of about three neurosurgeons that are still in private practice. I'd like to say that I'm a little bit shocked that we're here to discuss this. When I saw this, just all the other neurosurgeons here, were like decompression for a nerve root? Are you kidding me? This is absolutely ridiculous. This is what we do on everything, whether it's carpal tunnel, ulnar nerve, and trigeminal neuralgia. This may be the first time I ever say that I agree with Dr. Franklin on this. This is standard of care. This is absolutely unbelievable that we should be talking about this, yet, the way that this came around is some of these minimally-invasive procedures. I was the first minimally-invasive spine surgeon fellowship trained in the State of Washington. Christoph now is there, right? So, the whole deal of it is, is everybody that does a decompression should be visualizing the nerve root, whether it's done with an endoscope, whether it's done with your eyeballs, if Dr. Franklin is using the same glasses he used in 1978, that's ridiculous. We need good visualization. Nobody does decompression without visualization. If that's happening, it should be thrown out. No way. So, the other thing, too, is what are we discussing here with this minimally-invasive procedures? You're bringing up things that I didn't see in the book. I mean, what are we doing? We're decompressing nerve root. The decision that you guys are going to make is going to be determined on a CPT code, right? What are we going to approve? A decompression, 63030, 63047. Those are the CPT codes. Anything else that's being done by other people that are not surgeons should be looked at, but that's an NQAC [sounds like] or DOH issue. Okay? In 2004, when I got here, I was contacted that an anesthesiologist was doing these procedures, and they asked me to testify. That has to do with the actual hospital, and the surgery center giving privileges, not what we do. So, we should be able to have our patients undergo decompressions, whether it's a laminectomy, whether it's a discectomy, whether you do it with an endoscope, whether you do it with my aging eyeballs, a great new microscope, that's absolutely what needs to be done. And to go against standard of care is absolutely ridiculous. So, once again, I actually agree with Dr. Franklin for the first time. Decompression should be approved. Now, what I argued when I put in a couple of my nice little comments that no one else. Do you see other neurosurgeons out there, besides J.C.? No, because they're busy doing surgery, right? Probably two and three level fusions, because we can't do single-level fusions. We have to be careful what we're doing here. If you guys would have come to us before, we'd say, no. We're not going to allow some of these people to do these procedures. And if you're looking at actual specific procedures, what the Health Technology Assessment was supposed to do, new technology, whether it's a Coflex device, whether it's an interbody device, ask us. We'll say, okay. Look at that, but a decompression for a nerve root, ridiculous.

What we need to define are these other things that you're talking about, which isn't even in the, I mean, basically isn't even the results here. So, just talking to the WSANS, which we have a meeting today, which a lot of folks will be at. That's the Washington State Association of Neurological Surgeons, and the WSMA, which you guys are supposed to talk with us when we kind of review this, but decompression for nerve root stuff that we've been doing since 1978 with a microscope, and since 1934 when Mixter and Barr first notified us about the disc herniations and radiculopathy, this is kind of a moot point. So, I implore you guys to actually allow us to continue to decompress nerve roots in Washington State injured patients and Medicaid patients. That's absolutely got to be paramount to this decision here. If we want to talk about other things, then use the Health Technology Assessment to go and look at the technologies that you're describing so that they're not being done. Thank you.

Josh Morse: Thanks, Dr. Tredway.

Gregory Brown: So, that's our scheduled and write-in. So, now the phone, is our phone line open? Okay. This is Greg Brown, Chair of the Health Technology Clinical Committee for the Washington State Health Care Authority. We are reviewing surgery for likelihood ratio, sciatica. Is there anybody on the line that would like to make a public comment? Please check to make sure you're not on mute if you're trying to let us know you're there. Okay. I am not hearing anything. So, that concludes our open public comment period. We are ready for our evidence report from RTI.

Leila Kahwati: Alright. Thank you all. I'm delighted to be here today on behalf of the RTI University of North Carolina Evidence Based Practice Center. My name is Leilaa Kahwati. I am one of our center's associate directors. With me here today is Rachel Clark in the back, and boy are we looking forward to presenting this topic. It sounds like it's going to be a very interesting discussion.

Here's just an overview of today's presentation. You'll find abbreviations that we use on the very last slide of our deck. I think there is a laser pointer here? Yes. At the very bottom of the left in this little orange box of each is the table, figure, or page number in the full technical report that contains more detailed information about what's being presented on the slide. In addition, I think we have a binder with a hard copy of the report and all the included study articles, which are on the back table, if needed for reference.

Okay. So, we'll go through the background quickly, because I think you've already heard a lot about it. So, as you know, lumbar radiculopathy also referred to as sciatica, is the clinical syndrome characterized by radiating leg pain with or without motor weakness and sensory disturbances in a nerve root distribution, as illustrated by the graphic here on the right of the of the slide. It results from spinal nerve root compression caused by a number of different things. So, intervertebral disc herniation, spondylosis or degenerative changes, or various other pathologic processes, like tumors and infections, as has already been alluded to. The diagnosis of radiculopathy is not standardized. While EMG could be a gold standard, it is rarely used in everyday clinical practice. So, diagnosis is usually based on history, physical examination, and/or imaging confirmation. The treatment objective of sciatica is essentially symptom relief, and whether that's through nonsurgical management of symptoms or surgical interventions to address the underlying cause of the mechanisms, or both.

In terms of epidemiology, as you can see, the prevalence estimates for sciatica vary widely, as you can see on these slides. These estimates are from a 2008 systematic review of 23 studies. The estimates vary so widely because of the different ascertainment techniques these studies use that range from just self-record of radicular pain to actual clinical assessment and verified diagnosis. Several risk factors for radiculopathy have been identified, and they are listed here on the bottom of the slide.

So, you've already heard a little bit about what the technology we're talking about here today. I have to admit when we first got this topic, we were a little challenged to understand how to translate the clinical diagnosis into actual surgery or a procedure. So, the way we went about it in consultation with our clinical advisor, a neurosurgeon at UNC, is to sort of group procedures into two basic categories. So, the first standard open procedures. This includes disc removal procedures, for example, discectomy, and decompression procedures, for example, laminectomy, removal of facet joints or other soft tissues impinging on the nerve root, and these procedures are often performed with each other to achieve an adequate decompression. Then microdiscectomy, or micro laminectomy, are a type of open standard procedure that they often use microscopes or microsurgical instruments to allow for smaller incisions or small areas of dissection. So, those are the two standard open procedures.

The other class of interventions are those that we termed minimally-invasive surgery. These procedures use very small incisions with endoscopy, or they are done via percutaneous approaches. The goal of these procedures is the same as standard open procedures, in terms of decompression, and they might vary in terms of which ablative mechanism

they use, mechanical, laser, radiofrequency, thermal, or co-ablation, also known as plasma, but the underlying goal is similar, to decompress the nerve root.

So, Dr. Franklin talked a little bit about this already, but I'll just kind of reemphasize that the FDA clears surgical instruments and devices. They don't clear surgeries, per se, and they typically do that through the 510K process, which is a process that requires manufacturers to provide evidence that the device is substantially equivalent to a device that the FDA has already cleared, or one that was marketed before 1976. The full report describes some of the instruments and devices. With this slide here, we've observed in some of the language in those 510K clearance documents for instruments specifically cleared for discectomy and nerve root decompression. Note, none of the instruments or devices were approved through the pre-market approval process, as Dr. Franklin mentioned, the PMA process, which requires manufacturers to demonstrate that a device is safe and effective, which is a higher standard than the 510K process. Lastly, the FDA has already cleared a number of endoscopes, arthroscopes, and lasers, which have been cleared for general incision, excision, resection ablation, vaporization during surgical procedures generally, not necessarily limited to discectomy.

I think Dr. Franklin went through that already, so I'll move on. So, in terms of the methods for this evidence, there's two parts. First, we will synthesize primary research studies. Then, we'll go through a brief synthesis of relevant clinical practice guidelines.

This is the analytic framework that guided our primary use of synthesis. Our main efficacy question, or EQ1, looked at the effectiveness and comparative effectiveness of surgical interventions. Then, we also looked at a subsidiary efficacy question 2 on two specific patient populations. First, in patients who are not employed because of disability, and second in patients undergoing recurrent symptom for relapse. We considered one safety question as EQ1 over here to look at the adverse events associated with surgery, and finally, we considered one cost question to look at the cost and cost-effectiveness of surgery. Over here on the right are some of the outcomes that were eligible to be included in the review.

Here are the criteria for study selection. We focused on adult patients with primary symptoms of lumbar radiculopathy and focused on decompressive procedures, including discectomy, laminectomy, and closely related procedures designed to relieve nerve root compression. This included both standard open procedures, as well as microsurgical and minimally-invasive approaches. We required studies to have a comparator group,

either a placebo or no treatment group, or an active comparator group, thus case series of single cohort designs were not eligible, and we required studies to report at least one efficacy, safety, or cost outcome to be eligible. Because a sufficient number of trials were available, we limited study designs to control trials and specifically to randomized trials for the comparative effectiveness studies. Studies conducted in inpatient or outpatient settings were eligible, and we only included studies conducted from countries categorized as very highly developed on the U.N. Human Development Index, which is sort of a standard approach in most reviews, and this includes the U.S. Canada, Europe, Australia, New Zealand, Japan, South Korea, Singapore, Hong Kong, and a few selected middle Eastern countries.

I think it's important to understand what's not included in this review. So, populations and interventions that are designed primarily to treat neurogenic claudication or symptoms related to central spinal stenosis, non-radicular leg or back pain, spondylolisthesis or instability, for example, spinal fusion is not included in this review or patients with indications for spinal fusion, and as mentioned, we did not include observational studies or as treated analyses that were presented in some of the randomized trials.

The outcomes and the timing of the outcomes that were reported across studies varied. So, for this synthesis, we identified sort of three general follow-up time periods. So, short-term were for outcomes that were reported between four weeks up to 12 weeks, medium term were for outcomes reported between 12 and 52 weeks, but in actuality, there were really no studies that reported outcomes between 26 weeks and 52 weeks. So, mostly medium term is up through 26 weeks or six months. Then, long-term were outcomes reported at 52 weeks or longer.

This next bit is pretty important to our interpretation and conclusion. So, if you're starting to nod off, now would be a good time to tune back in. So, when we looked at intervention and comparatives, we concluded between group differences if the magnitude of difference was above a minimally important difference threshold for the outcome, if that was applicable to the outcome, and the estimate of the difference was precise enough to rule out the null effect or to exclude the null effect, i.e., it was statistically significant. So, together, those two things is what we used to kind of determine whether or not there was a difference between groups.

Christoph Hofstetter: Christoph Hofstetter. Can I comment, writing a lot of these papers, typically the minimally important clinical difference is applied to individual

patients in a group? Then it's taken as a proportion rather than taking it at the mean outcome difference, just as a comment. Thank you.

Leila Kahwati:

So, we evaluated the risk of bias for individual studies included in the report using the Cochrane Risk of Bias 2.0 instrument, which is designed for trials. With this instrument, studies are assessed as having a high risk, some concern for risk, or a low risk of bias and our detailed risk of bias assessments for all the studies are provided in Appendix F of the report. For economic studies included, we used something called the Quality of Health Economic Studies, which results in a numeric assessment of quality, which we translated into three categories, good, fair, or poor.

As Dr. Franklin mentioned, to generate a strength of evidence rating, we used the modification to the GRADE approach. You may be familiar, but let me just orient you to GRADE. So, with GRADE, a rating of very low, low, moderate, or high can be assigned. Bodies of evidence comprised of randomized trials actually began at a high strength of evidence rating. Then, they're downgraded because of serious or very serious concerns in one or more of the five domains that are listed over here on the left. So, we started high, and then we downgrade every time we identify a serious or very serious concern. We actually, for this report, modified the GRADE approach to allow for insufficient strength of evidence rating for two situations, first when there was only a single study body of evidence that had a very serious concern in one or more domains, or when we were unable to draw a conclusion about the treatment effect because of inconsistent findings within the body of evidence. So, those were the two examples of when we applied an insufficient rating.

In the report in the back of the slides, on slide 61, we've provided some language to help convey the overall mean of the strength of evidence rating. So, for example, an outcome that's rated as a strength of evidence of low, it can be interpreted as follows: We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies or both, and we believe that additional evidence is needed before concluding either the findings are stable or that the estimate of effect is close to the true effect. So, that's sort of the interpretation of a low, and the adjective used in the certainty language goes up for moderate and high and goes down for very low, essentially from that point.

So, now we'll move into the results. So, first we'll summarize the primary research synthesis and then move to the clinical practice guidelines.

This slide shows the result of our search. We screened over 1800 titles and abstracts and eventually included 25 studies that were reported in 39 different articles; 24 of those studies were randomized trials reporting efficacy or safety outcomes, and in some studies, one cost study, and six cost studies related to included trials were reported cost outcomes, and we identified 14 clinical practice guidelines for that part of the synthesis.

Because there are many comparisons and many outcomes that I'm going to be presenting, I'm just going to orient you a bit with this slide. So, for efficacy question one, and safety question one, and cost question one, I'll be presenting results from three different comparisons. So, surgery compared to nonsurgical interventions, and that sort of uses the color purple throughout the report and the slides. Then, the comparative effectiveness study, so this is looking at minimally invasive surgery versus standard open surgery. So, this is in the darker blue, and in North Carolina, we call that Duke blue. This other comparison is microdiscectomy to discectomy, and that's in the lighter blue, and we call that UNC blue. The last comparison is the one that Dr. Franklin already alluded to that there's not much evidence for. We looked at repeat surgery versus a comparator, and there's only two studies, and they each use a different comparator. So, we'll really only touch a little bit on that particular comparison.

So, moving into the efficacy studies, so this slide summarizes the study characteristics of the seven trials that compared surgery to nonsurgical interventions. Two evaluated percutaneous disk decompression. That's the Gerszten 2003 study and the Erginousakis 2011 study and Gerszten compared to epidural steroid injection. Erginousakis compared it to conservative management. Five studies evaluated discectomy or microdiscectomy, so McMorland from 2010 compared it to spinal manipulation, and Osterman from 2003 compared it to physiotherapy. Then, the other three, Weber, Weinstein, which is also known as the SPORT trial, and the Peul study compared discectomy or microdiscectomy to conservative management. Now, a word about conservative management. So, conservative management was not done consistently across all the studies. It typically involved... was directed by treating clinicians. It may or may not have been per a specific protocol. It often involved pain or anti-inflammatory medication, bed rest in case of the Weber study, which is the oldest study here, physical therapy, home exercise instruction, or education and counseling about the natural course of disease. A key point for all these studies is that a comparator was some kind of active treatment. It wasn't no treatment. And I'd also like to point out that the surgical intervention here is not really just the surgery itself, but it's the whole bundle of preoperative and postoperative care, which may have also included pain medications, some degree of physical

therapy, or home exercise instruction. The patients enrolled in these trials, and this speaks to some of the comments that were said shortly before we began, were basically patients with symptoms consistent with radiculopathy at nerve root compression confirmed with imaging, and that had failed six to twelve weeks of conservative treatment, and had no immediate indications for surgery. So, people with tumors, infections, cancers, cauda equina syndrome are not in these trials. Those are people that were not eligible to be included in these trials. So, you may want to keep that in mind, in terms of the applicability of findings from this to whatever policy you end coming up with.

The mean duration of symptoms across studies ranged from eight to 52 weeks. Two of the studies, so the Weinstein and the Gerszten study were conducted in the U.S., and the rest of the five were conducted in Europe. Of the seven trials, we assessed five as high risk of bias, typically for a large number of crossovers between groups, and we'll come back to that in a little bit at the end. Inadequate randomization or allocation concealment or high attrition, especially at the long-term follow-up points, one year and out. Other sources of bias across this body of evidence included lack of participant blinding or clinician blinding, which is especially important for patient reported outcomes, like pain and function where basically the outcome [inaudible] are the patients themselves.

So, I'm going to spend a little bit of extra time orienting you to this slide, because all the subsequent result slides are organized in a similar way. The outcome that I'm going to summarize is at the top of each box. So, in this case, it's a digital analog scale of 100 for leg pain. This is a scale that ranges from zero, which is no pain, to 100, which is worst pain ever, and the minimally important difference on this scale is seven to eleven points. So, on this slide, in the right hand side of the box sort of summarizes the numeric or qualitative difference. Then, on the left is the strength of evidence rating. So, in this particular measure, which again is the VAS 100 for leg pain, pain improves across the body of evidence by 41 to 57 points for surgery, patients allocated to surgery, and 20 to 36.5 for patients allocated to the comparator. Pain improved 6 to 26 points more with surgery. So, that's the between group difference, and that's through about 26 weeks of follow-up. This is based on three studies. So, K means the number of studies, and all the citations are there across 429 participants. Then, the last bullet in the box is the long-term findings. So, for this particular outcome, pain improvements persisted in the long-term between 52 weeks and five years, as well as within group differences persisted, but by long-term, there was no between group differences anymore, and this was based on two studies with 339 participants. So, on the left hand side of the box are the strength of evidence ratings associated

with these findings. So, we assign these based on the modified GRADE approach I had previously described. So, for the VAS 100 for leg pain, we rated the strength of evidence as low for favoring surgery in the short to medium term, and we rated the strength of evidence as very low for no difference between groups in the long-term. So, are there any questions about how this outcome results is organized or presented, because I'm gonna go a little bit faster through the rest of the outcomes.

Okay. The next outcome is the VAS 100 for back pain. It's a measure similar as the VAS 100 for leg pain, but it's specifically related to back. Essentially, the pattern of the results was the same as for leg pain, though the baseline back pain scores started lower than leg pain. So, that pain was not as severe, as leg pain, which is what you would expect for a population selected for radicular pain. So, back pain had the same strength of evidence ratings.

Next are the results for the SF36 Bodily Pain scale. So, we found that pain improves in both the surgery and the comparator groups; however, for this outcome, the between group differences were mixed through 26 weeks. In some studies, the significant and meaningful difference in this outcome was observed, but in some studies, this difference was not observed at all. Time points in other studies the difference was less than the MID or it was not statistically significant, or there was no significant testing performed. So, we concluded a strength of evidence was insufficient in the shorter medium term for this outcome; however, over the long-term studies observed no between group differences at 52 weeks to eight years. So, we concluded the strength of evidence was very low for no difference between groups.

The next outcome is the sciatica index. It includes two subscales, the frequency subscale and the bothersomeness subscale. Similar to other pain measures, pain improved in both groups, and on both subscales. This short to medium term pain improves to 2.1 to 4 points more with surgery through 26 weeks, and we assessed this strength of evidence as low for favoring surgery in the short to medium term. Over the long-term, the within group improvements persist, but no between group differences were observed between 52 weeks and eight years. I do want to note, because it was raised in the public comments on the direct report and in the public comments this morning about the SPORT study. So, this outcome, sciatic index was reported in the SPORT study, and it did find statistically significant difference in one of the two subscales and nearly every long-term follow-up point, which is basically measured every year for eight years; however, the between group difference we found an order

of only about one point, which is less than the minimally important difference.

Christoph Hofstetter: Excuse me. May I interrupt you there? There was a study in spine 2014 that you're referring to? The SPORT 8, the eight-year follow-up trial, the prospective?

Leila Kahwati: Yes.

Christoph Hofstetter: Okay, because they had a 48% cross-over, 48%.

Leila Kahwati: We're going to get to that.

Christoph Hofstetter: Just making that statement.

Leila Kahwati: Yeah. We're going to get to that. So, the between grade difference was about one point, which is less than the MID, and so we concluded that this was not a meaningful difference. We also note that the sciatica index, this particular outcome, was not listed as an A-priority outcome in the clinical trial registry, and the authors only report one of the two subscales. So, that raised our concerns for selective outcome reporting bias, since it was a significant finding.

Moving on to function, as measured by the Oswestry Disability Index, function improves in both groups and improves four to seven to ten points more among patients who received surgery in the short to medium term. So, we assessed the strength of evidence as very low for favoring surgery; however, in the long-term, within group differences persisted, but no between group differences were observed. So, this led us to a very low strength of evidence rating for no difference between groups. Function also improved in both groups, as measured by the Roland-Morris Disability Questionnaire; however, for this particular measure, which was only reported in two studies, the findings were mixed. Thus, we concluded the strength of evidence was insufficient, and only one of those two studies reported long-term findings, and in this study, the within group improvements persisted, but no between group differences were observed through five years. So, we concluded the strength of evidence was insufficient for the Roland-Morris.

Lastly, the SF36 physical functioning scale, this was reported by some studies, and similar to the Oswestry and the Roland, function improves in both groups; however, between group differences in the short and medium term were mixed across the three studies reporting this outcome, resulting in an insufficient strength of evidence rating. In the long-term,

no between group differences were observed at 52 weeks to eight years. So, we rated the strength of evidence as very low for no difference.

So, the other efficacy outcomes other than pain and function included quality of life, neurological symptoms, return to work, and measures of global recovery, and they were re-reported on this slide. So, for quality of life and neurologic symptoms, they generally improved in both groups so that no between group differences were observed at any of the time points reported. Five studies reported an outcome related to return to work. As has already been alluded to, there was a lot of variation in how studies define this measure, how they ascertained it, and overall, we think these measures probably have poor validity. Further complicating this is that there are differences in work culture between U.S. and Europe. So, that makes interpretation difficult. In general, no between group differences were observed for these measures. So, we concluded a very low strength of evidence for no difference between surgery and comparator groups. Lastly, four studies reported measures of global recovery. These were heterogeneous measures. So, we could not do a strength of evidence rating for them, but in general, the measures generally mirrored the pain and functioning outcomes, in terms of favoring surgery in the short and medium term, and no difference between groups in the long-term.

Moving on to safety outcomes, no surgery related deaths were reported, and all-cause mortality was similar between groups in the three studies that actually reported all-cause mortality. Thus, we concluded a low strength of evidence for no difference in all-cause mortality. Six of the seven studies reported adverse events related to surgery in general. These were infrequent. Dural tears were the most commonly reported adverse event. As an example, among the 245 participants in the allocated to surgery in the SPORT trial, 4% had dural tears or spinal leaks, which is the most commonly reported event. Then, reoperation has already been discussed. It is an outcome that was variably measured and reported. When it was reported, the reasons for reoperation were generally recurrent symptoms. Across the five studies that reported this measure, the incidence of reoperations ranged from zero to 10%, and that was over about one to five years of follow-up. Only one study reported on persistent opioid use. It observed no between group differences through 26 weeks. We concluded the evidence was insufficient because of only a single study body of evidence.

Moving onto cost outcomes. There were three studies that reported findings related to cost-effectiveness. The first two studies reported on this slide were analyses that were conducted as part of randomized trials we already included for efficacy and safety. One was from the Netherlands

that compared discectomy to conservative, actually, I think it was microdiscectomy to conservative management. Then, the SPORT trial, which compared discectomy or microdiscectomy to conservative management. The third study was not related to any specific trial, but it did use estimates of effectiveness from various studies, and then it combined it with U.S. cost data inputs to conduct the analysis. The first two studies we evaluated as good quality. The third one we evaluated as fair quality.

In terms of results for this key question, all studies reported higher quality adjusted life years but similar or higher costs for surgery when compared with nonsurgical intervention. So, the mean cost per additional QALY gained from a payer perspective, ranged from about \$51,000 to \$83,000 in 2010 U.S. dollars. Just for some context, the cost per QALY gained for an implantable cardiac defibrillator for preventing sudden cardiac death among people with left ventricular systolic dysfunction is roughly \$38,000 to \$78,000, and the cost per QALY gained for biennial screening mammogram among women is about \$112,000 to \$214,000. So, I provide those numbers so you have some context for how maybe interpret a value like this.

That was the warmup. Now, we're going to talk about the minimally-invasive surgeries. So, these are the comparative effectiveness trials. So, there are 15 trials that compared one surgery to another surgery, and actually one of those trials had three arms. So, there are actually 17 comparisons. Ten studies compared minimally invasive procedure to a microdiscectomy, and these are the studies that are located here in the top of the table. Four studies compared a minimally-invasive procedure to discectomy, and these are located in the middle of the cell. Then, the three studies that compared microdiscectomy to discectomy, these are located here on the bottom of the table. Overall, the patients enrolled in these trials had symptoms consistent with radiculopathy, had nerve root compression confirmed with imaging and had failed some amount of conservative treatment, though the specific duration of conservative treatment was not specified in most studies. The mean duration of symptoms across studies varied from eight to 30 weeks. Two of these studies were conducted in the U.S. The rest were conducted in Europe or Asia. We assessed five of these trials as having high risk of bias, nine of them had some concerns, and one was low risk of bias. Typically, the sources of bias were inadequate randomization or allocation for treatment, high attrition, and lack of participant or clinician blinding. Cross-overs were less of an issue for this set of studies.

First, we'll go through the pain outcomes. So, for the VAS leg pain outcome, among the five studies that reported this measure, pain improved in both surgical groups, and there were no between group differences observed at any short, medium, or long-term follow-up point. We were able to conduct some quantitative synthesis for this outcome at some time point. This is the forest plot here at the bottom. It's based on four studies that reported this outcome between 12 and 26 weeks. As you can see, none of the studies had a between group difference that was above the minimally important difference, and the pooled estimate was 0.3 points in the direction of favoring standard surgery, but you can see the confidence interval goes from -2.2 to 2.9, but still well between the minimally important difference threshold of seven to 11 points. You also note that despite the fact that these are different minimally invasive procedures, the I^2 statistic, which is the measure of the consistency of effect, is 0%, which essentially means no statistical heterogeneity. At two years, a pooled estimate, which is not shown on this slide, also suggested no between group differences. Thus, we assessed the strength of evidence as moderate or no difference between groups to this outcome.

The next is the SF36 bodily pain subscale. Again, we see that pain improves in both groups, and no between group differences are observed in the short, medium, or long-term. The pooled mean difference for this measure at 12 to 26 weeks was close to MID. So, it was three points, again favoring standard surgery, but you can see the confidence intervals are still wide, and they still include the null effect. This estimate, however, did have a moderate degree of heterogeneity, which is quite interesting, because it's essentially three of the same four studies from the earlier meta-analysis, which did not have any heterogeneity. So, it may be something related to this particular measure, and it's sensitivity to change, driving the heterogeneity, since the intervention, the study populations were essentially the same from the prior outcome. So, we assessed the strength of evidence for the SF36 as low in the short term and very low in the medium and long-term for no difference between groups.

Gregory Brown: I'm sorry. Can I interrupt for just a second? I just want to get some clarification, so I understand moving forward. Christoph, I'm wondering if you could, is it tubular discectomy versus percutaneous laser, so which has visualization of the herniation, which does not?

Christoph Hofstetter: I think, again, that's an excellent question, and I think now that I've been here for a little bit, I think I'm starting to understand what we're here for. So, I think that's good. I think it's a very interesting and important question. You know, if you look at the CTP guideline code, percutaneous means a means of indirect decompression, it means that you have a C-arm,

you know, fluoroscopic guidance. You see roughly where your instrument is in relation to the bony structures, but you don't see the neurological structures, like nerve roots and then stuff around it. Percutaneous, per definition, means no visualization. Then, comes a little bit more, like, basically as Dr. Leveque alluded to, the more interesting definitions, which were defined by multiple interests and not so much to do with either surgeries or patient care. There was the differential between direct and indirect visualization. I actually see very few people in here who have direct visualization. Right? I think we are all here only for our patients right now, and I think the real question is going to really be to, even in your slide video of the MIS techniques, I noticed that you had three different technologies there. So, all surgeries that we do as neurosurgeons use indirect visualization, or we have visualization aids, and that includes glasses, contact lenses, microscopes, and endoscopes. Again, I speak as a surgeon here. Then, we have the procedures that are percutaneous, and there is a procedure that is called the mild procedure. In fact, there's some... you might allude to that later on where you basically have a blind... it's, again, it's guided by fluoroscopic guidance, and you try to accomplish the same goal, but the control of what you have done is different, because you don't see the pathology. That's the difference. Then, the intradiscal procedures where you put some enzymes in there or you try to ablate the disc, but you don't see the real pathology or compression of the nerve root. I think what we have to do in order to start talking about this, I think, to define, first of all, what the problem is. I think, now I kind of know what I think we're talking about. So, it's disc herniations and compressions of nerve roots that cause pain but no neurological deficit. Right? When to pull the trigger and if? Then, the second question appears to be, what technology is valid and good for our patients, and what should we support?

Gregory Brown: Could you go back to 29 just for one second? So, let me, I think I'm... let me rephrase my question. So, let's just do the four that are up there, tubular discectomy, do you directly visualize neural structures?

Christoph Hofstetter: So, tubular discectomy, typically it is usually retracted. It is round. It looks like a tube. So, any tube that you have at home, a PVC tube would do, and the reason why we use these is, it retracts the muscle in a very gentle fashion, and typically that's [inaudible] or a microscope. So, it would be indirect visualization.

Male: You are saying something wrong, and I know I shouldn't say this, but...

Christoph Hofstetter: Yeah. You see it. So, sorry, I think, you know, again, the definition of direct visualization means if you're [inaudible] and there's nothing in between [inaudible]. So...

Gregory Brown: Sure.

Christoph Hofstetter: ...like I said before, why don't we cap it out right now and just say visualization versus no visualization of the pathology. Okay.

Gregory Brown: Well, it... right, so.

Christoph Hofstetter: So, the first one is visualization.

Gregory Brown: Neural visualization in tubular discectomy, yes.

Christoph Hofstetter: Yes.

Gregory Brown: Percutaneous laser, just decompression.

Christoph Hofstetter: I would have to look at the study. Some people use endoscopes and use a laser in there. Some of them see the nerve root. What they do in the disc herniation other ones do not see it. So, I would have to look at the study and analyze that study.

Gregory Brown: Okay. So, microendoscopic discectomy would be visualization?

Christoph Hofstetter: Yes.

Gregory Brown: And sequestrectomy is if you are removing a sequestered fragment. Is that?

Christoph Hofstetter: Yes.

Gregory Brown: So, you directly see it?

Christoph Hofstetter: You see it directly, and that's, I know Thome. He's a good friend of mine.

Gregory Brown: Okay. So, the question on the laser is whether or not you're directly looking at the laser or the neural structures.

Christoph Hofstetter: Exactly.

Gregory Brown: As opposed to just doing an intradiscal ablation.

Christoph Hofstetter: Exactly.

Gregory Brown: Okay. Thank you. Sorry to interrupt. I just, I can't move forward if I'm not... thank you.

Leila Kahwati: Alright, I think we were on the sciatic index outcome. Again, for this outcome, pain improves in both groups. No between group differences are observed in the short, medium, or long-term. The pooled mean difference for this measure... I'm sorry. Back up. Sciatica index was reported only by two studies, and the findings essentially mirror the other pain outcomes with improvements in pain in both groups and no between group differences in the short, medium, or long-term. So, we rated this strength of evidence as moderate for no difference.

Moving onto function. Four studies reported function using the Oswestry Disability Index, and similar to the pain outcomes, function improves in both groups, but no between group differences were observed in the medium to long-term. We assessed this evidence as very low for no difference. Three studies used the Roland-Morris Disability Questionnaire. Function improves in both groups again. There were a few between group differences at selected time points. For example, there were some short term differences in the Roland-Morris that were statistically significant in the Brouwer Trial, which is the percutaneous laser disc decompression one that we were just looking at. Those differences were significant at four weeks, favoring minimally-invasive surgery, but not at eight weeks or any other time point reported. Then, there were long term differences in the Roland that were statistically significant favoring standard surgery in the Arts trial, which is that tubular discectomy trial at 52 weeks, but not at any of their other time points reported. So, on the whole, despite a few blips at certain time points, we assessed the strength of evidence as low for no difference in the short term and very low for no difference in the medium and long term.

Finally, four studies reported function with the SF36 physical functioning outcome. For outcomes between 12 and 26 weeks, there were no between group differences. The forest plot at the bottom of this slide shows a pooled estimate, which was 2.4 points more favoring standard surgery, but you can see, again, the confidence interval is somewhat wide and it includes the null effect. This estimate, again, had no statistical heterogeneity despite the fact that different interventions were used here. Thus, we concluded a very low strength of evidence for no difference between groups in the medium term. The findings in the short term and long term were mixed. So, we ended up assigning an insufficient strength of evidence for those two time points.

On this slide are the other efficacy outcomes reported for this comparison. So, quality of life and neurologic symptoms improved in both groups, and no between group differences were observed in the short, medium, or long-term. We assessed the strength of evidence for both outcomes as very low for no difference. Then, six studies reported some kind of return to work measured, and as previously mentioned, this outcome should be interpreted with caution, because it was variably defined, ascertained. Patient participants may, in fact, have been instructed to return to work based on which procedure they received. So, I'm the messenger here. This is what the evidence says. The mean duration of postoperative work disability is lower by 3.4 to 15.2 weeks for a minimally-invasive surgery. So, because of that, we assigned a very low strength of evidence rating favoring minimally-invasive surgery for that outcome.

And then, lastly, most of the studies reported measures of global recovery. These are very heterogeneous measures. We were unable to really pool them and talk about them as sort of one holistic measure. In general, few between group differences were observed, but we did not do a formal strength of evidence rating because of the heterogeneity.

In terms of safety, there were no surgery-related deaths reported by the five studies that specifically reported that outcome. All-cause mortality was similar in the two studies that reported that outcome, and that's why we assessed the strength of evidence as low for no difference. For surgical morbidity, a few studies actually recorded statistical significance testing for differences in adverse events between groups. These were not usually the primary or even secondary study aims. We calculated it when it was possible to do so, and all of that is in the full report with the exception of one study, which I think Dr. Franklin already mentioned. Between group differences were similar for nearly all adverse events reported. The one exception was the Ruetten study, which was, I believe, I have it written down, endoscopic discectomy. It had fewer complications compared to microdiscectomy, but in general, the rest of the pool of the evidence, there were a few between group differences. So, we assessed the evidence as very low for no difference. Then, only one study reported on persistent opioid use. It reported no between group differences, and that was through 26 weeks, but that evidence was rated as insufficient because it was a single study body of evidence.

With respect to reoperations, similar to the previous comparison of surgery versus no surgery, this outcome was variably ascertained and reported by studies in terms of what follow-up time they reported. Across the ten studies, the incidence of reoperations range from as low as 2% in study groups to as high as 64.5%, which was the Chatterjee study that Dr.

Franklin previously described. So, the difference in incidence of reoperations is depicted on the forest plot. So, this is plotting the difference in reoperations between groups. You can see that for all but two studies, Brouwer and Chatterjee, the rest of them hover around zero and have confidence intervals that withstand the null effect. The two studies that found statistical differences favored standard surgery, meaning there was a higher incidence of reoperations in the minimally-invasive groups. When we pooled the difference across all the studies, the incidence was 7% higher for minimally-invasive surgery, but you can see the confidence interval goes to as low as -2% to as high as +17%, and similarly, the pooled relative risk, which was 1.37 also stands the null effect, but this particular analysis had a very high and substantial degree of heterogeneity. So, we conducted sensitivity analysis. We took out the Chatterjee trial. That trial was unique, because it did stop enrolling participants after 71 people had been enrolled, because it became obvious, this is what the study reported, it was obvious to the surgeons involved that it was producing inferior outcomes, and the procedure they used in that study was automated percutaneous lumbar discectomy. So, I believe that would count as no visualization in this scheme we've been discussing lately.

Christoph Hofstetter: That is correct. Yeah.

Leila Kahwati: Okay. So, we took, in that particular study, the reoperation rate in the minimally-invasive group was 64.5%. So, that is the big outlier amongst these studies. So, we took that study out, and we did the pooled estimate, and it still came out to about 2% without Chatterjee. So, 2% higher incidence of reoperation in minimally-invasive surgery groups, but again, the confidence interval goes from -4% to 8%. So, it's still not very precise. So, with or without Chatterjee, the point estimate suggests a higher incidence, but the confidence intervals are not at all precise. They [inaudible]. So, because of the imprecision in this estimate, we ended up concluding the evidence was insufficient to draw an overall conclusion on reoperations.

Moving on to cost outcomes. Three studies reported findings related to cost-effectiveness and one reported only cost. None were conducted in the U.S., and all these cost studies were conducted as part of trials that we also included for efficacy and safety outcomes. So, this was... Arts is the tubular discectomy trial, Brouwer is the percutaneous laser decompression. Chatterjee is the trial we just talked about. Then, Teli is looking at microendoscopic discectomy to open.

Bottom line, overall findings were mixed for this group of studies. One reported higher costs and lower effectiveness. One reported lower costs and lower effectiveness. One reported an unusual measure of an additional cost of 3.5 thousand per successful outcome compared to standard surgery. Then, the last study only reported cost. This study was conducted in Italy, reported a higher cost of \$722. We converted all the values in the original studies to 2010 U.S. dollars just for comparison. So, overall, these are mixed findings. We've concluded the evidence was insufficient to draw a conclusion.

Second to last comparison. So, now, we're looking at microdiscectomy versus discectomy. So, these are one open procedure compared to another open procedure. There were only three studies for this comparison. So, many of the outcomes were rated as insufficient evidence, because they ended up being based on a single study body of evidence. In terms of pain, so VAS leg or back pain, no between group differences were observed in the one study that reported this measure in the short term, and then two studies observed no between group differences in the medium to long term. For function, only one study reported outcomes that used the Oswestry Disability Index and found no between group differences in the medium to long-term. Again, single study body of evidence, so the strength of evidence is insufficient. Quality of life only one study provided evidence. There were no between group differences from 26 weeks through two years. Then, return to work, again, only one study. There was a similar duration of postoperative disability, 10.4 versus 10.1 weeks. Again, single study body of evidence so insufficient strength of evidence rating.

In terms of safety for this comparison, there were no surgery related deaths in any of the studies. Surgical morbidity was similar between groups. The incidence of reoperations for this comparison in the two studies that reported was 3.3 to 4% across the four individual study groups, and there were no between group differences. Then, no studies reported persistent opioid use for this comparison.

The last comparison, and this is related to efficacy question two, so looking at specific populations, we identified two studies looking at the effectiveness of repeat surgery on patients with recurrent symptoms, and we only identified two studies. The first compared repeat lumbosacral decompression to spinal cord stimulation. This study reported similar function, disability, and return to work outcomes. The incidence of reoperations was zero in the surgery and three subjects in the spinal cord stimulation group had to undergo reimplantation of the simulator. Patients undergoing spinal cord stimulation had a higher percent use of

stable or decreased opioid use compared to patients who had undergone surgery, and that was a significant difference. The other study compared revision endoscopic discectomy to revision microdiscectomy. This study reported similar improvements in pain, function, and neurologic symptoms. Few complications were reported for endoscopic discectomy, and a shorter return to work was also reported, four weeks versus seven weeks. The incidence of reoperations was similar between groups. Because both comparisons only had single study body of evidence, we rated all of the outcomes as insufficient strength of evidence.

Mika Sinanan: Sorry. Before you get into the clinical practice guidelines, Christoph, assuming you have a surgeon who could do... could you go back three slides? Actually go forward. Microdiscectomy versus endoscopic discectomy versus discectomy. What's the... could you just describe OR time and length of stay for those three?

Christoph Hofstetter: Thank you, so much. That is a great question. Actually, it would have been perfect... I have some slides. I don't know if you have time. I think that showing just one picture, I think, would explain everything. I don't know. Do you have time for that, or just, you know? I really feel that it would be nice to sort of see what we're talking about, but basically, the difference is, I want to pull up, before we talk about that, again, I was in Singapore with the biggest spine organization that we have, the AO, and we defined what minimally-invasive means. Okay, just so we're all talking about the same thing. We said the consensus statement of the AO of the world's spine organizations, minimally-invasive is a [inaudible] of technology dependent techniques and procedures that reduces local operative tissue damage and systemic surgical stress, enabling earlier return to function, striving to better outcomes than traditional technique. Minimally-invasive surgery, the traditional surgery of today was minimally-invasive surgery of 15 years ago. I think one thing of all this discussion, it puts the U.S. backwards if you really badmouth everything that is new. I think it's coming from... going back to China in a couple weeks and teaching these courses, the U.S. is far behind in terms of surgical treatment and technology. So, open surgery is standard retractors. You typically have to filet off the muscles to get to your target and use your retractors. Then, the surgery for discectomy, you retrieve the sequester, that means expelled disc fragment, or if it's still contained, then you sometimes decompress. Now, the rate of reherniation can be either zero or 7%. It depends on the surgeon. I can get you a zero percent reherniation rate guaranteed if I take the entire disk out. Any technology that allows visualization, we don't do that anymore for obvious reasons. So, the reherniation rate depends on how aggressive the surgeon wants to be and with young patients, often you have a discussion. So, the surgery part of

all surgeries that allow visualization is the same. Now, again, I think that's the difference. So, like Trent sort of explained, an open minimally-invasive and endoscopic surgery with direct visualization is the same surgery. Now, then we come to different surgery that is intradiscal percutaneous procedures where you try to shrink the nerve and indirectly pull back some [inaudible] fragments away from the nerve. There, you have less control what you do and also the study with 57% recurrent rate, because you don't see what you do. So, they work in some cases, but you obviously, that's again, for me as a surgeon, I wouldn't consider that as a surgical procedure if you don't see what you do. At the University of Washington, we have very, very well defined what we see, because if we don't see what we're doing, we cannot teach fellows and residents what to do. Anyhow, so that's the main difference, I think that we're talking about.

Gregory Brown: Then I can make a suggestion?

Mika Sinanan: So, length of surgery and length of stay for those three?

Christoph Hofstetter: So, we're publishing a paper right now. So, endoscopic discectomy is again, all of discectomy is done at the University of Washington for the last three years endoscopic. Most people go home, if they're not there, no medical comorbidities go home before I start my second case. Mika...

Mika Sinanan: But it's outpatient procedure?

Christoph Hofstetter: ...yeah.

Mika Sinanan: No length of stay? And how long in the operating room?

Christoph Hofstetter: Depends. I mean, it's a straightforward...

Mika Sinanan: Average?

Christoph Hofstetter: ...an hour.

Mika Sinanan: Okay.

Christoph Hofstetter: Surgical time, and MIS is very similar. It's a tube. It's just a microscope. Again, the same approach typically. I would say that...

Mika Sinanan: It's also outpatient?

Christoph Hofstetter: Typically, they leave the next morning or...

Mika Sinanan: Okay. So, one day?

Christoph Hofstetter: ...you know, again, like [inaudible], the same or again, the difference is very, very minimal. It's all outpatient.

Mika Sinanan: One hour?

Christoph Hofstetter: The same time, an hour roughly.

Mika Sinanan: And open discectomy?

Christoph Hofstetter: I would say with open, the patient stays at least overnight.

Mika Sinanan: And how long in the operating room?

Christoph Hofstetter: Surgical time may be a little bit shorter, 30 minutes. Again, we, as neurosurgeons try, like, what do you think, I mean, Tracy?

Male: [Unable to hear what he's saying.]

Gregory Brown: I'm going to, sorry Dr. Tredway. I'm going to interrupt for a second. So, I'm going to jump to the end game for a second to see if this can keep us moving forward, 'cuz we're bogging down. That is, I'm going to propose that we don't use minimally-invasive in our recommendation. I think we're going to, I'm going to recommend we look at visualization versus no-visualization. So, then, we don't have to worry about all these definitions. So, whether you're visualizing with an endoscope, with a tube, with microscope loops, direct visualization, we don't have to define all that. So we will look at visualization versus no visualization and then that hopefully won't bog us down quite so much here. Is that...

Leila Kahwati: I'm having a lot of fun, so.

Gregory Brown: Well, so let's keep going. I think we're running a little behind. So, okay. Thanks.

Leila Kahwati: Alright. So, moving on now to the synthesis of the clinical practice guidelines. We identified 14 guidelines or interventional procedure-guidance documents. They are detailed in the full report. For the sake of time, I'm only going to talk about the three that are the top of the list. These were the ones that we rated as the highest quality. I would like to mention the instrument we used to assess guideline quality is largely focused on the quality of the process used to create the guideline. It's less

focused on whether the evidence was interpreted correctly or graded appropriately.

So, first, this guideline is from the National Institute for Health and Care Excellence from the U.K. It's known as NICE. It's the most recent guideline on this topic. It's from 2016. This guideline says to consider spinal decompression for sciatica, and they list the specific decompressive procedures when nonsurgical treatment has not improved pain or function, and the radiologic findings are consistent with sciatica symptoms. This guideline was based on a review of the evidence and used the GRADE approach to evaluate the strength of evidence. In this guideline, all of the outcomes they've looked at were nearly all rated as low or very low. So, very similar to our strength of evidence ratings. This recommendation was based on nine trials. One of those trials did include patients with sciatica or central spinal stenosis, and it also included four cohort studies that compared decompression to fusion or conservative management. This particular guideline did not evaluate the comparative effectiveness of various decompression methods, and it doesn't say it was completely silent on minimally invasive procedures. They have a statement in the guideline that they suggest the comparative effectiveness of procedures, the choice of procedures should be 'suggest that this be determined by the individual surgeon and clinical appropriateness.

The next guideline is from the North American Spine Society. It's from 2012. This guideline is quite detailed. It did not... it uses an alternative to GRADE to evaluate the strength of evidence and the strength of recommendations. The full report has the details from the guideline. We've excerpted the most relevant recommendations from the guideline into the full report. Then, I've had it further summarized here that you can get them on a slide. As noted, this guideline was posted in 2012, and it didn't indicate the date of the search for the literature that it cites. So, we're not exactly sure how up to date it is. It was published in 2012, but the studies in it may have only been through 2011. This guideline does recommend discectomy for patients whose symptoms are severe enough to warrant surgery and states that earlier surgery is associated with faster recovery, and this is based on what, in their rating scheme, there is grade B evidence, which is lesser quality randomized trials, prospective cohort studies, or case control and retrospective cohort studies. So, several of the initial recommendations that are on this slide all relate to basically standard open surgical decompression procedures and timing related to it. The last three are related to these minimally-invasive procedures, and you can see the language that's used for these recommendations is a little less certain language.

Christoph Hofstetter: A little interruption. The third of the endoscopic automated is non-visualization. The next one is non-visualization automatic percutaneous.

Leila Kahwati: Mm-hmm.

Christoph Hofstetter: And then, the last one is visualization.

Leila Kahwati: So, these are all based on, you can see grade C evidence, which includes case series. So, it's a lower level of evidence for the minimally-invasive procedures. Then, they actually... there was only one study, so they rated the evidence as insufficient for tubular discectomy.

Kevin Walsh: Can I ask one question? What does interventional care mean? It says medical/interventional care?

Leila Kahwati: So, basically, I think, like, epidural steroid injections or anything that would technically not be called surgery.

The last guideline is from 2009 from the American Pain Society. It recommends open discectomy or microdiscectomy for radiculopathy, and this was based on four trials. They used an approach the evidence based on the U.S. Preventative Services Taskforce. So, this what they called a level B, which means it's something clinicians should consider offering to eligible patients based on pure evidence. It found the evidence insufficient for comparing alternative surgical procedures. Again, it's from 2009. So, the literature search probably only went through 2008 or 2009. So, some of the more recent studies on the minimally-invasive surgery would not have been available at the time of this guideline.

So, to summarize the guidelines, all three do have a recommendation for at least standard open surgery to treat symptomatic radiculopathy based on evidence of short to medium term benefit. They are mixed with respect to minimally invasive surgery. So, those surgeries won't in the scope of the NICE guideline. There were some specific recommendations related to them for the North American Spine Society guideline, and then the American Pain society rated the evidence as insufficient for those surgeries.

So, those were the main findings from the primary research synthesis, and this last part of the presentation, I'm going to do three things; briefly summarize the evidence, because I know it was a lot of outcomes, a lot of comparisons, then I'm going to spend a little time talking about the key limitations of the evidence base, and then we'll go through the existing

peer coverage policies, but I think we can do that quickly, 'cuz I think Dr. Franklin already showed a slide on those.

So, this is the evidence map that summarizes the treatment effect of surgery compared to nonsurgery across of the outcomes we evaluated. So, to create this, we looked across all the strength of evidence ratings for each domain, pain, [inaudible], etc., and so we placed the symbol somewhere along the X-axis here to indicate the treatment effect. So, either favoring nonsurgery, no difference, favoring surgery, or unable to determine. So, the strength of evidence itself is indicated by the color of the symbol. So, red is very low. Orange is low, and we don't have any moderate or high certainty evidence in this comparison. Then, the timing of follow-up is indicated by the shape of the symbol. So, the rectangle is short and medium term follow-up. The diamond is long-term follow-up. So, what you can see there is there's a total of seven studies that contributed to this comparison, but not all contributed to each domain. As you can see from the map, except for short-term pain outcomes, there is pretty much low certainty that surgery improves pain more. Everything else is basically no difference between groups with either very low or low certainty, and that's... for safety, we only included all-cause mortality and persistent opiate use because morbidity, reoperations, and surgical morbidity don't really make sense for a nonsurgical comparative group.

So, this is the evidence map for minimally-invasive surgery compared with standard surgery. Again, you can see for merely all outcomes, there is anywhere from very low to moderate certainty that there is no difference between procedures. As we previously discussed the return to work outcome, I did indicate the minimally-invasive surgery may improve return to work outcomes, or at least return to work sooner, although we talked about some of the issues related to the validity of that measure. For safety outcomes, there is low to very low certainty, but there is no difference in mortality or morbidity, and the evidence was insufficient regarding reoperations and persistent opioid use.

Lastly, for microdiscectomy compared to discectomy, the evidence is largely insufficient for most outcomes, because of the single study body of evidence. For pain, surgical morbidity, and reoperations, the evidence was very low that there's no difference between groups.

So, this slide, it has highlights of the limitations of the evidence base for the studies that were included. The first two reasons listed here are essentially the main reason why most of the strength of evidence ratings were assessed as very low or low. Recall with the GRADE approach an evidence based trial starts at high and then gets downgraded by one or

two levels depending on the degree of concerns in the domains we assess. With respect to risk of bias, nearly half of the studies we included were rated at the high risk of bias for multiple reasons. Some sources of bias were common across studies. All but one study did not blind participants and clinicians. Most did not blind outcome assessors. Although blinding can be challenging and very challenging in trials, it's still, nonetheless, a source of bias. In studies of surgery versus nonsurgery, crossovers were a major issue and was the main reason why most of those studies that had extensive crossovers ended up getting rated as high risk of bias. In studies with extensive crossovers, the intent to treat analysis, which is what we generally use for evidence synthesis, the effect estimate is likely to be bias and is likely to underestimate the true treatment effect. For example, in the SPORT trial, 46% of participants that were allocated to surgery had not received surgery by six months follow-up. So, nearly half the people allocated surgery did not get surgery at six-month follow-up point, and 40% still had not received surgery by eight years. So, all the outcomes that are being measured on the surgery group really only represents maybe as much as two-thirds of that group actually receiving surgery. Similarly, in the group allocated to conservative management, 36% of those participants had received surgery by six months, and 48%, or nearly half, had received surgery by eight years. So, basically, the two group are no longer distinct. There is a lot of contamination, and what that does is, it biases the treatment effect towards the null. Now, some people say, well just use the as-treated analysis, in which you analyze people to the treatment they actually received, and the SPORT trial does report as-treated analysis and as you would not be surprised to find, the treatment effects favor surgery through even two years of follow-up, and those between-group differences are larger than what was reported in the intent to treat analyses. However, just entirely relying on as-treated analyses introduces a different kind of bias into the estimate, since crossovers do not occur at random. So, you're essentially turning a trial into an observational study when you use as-treated analyses. That's my soap box. For studies reporting longer-term outcomes, high attrition was also [inaudible]. For example, in the Arts trial, that's the tubular discectomy trial, it lost nearly 40% of the randomized participants to follow up by five years, which is the study Dr. Franklin also had mentioned. So, that's the big limitation. Another limitation in this body of evidence is that studies were generally underpowered for many of the outcomes of interest. Only eleven of the 24 included trials designated a primary outcome and described the required sample size required to detect an A-priority effect size. Few described how they determined the effect size or whether they were represented a minimally important difference, and did not describe whether the study was powered for superiority, noninferiority, or [inaudible], which matters to the sample size that you need. Eight of the

eleven studies were powered on pain and function outcomes. Three were powered based on duration of surgery or hospital stay. One was powered on a difference in success. The bottom line of this is that many of the outcomes that we report, that we took and reported here, the sample sizes may have not been sufficient to offer a precise estimate. So, many of the strength of evidence ratings ended up getting downgraded because of imprecision around the estimates.

Real quick, most studies required participants to have a clinical diagnosis of radiculopathy with disc herniation and nerve root compression confirmed with imaging, but beyond that, the inclusion and exclusion criteria varied across study, including the duration of symptoms and/or how much conservative therapy they received prior to enrollment. I think this one we, I think, talked a lot about, the limited number of studies for any single minimally-invasive procedure. Although there were 15 trials, the variation in the nomenclature that's used, we extract as much detail as is provided for those studies, and it's in the appendix D1 or 2? D1. If there is a concern of wanting to look what the specific procedure is, but our sense was, from the way things remained, some of them were probably the same thing, maybe just named a little bit differently, or some things that were named the same may have actually represented different procedures. It was very challenging to tell from the reports of the studies. As a result, we ended up treating this procedure as a class [inaudible], which I know may make the policy decisions more difficult, but we do have all the individual studies and the details available if you decided you wanted to make a procedure specific policy.

Because of the time, I'm not going to talk about the last four limitations, but they are detailed in the full report.

Dr. Franklin, I think, already shared this slide. So, CMS does not have a national coverage determination related to standard open or microsurgical procedures. They do have a noncoverage determination related to laser and thermal intradiscal procedures, which I think Dr. Hofstetter had mentioned before. This particular group of procedures, CMS includes percutaneous disc decompression within that class of procedures. So, that is noncovered by CMS. Some, but not all, private payers have a policy related to this kind of surgery. Specific criteria varies by payer, but those that do cover decompressive surgery generally require failed conservative treatment for between six to twelve weeks, and most require imaging confirmation of nerve root compression that correlates to symptoms.

Okay. We're in the home stretch. Quick couple of limitations about our review. We're limited to English language articles only, and we only

included efficacy outcomes reported at four weeks or later. So, why that matters is because if you are judging a procedure on whether it's a shorter hospital stay or a shorter operating time, we don't have those kind of outcomes here to guide decisions based on those sort of outcomes. We excluded observational studies and the as-treated analyses from the formal part of the analysis, and this may offer only a limited perspective, particular around safety outcomes, since trials may not be representative of the community practice. A couple limitations related to our process. The search is limited to three databases and for efficiency, we used a single reviewer to screen titles and abstracts. However, we conducted extensive hand searches, and given, I think, that we identified more studies than in any of the clinical guidelines, we are confident that we didn't miss any relevant studies that would have been eligible. Then, lastly, I think we talked about this already, the grouping of the minimally-invasive surgeries and again, as you think about a policy, you may choose to group them in different ways, which is perfectly, obviously, legitimate.

Okay. I think that's it. So, in summary, surgery reduces pain more compared to nonsurgical interventions that follow up to 26 weeks, but these findings don't persist at one year or longer. There is no differences in function disability in the long-term, quality of life in the short to medium term, neurologic symptoms, or return to work, but the evidence is insufficient for quality of life in the long-term, function and disability in short to medium term and persistent opioid use. Minimally-invasive surgery is comparable to microdiscectomy and discectomy for nearly all efficacy and safety outcomes, but the evidence is insufficient for reoperations and persistent opioid use. Then, microdiscectomy and discectomy are comparable with respect to pain, surgical morbidity, reoperations, the evidence insufficient for everything else. Finally, the evidence is insufficient for repeat surgery among individuals with recurrent radiculopathy. I can't remember if I mentioned this before, but we didn't actually identify any studies solely on people on work disability. So, we only were able to address one of the two populations for efficacy question two, and that's it. So, I'm happy to take any questions or, I don't know, Josh. Do you want me to stay up here for a bit and then?

Gregory Brown: We're a little over. So, we're about 15 minutes past our break. How about we do a ten-minute break. Then, just something to think about as a group, maybe when we want to discuss it is, hearing from our public comments and our expert if we want to kind of remove the minimally-invasive from our discussion and even from our expert... or not our expert, but from Dr. Franklin that the medical directors and the Health Care Authority are not looking at discectomy or microdiscectomy for decompression for herniated discs. It's more the newer technologies. So, if we want to not

rehash whether it's effective, a discectomy is effective or not. So, we can just move forward on the new technologies. We got a ten-minute break. I have 10:18. How about 12 minutes, 10:30 we'll resume.

So, I heard some concerns from some of our committee members, as to where we're going. Now, I'm missing, there we go. If I could ask you to bring up table 35.

Leila Kahwati: Table 35?

Gregory Brown: Not table, slide 35. Sorry. That's correct. So, the concerns I heard from other committee members is that the evidence isn't granular enough to look at individual procedures. I think there's also, probably intentionally, confusion over marketing issues and what's minimally-invasive in there. So, that's why during some of the discussion, I'm trying to formulate it how I think about things and if this works for the rest of the committee, great. If it doesn't, then we'll regroup and try and find out what works for everybody. Again, to me, it's whether you have visualization of the disc that you're taking out versus not having it. To me, the most compelling slide, if I understand correctly, is this one, and the two studies, Brouwer and Chatterjee, those do not have direct visualization of the disc is my understanding. So, I will use the term, and I use it hesitantly of indirect decompression in the sense you are removing nucleus. You hope that that reduces the bulge or whatever, but you never visualization the actual herniation. So, to me, if you break out then, all the others have visualization, again, direct or indirect is... but optical visualization, how about that, eyeballs, loops, microscope, endoscope. So, if we reparse this meta-analysis of those with optical visualization versus no visualization, it would be everything, except Brouwer and Chatterjee. Is that correct?

Leila Kahwati: I believe so, although...

Gregory Brown: Okay.

Leila Kahwati: ...there... so, for example, this one, percutaneous endoscopic discectomy, to me, that's...

Gregory Brown: Sure.

Leila Kahwati: ...a little...

Gregory Brown: Again, that's why marketing and terms but the, an endoscope is a device with... it's a magnifying... same thing we use an arthroscope or endoscopy

for general surgery or any other surgical specialty. So, again, it's optical visualization. So...

Sheila Rege: I would say direct optical visualization.

Gregory Brown: Well, again, is a microscope direct? That's what I say, just some sort of optical visualization. Anyway, I just want to get comments from the rest of the committee. I've been talking a lot and others have not. Is this construct or approach... does this make sense to people? Does this help address some of the concerns?

John Bramhall: I'm not sure that it does. It seems it's semantic separation rather than a medical or biological one. The reason I say that is that I'm involved in cases where I work of visualization of tumors, intracranial tumors where this navigation equipment is used. We wouldn't classify that as visualization and yet, I'd like to believe that it's a superior way of demonstrating anatomically where a tumor is. We do percutaneous instrumentation on the spine, which doesn't involve necessarily all the time direct visualization with the eye, but it involves other ways of manifesting the structure. So...

Christoph Hofstetter: John, to that very point, I thought about it, but I didn't want to convolute this meeting any more. So, using percutaneous instrumentation to decompress or stabilize again is not direct decompression. This whole meeting is about direct decompression of neural structures, and can you meaningfully do direct decompression without seeing it. And I would, as a surgeon and as a teacher, I would say no.

Gregory Brown: I'm sorry. So, Dr. Hofstetter, we need some discussion amongst the committee. I appreciate your input, but right now, I want to, this is how we move forward, not the technical questions. So, if we could limit our conversations to the committee. I guess I share that same point. I'm not saying, today we're talking about... I think first of all, the title was misleading and concerning to spine surgeons, because it's any radiculopathy, but Dr. Franklin's presentation was very focused, essentially, on disc herniations. So, if we are going to make our coverage determination regarding not all radiculopathy but just for radiculopathy from disc herniations, that's my understanding of your intent. Is that correct, Dr. Franklin? Yeah? So, he's shaking his head yes. So, that changes the scope. Then, in terms of I agree with you in terms of do we need to visualize everything in every operation, the answer is absolutely not, but in this specific instance for herniated nuclear discs, if you aren't visualizing a disc, how you can know that you've decompressed it. So, I think that, to me, is the fundamental question here. I think this

meta-analysis supports that if we parse it slightly differently. So, that's what I'm trying to get at. Dr. Franklin?

Gary Franklin: Well, the problem is there were nine different devices and 14 or 15 studies. So, each of the devices had one or two studies. None of these actually described very, in great detail, this visualization point. So, we don't really know exactly how much is being seen or not seen in these studies. I was trying to differentiate between the level of the evidence and the quality of the evidence, and the reoperation rate in some of the studies among differentiating the open procedures from the nonopen procedures. I'm not sure that there's enough evidence to even get to, is it visualized or how much is it visualized? Is it indirect or direct? I agree that it's kind of... in a way it's somewhat semantic, but the open procedures are open, but these other procedures are not, so.

Christoph Hofstetter: Excuse me, very respectfully, very respectfully, again I totally agree. We are talking right now about can you see the pathology and open versus closed. For example, again, since five years from now, we have done not a single surgery of discectomy at the neurosurgical department at the University of Washington not being on the water. Is it open? Are you open on the water or not? You do everything under irrigation, and we have had zero infections, and I can give you thousands of my colleagues worldwide that reduce the risk of complication. So, I think, open or not, again, it's semantics. There's a lot of devices. I agree with you, and I think we have to pull together for our patients to get the outcomes we claim that we get, but I think it's... again, it's not about the tool, it's about the fool behind the tool that you're talking right now. That's us, and the surgeons sitting over there, and we have to do the right thing. So, I really disagree with that, also which is... we had talked about the tool is not... it doesn't matter. It doesn't matter, and open versus... it's just mingled with...

Sheila Rege: I would... this is Sheila Rege. So, if we were to follow Dr. Brown's thought of visualization, can you comment how that would change, because we're still in the presentation and asking the... how that would change your data?

Leila Kahwati: This particular analysis?

Sheila Rege: Well, it sounds like effica-, more for efficacy. Safety, I don't think is...

Leila Kahwati; Yeah.

Sheila Rege: ...a question, so.

Leila Kahwati: I think this would be the main outcome that would change it, and I'm just eyeballing it. If we were, so we've already dropped Chatterjee here. If we were also to drop Brouwer, then we would probably be down to a relative risk closer to one. So, without Chatterjee, it's 1.17. If we drop Brouwer, which again, favors [inaudible], we'd be closer to 1. There would be essentially no difference in reoperation rates, and our confidence interval might be a little bit narrower, but it probably is going to still include the null effect. So, for the other outcomes, I would have to look at our details. Brouwer generally, I don't want to say anything that's not correct, but there, there was one or two outcomes at certain time points that were statistically significant, but in general, I don't think dropping Brouwer or Chatterjee out of any of the other outcomes is going to fundamentally change my mind of no difference. Rachel, do you have the Brouwer details in front of you?

Seth Schwartz: So, this is Seth. I'm also a surgeon. I'm sort of struggling with this a little bit, because I think what we're seeing is that there's fairly convincing data that decompressing the disc helps with pain in the first six months after that, and that's not really up for debate. There are numerous different ways to do that. We're not really seeing any differences between those, because there shouldn't really be any differences between those and the kind of outcomes that we're looking at. The differences I'm thinking about here are, so with the Chatterjee and the Brouwer paper is, you're not talking about decompressing the disc by actually removing tissue. You're using a different technology. So, you're using radiofrequency or whatever to try to shrink the tissue. So, I'm trying to think about this differently, which is, are we doing surgery to perform a discectomy of some kind, or are we using some other technology to shrink the disc? If you look at it in those terms and what we're seeing up here, the two studies that really use a different technology, other than decompressing a disk surgically but using something else to shrink it, has a significantly higher reoperation rate. Beyond that, we're not really seeing any differences in any of this stuff. We don't... so, we have basically two studies looking at different technology that is not surgery, and it doesn't look as good. Everything else is the same, and it should be the same. So, the fact that we're not seeing a difference is what we would expect to see, because all these things are doing the same thing. So, I don't know how you differentiate that. I mean, so percutaneous versus whatever. I mean, are you doing surgery to remove part of the disc, or are you not doing surgery to remove part of the disc is the only difference that I'm seeing in any of the data that we're looking at. So, visualization versus non-visualization whatever. I mean, it's really... that's almost not the question. It's really... it's what are we actually physically doing?

Gregory Brown: I think that's exactly how I'm viewing it. My concern is that if you say surgery and you, instead of doing it as an outpatient, you take somebody to the operating room and under fluoroscopic guidance put a probe to suck out the nucleus of the disc without ever looking at the protrusion, then you don't know if you've decompressed it or not. So, using the term surgery to mean... to me the thing that [crosstalk] different is, are you looking... I mean, I agree with you. If you indirectly decompress the disc, you should get the same result as direct decompression. The difference is, the indirect techniques, you don't know you've decompressed it. You're assuming you have with the visualization... optical visualization techniques, you're visually seeing that you've decompressed it. I mean, it...

Seth Schwartz: And I'm struggling with this next statement, as a surgeon, but so what? Right? I mean, if they both work, who cares? I mean, whether I see it or not...

Gregory Brown: The difference in reoperation rate says that they aren't the same, because the indirect ones, you have to go back a lot more.

Seth Schwartz: So, that's exactly... they may not be doing what they say that they're trying to do, but that's not, that doesn't... but if it technically worked, then who cares? So, in other words, we're kind of using the reverse, which is, it doesn't work. So, we're trying to sort out why... which, the ones that don't work, we're trying to go backwards and look at why they don't work, and you can justify it, as a surgeon, and say well, because you didn't see it. Well, that may be exactly the case, but we don't actually know. All we know is, it didn't work, as well. So, I guess I'm just struggling with... are we using our own... I guess, are we kind of ignoring the data and just trying to rationalize it rather than actually looking at what the data says? And if we, if we actually kind of forget about all, I mean, not that it doesn't make a lot of sense. Again, I'm sort of struggling with this, given that I am a surgeon, but I think what we need to try and do is understand the data, and then does the data give us some level of granularity to be able to answer this question. And if we look at the data, the only thing we're seeing here is that there are two papers that showed a high reoperation rate. Everything else is the same. So, maybe we need to dig into those two papers and find out what's different about what happened in those two papers versus everything else.

Tony Yen: So, for me, the question is really do these minimally-invasive techniques, are they superior or any better than microdiscectomy? I think that's how I'm trying to interpret the literature, and please let me know if I should be looking at it in any different sort of way. From what I can see, at least from the literature that we have available, that our vendor has presented to us

and actually looking at a more detailed report doesn't seem to be much of a difference in terms of outcomes. So, that's really what I'm trying to drive at is, I think we're trying to evaluate whether or not these minimally-invasive techniques. So, we can throw out the Chatterjee paper and the Brouwer paper out of it. I'm fine with that, but if we look at the minimally-invasive techniques as a whole, are these better than microdiscectomy? It doesn't seem like it is.

Christoph Hofstetter: Do you mind if I say one thing, a little thing?

Gregory Brown: Sure.

Tony Yen: Tony, I think that's a great question, and I recently gave a talk about that. I think the two factors to consider, first of all, from the scope that [inaudible] we talked about before, which I'm a member to, uh, from the SCOAP group, we know that the more invasive the procedure, the more complications you have, period. Very good data published a couple papers on that. The SCOAP group from the state of Washington, the more invasive procedure, the more morbidity, the more complications. Well-established from discectomy up to a deformity correction, which I did yesterday. The more invasive, the more complications. Number two, if you look at this procedure, we do different type of surgical procedures. Obviously, the difference in a very low complexity procedure like a discectomy, which is the easiest procedure we do, the difference between using a less invasive method is not going to be very big, right? So, you need thousands of patients and Dr. Tredway quoted a study from [inaudible] that looked at 5,000 patients and showed that the infection rate was lower. Guess what? We have never had an infection with an endoscopic discectomy at the University of Washington in the last five years, because we do this. I would need 10,000 patients to show that, because Dr. Tredway does it with a tube and calls it micro, it's going to have one out of 5,000. You know, the differences are so minute. So, are you going to be able to show it or not? That's why I showed the definition of minimally-invasive surgery. Being a minimally-invasive surgeon according to the new definition that we defined for the world in Singapore a couple weeks ago means you do less collateral damage and less systemic stress. Every surgeon wants to be a minimally-invasive surgeon.

Tony Yen: And I totally understand that. I agree. I can see how less invasive surgeries would result in less trauma, less infections, etc., but what I'm also looking at is, what I'm trying to focus in though here is, what is the evidence here that we have available in front of you, which [inaudible].

Christoph Hofstetter: You can't see the discectomy level. You can see, I can show you hundreds of cases and stuff. It's very convincing that using newer technology really saves patients from big fusion surgeries, from revision surgeries, and other stuff. We have to think bigger than, again, you're not going to be able to demonstrate it with the numbers that we can realistically get. I mean, you would need 10,000...

Kevin Walsh: With due respect, Dr. Hofstetter, the charge here is to make a decision based on the evidence we were given. I...

Christoph Hofstetter: There's enough evidence that decreasing the invasive mess...

Kevin Walsh: I would...

Christoph Hofstetter: ...is beneficial to patients. There's enough evidence on that.

Kevin Walsh: ...well, in your opinion, and I respect that.

Christoph Hofstetter: No. The SCOAP data, there's literature out there that...

Kevin Walsh: Thank you.

Gregory Brown: Dr. Hofstetter, please.

Kevin Walsh: We really need to respect the constraints that we were given by the State legislature, which is, look at the evidence, make a decision, and I would just ask that we remain faithful to that.

Gregory Brown: So, did we pull those two articles just to take a look at them?

Leila Kahwati: Right there.

Gregory Brown: Okay.

Carson Odegard: I had one quick question for Dr. Hofstetter. So, the only difference between, like, a tubular procedure and endoscopic procedure is just basically the retractors, right? It's less risk of...

Christoph Hofstetter: It's a smaller working corridor between open, minimally-invasive, and endoscopic. The working corridor gets smaller and smaller. That allows you to preserve the joint and the ligaments. And so, the hope is that it destabilizes the spine less and there is good data, scientific evidence for that.

Carson Odegard: So, can you give us an idea of the utilization of these different procedures, not as a group but just... is it a regional thing? Is it a global thing? What, what are they doing in other countries. I mean, is it just specific to the patient, and these things are done every day equally?

Christoph Hofstetter: So, in Germany, like, minimally-invasive and endoscopic surgery is 15%. South Korea is 65%. The U.S. 2%. We have the highest rate of arthrodesis surgery in the U.S.

Carson Odegard: 2% in the U.S.?

Christoph Hofstetter: 2% endoscopic. Then minimally-invasive surgery is roughly 15%. Again, that's kind of just, like, in the degrees of size. There's just no incentive to do the right thing for the patients in this country.

Mika Sinanan: Why is that? What do you mean there's no incentive? Financial incentive? Money?

Christoph Hofstetter: Of course. It's all money.

Mika Sinanan: No. It's not, but that's what you were alluding to, money?

Christoph Hofstetter: Yeah, because if you look at it, you need better technology to get a better outcome, and you spend more time... if I do an open discectomy, it takes 30 minutes. If I do endoscopic, it takes a little bit more time, because it's more thorough and more difficult. You need more training, but again, I think if the literature is very complex, because it's just very difficult to put together, but all over that's the trend.

John Bramhall: Do I have time? I'm curious the... this 20-year-old paper, the Chatterjee, it's 20 years old, right, '95. So, it's very old. What was the method of automation? That's the word that crops up in there. What were they automating?

Leila Kahwati: I believe it was mechanical, but Rachel can check. It was a nuclear tone made by surgical dynamics.

Christoph Hofstetter: Nobody does that.

Kevin Walsh: It doesn't matter that nobody does it. The reality is that the people who do it haven't bothered to generate data to help us make a decision. That's the reality.

Gregory Brown: So, just so I'm... I've got it in front of me, and I'm trying to see a description, and I don't see one. So, it's a mechanical...

Leila Kahwati: Are you looking at Chatterjee now?

Gregory Brown: Yeah. It's a mechanical removal of the nucleus but not of an individual herniation. Is that...

Leila Kahwati: So...

John Bramhall: Because we're thinking of eliminating that study, right?

Leila Kahwati: Read the description, yeah. I can read the [inaudible] intervention description. It states procedure was performed with an automated suction nucleosome under local anesthesia. It was necessary to achieve the position to center before disc aspiration was continued until no more nuclear material could be obtained.

Gregory Brown: It's like an arthroscopic shaver basically. Yeah. So, and then Brouwer, he says one of the minimally-invasive techniques is percutaneous laser disc decompression, which is based on the principal of decreasing the intradiscal pressure by applying laser induced heat to the nucleus pulposus. So, in other words, it's just ablating the nucleus but not going after the specific herniation. So, again, on was it 39 or 29. I can't remember, but those two procedures were the ones that are, like I said, indirect, just doing something on the nucleus without that. I heard what you said, Kevin. I guess, the... I mean you can look in virtually all aspects of surgery, general surgery progressing from open cholecystectomies, orthopedic surgery, rotator cuffs going from open rotator cuff repairs to arthroscopic rotator cuff repairs. Pick any subspecialty, and there's movement towards these less invasive techniques to minimize trauma to the soft tissues and faster recovery. Again, in this particular area, I don't know if there's enough evidence to say yes to those techniques, but again, to me, just as a surgeon, visualization for a procedure... there's isn't a difference in outcomes from open versus rotator cuff... arthroscopic rotator cuff repairs, but both you're directly visualizing the rotator cuff, either with an arthroscope or under direct visualization. So, it's again, it's... the visualization to know you did the operation you went in to do, and again, this is the meta-analysis that at least to me shows that.

Mika Sinanan: So, Mika Sinanan. Just to pull us back for a min to the 30,000 foot level, the efficacy questions, were the effectiveness and comparative effectiveness of surgical interventions. So, the first suggestion, as I understand it from you, is to not focus on all surgical interventions, which

gets into what is established practice for which there is a body of evidence that there's benefit. For example, open surgical practice. We're not trying to make a coverage decision about that today. We're trying to narrow the scope of what we're focused on. Is that correct?

Gregory Brown: That's my understanding of Dr. Franklin's.

Gary Franklin: No. I wasn't recommending not making a decision on the standard procedures. I think you do have to make a decision. That's what your job is.

Mika Sinanan: For the standard procedure, as well.

Gary Franklin: You still have to make a decision on the standard procedures. I'm not recommending... we were recommending coverage with conditions. Do they have radiculopathy or not.

Mika Sinanan: Okay. So, so we do need... you want a coverage decision on the basis of our standard treatment. Then, the next question is, is it visualization of the disc by any technique versus non-visualization? That's one way to think about it. Another way is visualization of the nerve or not. A third way is removal of a portion of the disc or pulp or not removing, simply ablating but not removing any tissue is a third way to think about it. You've suggested that we use the visualization as the primary means of narrowing down the technical innovations that are really the focus of our evidence base evaluation.

Gregory Brown: I guess, correct. I'm trying to figure out how to say it. So, Dr. Rege brought one up, is fluoroscopy visualization? Is ultrasound visualization? So, I threw in the term optical visualization. I mean, to me, the concept I'm trying to get to is, to me, there's a direct technique where there's a herniation. You go in there. You're directly looking at the disc, the nerve root, one or both and removing the herniation. Then, there's these indirect techniques that basically just as I was reading described well, if we reduce the pressure of the nucleus, then that should reduce the herniation, which in theory, yes. In practicality, this meta-analysis says not very well. So, now for me the question I have right now is, is a reoperation an effectiveness question or is a safety question. It's certainly not a cost-effective approach, but if you're assuming that you can just decompress the nucleus, and that'll fix everything, to me, those two studies say no. So, however we talk about a direct or indirect technique or visualization, I just... those are the concepts I'm trying to figure out how to put the words around. Is that what you're asking?

Mika Sinanan: Thank you. Yes. That's helpful.

Sheila Rege: This is Sheila Rege. In response to Kevin's ... our charter is to look at the evidence. So, I like what we did. And when we think of direct visualization what I was hearing from our surgeons in this room, you know, direct visualization optical, call it what you do, eyes, glasses, loops, microscopes, and then the question is, do you do direct visualization before and after the procedure if we get to using visualization as a standard. I don't know we're there yet, but my concern on this, and my... what I'm struggling with, I mean, I started reading from your... from what you had handed us. There was percutaneous electrothermal treatment. I've never heard of that. I don't think I've ever seen a patient with that. So, I actually texted some colleagues of mine and said, have you guys seen this? Never seen it. Then, radiofrequency, you can say percutaneously, and these device manufacturers have the most unusual devices that they will market. So, my worry is that not to have a patient go to what I call a sham kind of treatment and avoid that versus really allowing the real treatments. So, I don't know if I think listing everything that was in your... what you had given us, would be too time consuming. So, we do need to figure out something, and I'm struggling with what criteria to differentiate it. I don't know, Seth, if you have any ideas as a surgeon.

Seth Schwartz: Well, I mean, I'm struggling with that same point. I mean, I think, again, we've seen evidence that discectomy works, microdiscectomy works. Endoscopic microdiscectomy is still microdiscectomy whether you do it through a tube or not. It's all the same procedure. So, I think that's not a question. We've seen some evidence that the less invasive procedures have faster return to work, and that's one of the only differentiations. We don't expect any difference in pain, 'cuz you're doing the same operation. So, partly I'm trying to get at, what are we really trying to do, and if we're... because I don't have any problem approving any of those procedures with the right indications, but a few of these procedures are not the same thing. I'm still not sure how to call out these procedures that are not the same thing.

Christoph Hofstetter: Seth, do you mind if I just answer that very quickly. Again, I want to... one part that we are trying to do worldwide with the AO right now with this large organization is to... all these things that we talked about right now is just standardize the nomenclature, and to standardize these procedures, and we do that worldwide, and we're starting [inaudible] in December of this year where we really go over these procedures how to perform the minimally-invasive surgery and endoscopic, both of those direct... all of these procedures that are [inaudible], because as a surgeon, you want to see the pathology before and after you've taken care of it, right? And it's

true for all surgeons, basically, right? We want to see before the issue and afterwards. Again, for some procedures, indirect is enough, but for this what we're right now talking really about a procedure that you directly decompress a nerve root, and I think that's important.

Gregory Brown: I hear what you're saying, and I think you're coming from a surgeon's approach. What I heard from Dr. Franklin is his concern that it's the non-surgeons that are doing these indirect techniques, be it a neurologist, be it a physiatrist, be it a radiologist without visualization. That's why, anyway, I won't speak for him. Dr. Franklin, you were going to comment?

Gary Franklin: Yeah. We also, just to that point, there are two different CPT codes. There's a CPT code for endoscopic, which we currently do prior authorization on, and there's a CPT code for kind of everything else that's not open, a different CPT. So, that's kind of a catchall CPT code. The other thing to keep in mind is, Medicare has a national noncoverage decision for any of these procedures that are energy based that are heat based or I'm not sure about whether lasers and that or not. Is laser in that?

Christoph Hofstetter: Most surgeons I know in the U.S. that are serious about this don't use a laser, because there is risk of radiculopathy. If you hit the nerve root so high.

Gary Franklin: I'm pretty sure that laser and hydrothermal, whatever, thermal are part of the noncoverage decision from Medicare noncoverage decision.

Carson Odegard; Yeah. I'm considered about nomenclature, too, and I'm concerned about if we make a decision and we're talking about indirect or whether it's visualized or whatever, we really don't have any evidence on what we really call it, and the evidence that we have is a group of procedures that really has no evidence of comparability. So, if we're going to make a decision, we're going to either have to make it... we could exclude maybe a couple things and call it something different, you know? I don't know what you'd call it that you exclude, but you're going to have to include a group, and...

Gregory Brown: So, the surgeons... so for an all... well, is tube billed under open then, because you've made an incision and inserted a tube, a tube discectomy? Okay.

Gary Franklin: There are a series of CPT codes for the regular open procedures.

Gregory Brown: Okay.

- Gary Franklin: There's a different CPT code for the endoscopic procedures and a separate code altogether for all these other things.
- Gregory Brown: So, it's really that third code then...
- Leila Kahwati: Yeah. I think it's for thermal intradiscal procedures. Is that right?
- Male: Yeah. Those are not covered at all. [Inaudible] He's talking also there's an endoscopic code, [inaudible], but you're exactly right. [Inaudible]
- Josh Morse: We really appreciate your input. We're going to have to get you a microphone, because you're adding significant substantial comments to our record here. Let me get you a microphone.
- Gregory Brown: Okay. So, I guess my only question with that is, is the Chatterjee paper, like I said, is a mechanical shaver. So, that's that not thermal, but would that be the code that they billed under, or this third code?
- Male: They couldn't do that, because they're not performing a laminotomy or a [inaudible].
- Trent Tredway; I'm Trent Tredway. I'm just here to hang out. That's the key, because if we were doing a decompression, you have to take, you have to do a laminotomy, and you either do a discectomy or you just do a foraminotomy. Those are the CMS codes, CPT codes that you're approving for decompression of the nerve root. We're not really decompressing the disc, we're decompressing the nerve root. Those other procedures that you're talking about would have to be under a different CPT code, and that's what gets a little bit different. No, I don't know if Dr. Franklin has other CPT codes that people are trying to put in, but none of those will be approved. They're not approved by CMS. We're not going to get paid for them. So, that's really kind of the tricky part. There are some other devices, intraspinous, basically intraspinous devices that expand open. That does an indirect decompression. It doesn't do a laminotomy. It doesn't do a decompression. So, you can bill for that. So, that's really where the question of it is, if you guys are going to talk about that type of technique or that type of procedure, then that needs to be addressed, and that's what this was kind of a question where we're talking about surgical decompression for radiculopathy, and so we kind of run down these rabbit holes. If there are procedures that you guys are questioning and don't want to cover or shouldn't cover, then let us know. I think that's really reasonable, but there are certain procedures that CMS, CPT codes that are already there that are a standard of care. That's why we're here so, you know, and thank you for letting me talk, because it's important that we get

those approved, but some of those other ones that are out there, that's really the Health Technology Assessment's job to say should we do lasers? Well, look at it and probably come up that there's not really good data for that. This automated thing that you guys are talking about from Chatterjee, nobody does that. That's in a different country. Most of these studies are from different countries. We don't do that. So, that's what really is kind of interesting about this whole process. There are certain standard of care, certain data that we would actually say, absolutely. Decompress that nerve root. Rob Gronkowski would be happy with that, too, right? So, people get discectomies, and they do pretty well, but there are some other people out there that are doing some procedures that we should look at. Same way with stem cells, right? I mean, that's not going to be covered. It's not covered by CMS. There are people that are doing some things out there that are not going to be covered, and Washington State should not cover those, right? They look at the Health Technology Assessment. So, that's the way I look at it.

Gregory Brown: Thank you, so, Dr. Franklin.

Gary Franklin: Can I just ask, the endo-, any of the endoscopic procedures, how good, how complete is the pre and post-visualization from the endoscopic procedures compared to the open procedures?

Christoph Hofstetter: I think [inaudible] answered it the best here. We are really the center of excellence for the U.S. here. So, most of these studies are coming out or not. They're on their way right now. We're studying it. We have a prospective trial going on right now, open laminectomy versus endoscopic laminectomy. So, we are really leading in the country right now. The thoroughness of decompression is the same as a tubular microscopic decompression, and the visualization is superior, because you can go and put your camera 2 mm next to a nerve root, underneath, in front, below. So, the visualization is absolutely far superior. Again, we are publishing a paper right now with a one-year follow-up that of which the VAS microsurgical decompression is 3.4, endoscopic it's 1.6, because it's more thorough. So, the outcomes appear to be superior. Again, it is a cohort study with matched controls, not randomized, but the randomized studies are on their way. So, I am a true believer in it, and patients... my office staff almost kicked me out when they knew that I would randomize open laminectomy versus endoscopic laminectomy.

Gary Franklin: I just wonder, just because you can get 2 mm away and see it, like, that part of the nerve that closely is not the same as knowing that you left a fragment, a bigger picture that you can visualize when you're in there. So,

I'm just wondering about the reoperation rates in these other studies, no matter what it is, and whether you were actually seeing it, as well.

Christoph Hofstetter: So, the reoperation rate in a large cohort of five major centers in the U.S. who, that's...

Gary Franklin: That's not published yet, though, right?

Christoph Hofstetter: We have the data, I can show you.

Gary Franklin: No, but this committee can't look at that.

Gregory Brown: We have to deal with published... so, again, back to 29, I keep, you don't have to go back. There is endoscopic discectomies in there. So, if what I'm hearing from Dr. Tredway and Dr. Hofstetter is, even with an endoscopic discectomy or microdiscectomy, you're still doing a laminotomy to get there and do the...?

Trent Tredway: That's right.

Christoph Hofstetter: Correct. Laminotomy, foraminotomy.

Gregory Brown: So, the key is... well, it sounds to me, and again, everybody else, if we then include laminotomy or foraminotomy, as part of the procedure, whether it's full open tube or endoscopic, it's that foraminotomy, laminotomy with discectomy that's the effective part of it?

Kevin Walsh: I'm really frustrated right now.

Gregory Brown: Okay.

Kevin Walsh: There's a process, and we're not following the process. We've been asked to look basically at three things, surgery versus nonsurgery, microinvasive surgery versus everything else, and endoscopic. Am I correct? Am I conceiving this correctly?

Gregory Brown: Yes.

Kevin Walsh: I feel like there's been an assumption that we're talking about the third one only, because we've already approved the first two. There's been no discussion about the first two, in spite of the fact that they're the standard of care, we were asked to evaluate them. We haven't done that. So, I feel like, because my perspective is very different than yours. I understand that I'm going to be defeated in a nine to one or ten to one vote. I don't care.

What's important to me is that we didn't talk about this other stuff, and we didn't apply the effectiveness question to this other stuff. Seth has made an assumption very emphatically that this stuff works. I have a different opinion about that. I would like us to do a straw vote about open procedures, to look at all three levels and get a straw vote and get a sense of where we are. Then, we can dig into the weeds of the details about trying to parse this stuff out the way that you feel is most appropriate.

Carson Odegard: I have to agree. I think that would be a good approach. It would keep us on track. I think though, Kevin, that we jumped the gun. What we're looking at is more of conditions for the third.

Kevin Walsh: But that's not the process...

Carson Odegard: I know. Right. Right.

Kevin Walsh: ...that we've been asked to follow.

Gregory Brown: I agree with you. Again, I heard Dr. Franklin's presentation and their request was not to revisit that, but I agree with you that the process does ask us to. So, if I'm hearing you correctly, are you asking for a straw vote whether we think that open laminectomies, foraminotomies, discectomies are effective.

Sheila Rege: Surgery versus conservative, 1A is what you're looking at.

Gregory Brown: Versus conservative? Okay.

Kevin Walsh: I'll let you do that.

Gregory Brown: So, this is a straw vote.

Sheila Rege: And this is assuming the similar criteria that...

Gregory Brown: Appropriate indications.

Sheila Rege: ...conservative is given, appropriate conditions, conservative, you know, you're waiting to give conservative some time to work. So, six to twelve weeks is what all the studies showed.

Josh Morse: To get to the nonbinding voting, typically you refer to your decision aid.

- Seth Schwartz: We can do that, but a straw vote is something that's just a quick show of hands, like, where are we. So, I think it's not unreasonable to do that before we move on to this stuff.
- Gregory Brown: Sure, yeah. So, do we think that... well I'll state it as in appropriate indicated patients that have failed six to twelve weeks of conservative treatment is open laminectomy, laminotomy, foraminotomy, discectomy are more effective than conservative treatment.
- Gary Franklin: With imaging to show disc disease.
- Gregory Brown: Well, right. That's what I mean by the indications.
- Gary Franklin: Right. Okay.
- Gregory Brown: Yeah. So, those that think it's more effective?
- Josh Morse: I see five hands.
- Gregory Brown: Same?
- Josh Morse: Two, three, four.
- Gregory Brown: Alright. So, I mean, that's close. So, the point, I guess...
- Mika Sinanan: So, we're not arguing that it's not effective.
- Gregory Brown: Right.
- Mika Sinanan: Well, your question was structured, do we think that the surgical intervention, where so much money is spent and so much time is any better than conservative therapy. The data that we're presented convinces me that there's no distinction. So, I wouldn't argue that neither therapy is effective. The question you asked is, is the surgical intervention demonstrated to be more effective than the conservative therapy. That's why I voted the way I did.
- Gregory Brown: Okay. So, let me...
- Seth Schwartz: I think Kevin has a valid point, that I think we should clarify this. I think that's a big generic statement, because what we were presented with was a lot of data that said at early to moderate outcomes, there was significant improvement in pain outcomes with surgery versus nonsurgical treatment. I think that, in the short term outcomes up to six months that that was

pretty clear. I think it becomes a little less clear in the moderate term outcomes, two to five years, but there's... a lot of the challenges to the studies that we saw was that there was a tremendous amount of loss to follow-up in crossover in those trials. So, it makes it very hard to assess the fact that there's... the difference sort of... I don't know if it goes away completely, but a statistical significance of the difference is significantly mitigated but these studies sort of fail us at that outcome. So, it makes it harder to comment on that. So, the question sort of comes down to, okay. We're unsure about those longer term outcomes, but... so, how much do we value an improvement in pain outcomes up to six months.

Kevin Walsh: And as a primary care physician who takes care of people with chronic pain, who takes care of a lot of people with low back pain, the perspective I have is that I'm told increasingly to ignore pain as a measure and to look at function, because we can't get rid of chronic pain, unless we anesthetize people. So, all we can... what we can hope for is to improve their function, and there's a huge thrust right now in primary care toward that, and I'm wondering why we're using a statistically significant but small improvement in pain over a short term that's not reflected in function gains, measures, it's not reflected in return to work, why that becomes sufficient to let this behemoth roll. I do not think that the evidence is there to support it. I don't feel it's significant. I don't feel that measure in itself is significant. I understand I'm in a minority.

Gregory Brown: I'm not sure you're in the minority. I agree with your perspective. I am coming from the position that I don't think the evidence that we're presented with today is sufficient to, shall we say, overrule the standard of care.

Kevin Walsh: I respect the difficulty of that idea. The reality is, we were asked to make a decision about this stuff based on the evidence we were given, not, oh, but because it's the standard of care, we have to accept it.

Gregory Brown: No. That's...

Kevin Walsh: It was never, the question was never asked in the first place.

Sheila Rege: But would the standard of care be... would be data we'd have to accept as data. I mean, is that?

Kevin Walsh: The standard of care is not data. That's the standard of care is [crosstalk].

Sheila Rege: I'm sorry, guidelines.

Kevin Walsh: It's culture.

Sheila Rege: The fact that there is...

Kevin Walsh: Well, we're asked to make a decision and then compare it to the guidelines that exist. We are not asked to be driven by the guidelines.

Seth Schwartz: I think you make a valid point, but one thing I would want to clarify is that I don't know that we're necessarily talking about chronic pain here. A lot of the things that we do talk about [inaudible] chronic pain, you know, chronic degenerative disc disease and all those kinds of things, but this is acute herniation. So, I think the difference in acute pain, if you improve pain three months versus six months of acute pain may be a very different outcome. So, it's not clear to me at all that we're talking about chronic pain. We're talking about pain from an acute disc herniation. So, I think pain is a significant outcome.

Kevin Walsh: I would argue we're looking at different time periods. One of them is an acute period. Then, we're looking further out and further out and further out. It's always interesting to me that orthopedic studies don't look further out, because by one year, usually whatever improvement they were able to gain at six weeks or three weeks or six months is gone at a year. There's no difference anymore. So, why is that not relevant? You're living with this back issue for the rest of your life. You're not living with it for six weeks and then you get a pass.

Gregory Brown: So, John, you had concerns about how I phrased the straw poll question. So, how would you phrase it differently?

John Bramhall: So, I would find it shocking if we, as a group, said that an acute disc herniation could not be treated surgically and then compensated by the State. I would find that shocking, because I think it should, but...

Gregory Brown: So, how would you rephrase the question so that the answers that you...

John Bramhall: ...so, the graph that's up there is... what it really says is surgery and non-surgical interventions, which may be cheaper, may be more expensive, don't know. We're not invited to sort of discuss that at the moment, but they're equally effective, right? I mean, there's no difference, according to that graph. There's no difference. That doesn't mean that they're not effective. That was my point. It means that they're equally effective.

Gregory Brown: Okay.

John Bramhall: And then as a ... from a societal standpoint and a healthcare economic standpoint, there would be an opportunity at some point to say, well, the nonsurgical interventions, they work just as well as surgery. Someone used the word behemoth. There's this grinding energy behind the surgeries going on day after day after day, mainly open procedures, because they're compensated, and not the good procedures, because they're not compensated. This machine running, well, you know, Kevin, you work in a different world, and you see the benefit of perhaps some nonsurgical interventions. What this graph to me says is that both are as effective as each other. I actually don't have any information about how effective they are in absolute terms. So, I'm not, again, don't get me wrong. Personally, I'm not arguing that we should not pay for decompression of a bulging disc that's impinging and causing radicular pain. I'm not arguing that, but it could be argued from this data that it's just as good to send that person to a physiotherapist and they would get the same result, I mean, over a long term, not pain... function.

Kevin Walsh: I mean, the evidence, when I look at the evidence identification material that we have at the end of the section, we're asked to look at efficacy considerations. What is the evidence that the use of the technology results in more beneficial, important health outcomes? What is the evidence confirming that the use of the technology results in a more beneficial outcome compared to no treatment or placebo treatment? I feel like that's the question, and I'm asking us all to commit to whether we think for open procedures, that the evidence says yes, it's... we feel it's more beneficial than conservative therapy. I think we should honor each other's vote and do what we always do and move on.

Laurie Mischley: This is Laurie Mischley. I just want to say I really kind of agree with Kevin. When I was preparing for this meeting, in preparation, I thought the conversation was going to come down to how much do we value this six-month reduction in pain given the cost and burden of surgery? Given what sticklers we have been for the data presented to us, I really... I'd say this is the muddiest conversation I've ever participated in where we jump to the assumption that standard of care is what we're going to go with and buy into, and kind of ignore the lack of data that we've been given. I don't think that we have the granularity of data to get into visual, not visual. I don't think that that's even a legitimate conversation to have. I do agree that we skipped over what I expected to be a difficult conversation to have about the standard of care is not supported by the data that we have, and how are we going to handle that.

Gregory Brown: Are there any more data questions that we have for our contractor.

- Leila Kahwati: Lest you give me a disc herniation from standing here anymore.
- Gregory Brown: It's usually sitting that's worse. So, standing is to your benefit. I think you're both right. Then, I think we need to move to our tools and answer each of the questions we were specifically given. So, any other data questions? Okay. So, can we move to our...
- Gary Franklin: Can I just say one more thing... I think I got a little clarity from talking to Dr. Leveque and Dr. Tredway. If you bill 63030, which is the typical open procedure with either foraminotomy or laminotomy, laminectomy, whatever, to get to the disc, and if you use an endoscope to do that, you're still billing 63030, but you're using an endoscope to do that. That's, like, part of the open procedure. It doesn't matter whether you use endoscope or not. It's the other procedures that are to me the more questionable ones, especially, well, you're not going to do anything with the thermal procedures, but even some of the other ways of getting at this with the other CPT codes, including 0275T, the T-codes. Those should probably... those are not open... those are not, in any way, shape, or form, these open procedures. They should probably be you uncovered. Then, this other code that's just endoscopy but not 63030 with the foraminotomy and ways of getting at the disc so you can actually remove it, that's another question. So, endoscopy, per se, if it's just part of 63030, right?
- Trent Tredway: The 63030 is for the microdiscectomy. So, laminotomy, microdiscectomy. The decompression is 63047, and if you have to do another level, it's 63048. So, those are three codes. Now, Christoph, you actually do it basically using an endoscope on yours. Do you bill the 62380 or not?
- Christoph Hofstetter: Honestly, at the University, I have, you know, we have a department billing for us. So, what I do is, I deliver the operative report, and we describe exactly what we do. So, I would have to look into our billing department. I am very remote from that. So, I could not answer that question right now.
- Trent Tredway: Dr. Franklin, correct me if I'm wrong. I don't think that L&I has basically ever covered T-codes in the past. I don't think that that's something.
- Gary Franklin: T-codes and all this other stuff is uncovered, which is why I recommended...
- Trent Tredway: Right.
- Gary Franklin: ...noncoverage for some of this stuff, but we, the confusion in the visualization, nonvisualization, and then... are you actually doing

essentially the same thing with an endoscope, as you would with an open procedure? Yes. 63030. That would be essentially what you usually do, except it's using an endoscope. ANBG does not have a problem with that. It's just more the outlier stuff that we're confused about and concerned about. With pain guys doing this stuff in their centers, and there's no way, by the way, for the medical board to do anything about that. That's not what they do. They only go by complaints. They don't do anything else, so.

Gregory Brown: Okay. I think we're ready for our... to use our tool. So, I have it on page five here. So, we have slide 18 that talks about our questions, in terms of effectiveness, safety, and cost-effectiveness. For effectiveness, we have surgery versus nonsurgical interventions. Should we... is that how we want to do it? Do we want to do it surgery versus nonsurgery, minimally-invasive versus open surgery, and then...

Sheila Rege: Microdiscectomy?

Gregory Brown: ...microdis-, well it's got microdiscectomy versus discectomy. I'm not sure of the difference there between minimally-invasive surgery and open and microdiscectomy versus discectomy. Then, in terms of revision surgery. Would those be our three questions? Or, I guess the fourth, I guess the fourth...

Male: [inaudible]

Gregory Brown: ...Okay. So, I was going to say, the T-code procedures, we can... let's discuss those then and non-... well, okay. Well, I mean, the answer may be we have no evidence for it and so, therefore, right, but we should at least, let's, let's run it through. Okay? So, our safety outcomes, surgery versus conservative treatment. Mortality is rare. Surgical morbidity is rare. Probably the biggest issue is any infection, there's always a risk of infection, but it's low. Reoperation is probably the biggest safety risk. Okay? Persistent opioid use, certainly a safety issue. I don't know if there's any evidence. There's no long-term pain difference.

Seth Schwartz: I don't think reoperation is a safety issue. I think that's an effectiveness question. If the patient has persistent symptoms, then they may have a reoperation, but reoperation, unless it's reoperation for a complication, but that's a different story.

Gregory Brown: Well, yeah. That's right. I asked that earlier. Is it an effectiveness or is it a safety? I guess I would view it also as both. It's a safety issue because you've got all the risk of surgery again, whatever those are, but...

- Seth Schwartz: But that's an extrapolation. Again, this is Seth, because they may choose not to have the reoperation. That's always a choice.
- Leila Kahwati: Can I weigh in here? So, we actually included reoperations as both an efficacy and safety outcome, but the empiric data basically reported it all in terms of for symptoms. So...
- Gregory Brown: Okay.
- Leila Kahwati: Or they did not specify whether it was for complications or symptoms. So, we just put it into safety, so it wasn't in two places.
- Gregory Brown: Okay. Fair enough. So, in terms of surgery versus conservative care, safety, are they equivalent? Is surgery less safe, more safe, equivalent?
- Josh Morse: One, two, three, I see six equivalent, two less, and one unproven.
- Gregory Brown: Okay. And then, safety for open versus minimally-invasive.
- Josh Morse: Seven equivalent, two unproven.
- Gregory Brown: And then safety for... I guess if we're saying reoperations is an effectiveness, are we agreeing with that? We're going to just put it there. So, we'll take it out of safety? Okay. So, then, the T-codes, the indirect decompress the nucleus but not surgically so. Safety is...
- Josh Morse: Eight unproven, one less.
- Gregory Brown: Okay.
- Josh Morse: And can you, I'm sorry, define for me the T-code issue?
- Gregory Brown: The T-code are the indirect procedures, such as thermal ablation, laser ablation, radiofrequency, nucleus ablation, mechanical ablation.
- Josh Morse: Okay. Thank you.
- Gregory Brown: Okay. So, efficacy, we've discussed those.
- Sheila Rege: Those are defined as indirect image guidance, officially on the CPT codes. Indirect, yeah.
- Josh Morse: T-codes are indirect image guided?

Sheila Rege: Yeah.

Josh Morse: Okay.

Sheila Rege: For example, but that's what they are in the CPT world.

Gary Franklin: That's an example of the kind of code that we get billed for these procedures that do not include foraminotomy or laminectomy or whatever.

Gregory Brown: Okay. So, efficacy of open versus conservative.

Josh Morse: Do you want to make sure that I've added the right outcomes here, pain, function, disability, quality of life, neurologic symptoms, return to work?

Gregory Brown: And reoperation. Yeah.

Seth Schwartz: Indications under some or any circumstances where surgery is more effective than conservative management.

Sheila Rege: So, you're looking at, like, can we just band it all together, just pain, improve in function, neuro symptoms, and return to work? Or do you want to separate them out?

Seth Schwartz: no, I don't think, I mean, I'm just, the way we typically go through this question is, under is the intervention...

Gregory Brown: Under some conditions...

Seth Schwartz: ...which, the intervention is surgery for lumbar disc herniation with radiculopathy, are there... is there evidence that surgery is more effective under any circumstances than conservative management. That's the way we usually state that question.

Gregory Brown: Thank you.

Josh Morse: Six equivalent, three more, three some.

Sheila Rege: All the surgeons said more.

Gregory Brown: Okay. Is there sufficient evidence that... I'm sorry. So, now we're doing open versus minimally-invasive effectiveness.

- Josh Morse: Nine equivalent.
- Gregory Brown: Then, indirect visualization techniques?
- Sheila Rege: Or the thermal and all that other stuff?
- Josh Morse: Three less, six unproven.
- Gregory Brown: Okay. Then, cost-effectiveness, surgery versus conservative treatment. So, surgery costs more so is less cost-effectiveness than conservative treatment, the way I'm viewing the question.
- Sheila Rege: Surgery is less cost-effective. That's what I'm saying.
- Josh Morse: Five unproven, three less, and hang with me, please.
- Christoph Hofstetter: So, that's all about crossover patients, right, six weeks of nonoperative crossing over to surgical, right? Okay.
- Josh Morse: Okay. Got it. Thank you.
- Gregory Brown: Then, cost-effectiveness of open surgery versus minimally-invasive surgery.
- Josh Morse: Seven unproven, two equivalent.
- Gregory Brown: Then, cost-effectiveness of indirect visualization techniques compared to open surgery.
- Josh Morse: Seven unproven, two less.
- Gregory Brown: I think this is the most unproven I've ever seen in a vote. Okay. So, given this vote, what is the feeling, I guess the...
- Kevin Walsh: I would propose we vote on each one, the three.
- Gregory Brown: Okay. So...
- Kevin Walsh: We've essentially divided the types of surgery into three. That's how we've gone through the preliminary questions. I would propose that we vote to cover, cover with conditions, or not cover each of the three.
- Gregory Brown: Okay. So, let's do... so open surgery and this is a straw vote, or is this our full vote?

Kevin Walsh: This is the full procedure.

Gregory Brown: Okay. Yep. So, we're talking... so, for open laminectomy, foraminotomy.

Josh Morse: Eight cover with conditions, one not cover.

Gregory Brown: Then, minimally-invasive versus open. Or, I guess, just minimally-invasive.

Josh Morse: And we have not developed your conditions yet.

Gregory Brown: Yes.

Josh Morse: Eight cover with conditions, one not cover.

Gregory Brown: Then, indirect visualization, T-codes.

Sheila Rege: So, with all the thermal and all that?

Gregory Brown: Yep.

Sheila Rege: The same language?

Josh Morse: Eight not cover, one cover with conditions.

Gregory Brown: Okay. So, now we need to come up with conditions. Do you want to start with Dr. Franklin's recommendations? Okay.

Carson Odegard: I have one comment on that.

Gregory Brown: Sure.

Carson Odegard: I agree with the four weeks of nonsurgical care; however, these studies went beyond, they were picking patients that were obviously out into the months of symptoms, radicular symptoms. So, I would suggest probably six to twelve weeks, something like that.

Gregory Brown: Okay. So...

Carson Odegard: It's hard to get a control... or hard to control symptoms, especially for the acute, um, patient within four weeks. It's...

Gregory Brown: So, I guess, just to make this... if we're going to... so, we're going to do both the open and the minimally-invasive techniques or cover with

conditions, is it going to be the same conditions for both? Do we agree on that? Okay. So, we only... well, we're talking about the indication. So, gain, if we start with what Dr. Franklin proposed here. So, what I'm hearing from you, Carson, is that the second bullet point is minimum, you'd say six to twelve weeks?

Carson Odegard: Yeah. What does everybody think?

Gregory Brown: I think that's... yep. As long as we have that exception, I think with the progressive motor weakness, I think that's a different category.

Mika Sinanan: Can we say a minimum of six weeks?

Sheila Rege: Yeah, because six to twelve, everybody's going to go with six. So, are you Okay with six weeks?

Carson Odegard: Fine.

Gregory Brown: Yep. Okay.

Mika Sinanan: And if there is progressive motor weaknesses, clear it should be decompressed? Clear, right?

Gregory Brown: Well, again, and, I mean, it'd still meet the... you still... something's progressing, but you don't have an MRI to show what's causing it. So, you'd still need the imaging and stuff to document that that's the cause. Then, I guess on the second part, I would just say indirect visualization techniques, as defined in CPTT whatever?

Sheila Rege: They don't define. They just said example. Can we do a straw poll on whether Dr. Brown's direct visualization optical visualization is something we would want to consider in the second point? Or is everybody not comfortable with adding that? The straw poll... so, one thing that was suggested was in the microscopic, in the second point, to have something about direct visualization be it, you know, eyes, glasses, loops, microscopes, and direct visualization before and after decompression to kind of address Dr. Franklin's concern that if something happened. Should we do a straw poll on that of whether that's language that we even want to add in there or not?

Gregory Brown: Can I make a... I mean, I think we've switched to the term just indirect nucleus decompression procedures are not covered. Is that?

- Gary Franklin: I think, again, talking with my surgical colleagues over here from the first decision, you could say that the open procedure done with or without endoscopy. That could include procedures done with endoscopy under the first category, because they are still doing all that other stuff, like foraminotomy. It's the other procedures that aren't really getting that kind of visualization. I agree, I wouldn't refer to the term visualization, whatever, 'cuz somebody's going to take that out of context. It's indirect, whatever. So, I think it's... you're doing these classical procedures, and they might be done with an endoscope. That's okay under this first thing, and everything else would be noncovered.
- Sheila Rege: So, you could say covered... you would just add with endoscopy, open or with endoscopy?
- Gary Franklin: As long as they're doing these other things, like the foraminotomy and cervical...
- Christoph Hofstetter: Laminotomy, foraminotomy to get to the pathology.
- Sheila Rege: So, how would we change that first... because then we don't even need the second one.
- Carson Odegard: Right. Yeah.
- Seth Schwartz: I would recommend we should take the endoscopic out of the second one and just say OD/MD +/- endoscopic or with [crosstalk].
- Sheila Rege: No, actually, if you say +/-, then they can do it without endoscopy, but not open either.
- Seth Schwartz: No, no. For the first one, it's clear. You're saying lumbar laminectomy, laminotomy, discectomy, all that stuff. So, it'd be open discectomy or microdiscectomy with or without endoscopy.
- Sheila Rege: Okay. That would solve it, I think.
- Josh Morse: You want me to add that here?
- Gary Franklin: I think that's what we're saying.
- Gregory Brown: Whatever you said, go ahead and give it to him.

Seth Schwartz: Then, I would take endoscopic out of the lower one, because the other things are all ways of removing the... or manipulating the disc. Endoscopy is just a way of looking.

Sheila Rege: That makes it...

Gregory Brown: Yeah. We don't, I mean, we don't need the bullet point below. We're not covering it.

Gary Franklin: Sorry. I guess just one question. Are some people doing endoscopy without doing those other surgery things?

Christoph Hofstetter: That is what I'm working. This is the role of the University, of training people, doing the, and there's a very prominent example in the city here that is a thorn in my both eyes, and we're working on training the next generation. Again, as indicated back there, it is an evolution. The surgery that we do is evolution of what's been done for hundreds of years.

Gary Franklin: We'll come back in four years after you have all your stuff published.

Male: [inaudible]

Gary Franklin: Right. So, you wouldn't take endoscopy out of the second noncovered piece, because somebody could be doing endoscopy and not be doing those things, and they shouldn't be doing those things. [Inaudible] data comes out.

Christoph Hofstetter: No, by including those anatomic landmarks ensures that you have the normal traditional surgical trajectory. Anyway.

Sheila Rege: I do like adding it back in.

Male: [inaudible].

Gregory Brown: I tend to agree, because I mean, we're trying to write a coverage decision, anticipating what's coming down the road. That's hard to do. So, I would tend to agree, leave it out of there.

Sheila Rege: Do you want to say endoscopy alone is not covered?

Gregory Brown: Well, again, I would rather not say anything. So, if it does come out, and there's good data and L&I decides that we want to cover it, then they don't have this decision they have to come back to. Correct? I mean, that's my understanding.

Kevin Walsh: I'm sorry.

Seth Schwartz: But it doesn't mean anything. That's like saying microscope alone is not covered. It doesn't mean anything.

Gregory Brown: So, did we say, did we say indirect... I mean, instead of the MID/S, are we saying indirect nucleus decompression procedures.

Sheila Rege: I'd just leave it the way it is.

Gary Franklin: I don't think we have to use those [inaudible] terms. It's...

Gregory Brown: Okay.

Gary Franklin: ...the standard of care is the first thing with or without and endoscope, and everything else...

Gregory Brown: Okay.

Gary Franklin: ...is sort of not covered, at this point. We can come back and look at it, if there's new data.

Gregory Brown: Okay. So, and then, in terms of reoperation, Kevin, I heard you say earlier we have no evidence on which to make any recommendations on...

Kevin Walsh: I don't feel that we do.

Gregory Brown: ...yeah. Does everybody agree with that? So, remove the reoperation.

John Bramhall: Reoperation not covered. Is that right? Or take it out?

Gregory Brown: No. If we say that, that's huge. So, I mean, again, it's...

John Bramhall: Let's not make a statement about it.

Gregory Brown: We would make no statement about it. I mean, I could be persuaded to say I like some of the ideas of if the herniation isn't any bigger than the previous one, and there wasn't a, you know, but again, we don't have any data to [crosstalk].

Seth Schwartz; Yeah. I agree with Kevin on this. We have no data, and if we say nothing about it, then you guys can make your own determination on a case-by-case basis? Correct?

Sheila Rege: I like that.

Gregory Brown: Okay. So, Josh, are you doing the, or Christine? Josh? The four to six weeks...

Sheila Rege: Yeah, six weeks.

Seth Schwartz: Before we change that, I mean, what's that based on? I mean, I thought some of the papers said they used four weeks. Some of them used six weeks. Some of them used six to twelve weeks. I don't know where that number comes from.

Sheila Rege: Most of them had six to twelve weeks, it seemed like.

Male: I think for most of in the neurosurgical community, six weeks tends to be our standard of care. I know it's a [inaudible] statement, but [inaudible].

Seth Schwartz: I mean, we try to go with data. So, if we, so if that was the entrance criteria that showed this limited amount of efficacy that we're actually seeing here used six weeks, then we should use six weeks, I think, but we should at least try to be somewhat.

Leila Kahwati: Yeah, six to twelve weeks was the standard sort of waiting period.

Seth Schwartz: So, a minimum of six weeks then. That makes sense.

Gregory Brown: Yep. Okay. Any other comments, questions?

Josh Morse: Can we group this? Is that Okay?

John Bramhall: There's no... I mean, nonsurgical... is there an assumption here that nonsurgical care refers to a coordinated category of nonsurgical care. Do we know that?

Gregory Brown: Say that one more time?

John Bramhall: So, nonsurgical care seems a little bit amorphous. Is it implied that it refers to a standardized regimen of PT/OT, you know, nothing? So, someone can say that they've had no surgical care for six weeks, and now they want the operation. Is that the way we want it?

Gary Franklin: It's just the studies were all over the map and not really systematic in that arm.

- John Bramhall: No. I understand that, but we're dealing now with what the coverage should be. Would it be the case that if I have radicular pain, and I do nothing for six weeks, I am then eligible for coverage for surgical procedures? Is that the way that would be read?
- Gregory Brown: Do you want to say conservative treatment?
- Carson Odegard: Yeah. The studies said some kind of care.
- John Bramhall: It just seems like, well, I could, I could have an intensive regimen of nonsurgical therapy, which might get me better, or I could just do nothing and put up with it for six weeks and... because I want the surgery.
- Gregory Brown: I want my surgery. Right.
- John Bramhall: I mean...
- Gregory Brown: No. I, I...
- John Bramhall: I don't know if that's a problem, but...
- Gregory Brown: So, do you like conservative better?
- Sheila Rege: Conservative care instead of treatment?
- Christoph Hofstetter: Well, it should include, it normally includes, like, NSAIDs, physical therapy, steroid injections, I mean, all these...
- Leila Kahwati: Yeah. The studies defined it differently, but it included pain medicine, anti-inflammatory medicine, physical therapy, home exercise instruction, epidural steroid injections is in that bucket.
- Gregory Brown: Yeah. I don't think we want to list them all, though, because then it becomes a checklist.
- John Bramhall: Actually, I like nonsurgical care, because first of all, they're all over the map. Secondly, the important thing is not that we tried something and it failed, necessarily. It's that we waited a period of time to see are they going to get better, or do they need immediate surgery. Would they... is there a value in doing it at one week or two weeks, as opposed to giving them six weeks to see, are you just going to get better on your own.

Sheila Rege: So, what if somebody comes in and says, oh, I've had this for eight weeks. So, I need my surgery right now. How do you stop that? So, I think what John is trying to say is some required treatment be it whatever.

Gregory Brown: Yeah. I mean, I think the diagnosis, you're going to be six weeks from your diagnosis. I mean, it's not whenever you get your imaging. I don't think you're going to... yeah. You could say I've had it for the last six months. Well, you didn't show up until yesterday. So, the clock starts when we get the MRI, you know, to me.

Sheila Rege: I think we understand the intent.

Gregory Brown: Okay. So, did we leave... are we staying on surgical, or are we switching to conservative? What are . . . ?

Sheila Rege: We're on surgical.

John Bramhall: We could argue that surgery may be more conservative. I mean, it's conservative... it's all in judgment. Nonsurgical is clear.

Gregory Brown: That's too much for what we're expecting here. Spoken like a true surgeon. Okay. Any other suggestions? Are we in agreement on this?

Josh Morse: So, the final bullet, not covered other. Is there a way to phrase this as what is not covered, other . . . ?

Sheila Rege: What...

Gregory Brown: So, that's why I said...

Josh Morse: Procedures not included in the above bullet?

Sheila Rege: So, what I...

Gary Franklin: I think that would be minimally-invasive procedures that do not include the other things that help you get to the disc.

Gregory Brown: Well, that's why I say, they're all indirect techniques. They're all focused on the nucleus and not the [crosstalk].

Gary Franklin: Yeah, but they also all do the other procedures, as part of number on. That... and only surgeons, pretty much, can do that. The other pain guys and the neurologists and the PMNR guys, they generally... they would be found wanting by the board if they did that.

Gregory Brown: Well, can you say nonsurgical treatment or?

Sheila Rege: They would call it surgical if they do anything.

Gregory Brown: Yeah.

Sheila Rege: They put a needle in. It's surgical.

Gary Franklin: I would just say minimally-invasive procedures that do not include...

Gregory Brown: Okay.

Gary Franklin: ...such things as foraminotomy and laminotomy.

Gregory Brown: Sure.

Gary Franklin: Are not covered.

Gregory Brown: Okay.

Gary Franklin: And the other point you might want to make is that the ones that deliver energy are also not covered, because there's a Medicare national coverage decision, and we're supposed to follow that.

Gregory Brown: Right.

Josh Morse: You want to add that in?

Gregory Brown: So, minimally invasive procedures that do not include laminectomy, laminotomy, discectomy or foraminotomy.

Christoph Hofstetter: Because we're talking about surgical corridors, and I think, Gary, actually, I like that actually a lot, defining the surgical corridor, because that defines where you're going to end up and what you see. So, I think it's actually a brilliant way of getting around that.

Sheila Rege: That's good. Then, would you need what's in there already? Do you want a...

Gregory Brown: Yep. So, then...

- Sheila Rege: ...say including, obviously, but not limited to, including, because what if somebody comes up with some shockwave therapy, some weird thing that they... high energy thing that they come up with?
- Gregory Brown: And you can put in there energy ablation tech... you know?
- Sheila Rege: Thermal or high energy.
- Gary Franklin: All energy ablation techniques are also not covered under the Medicare National Coverage Decision, such as intradiscal electrothermal therapy, or laser techniques.
- Gary Franklin: And then, we can work it a bit between the meetings to make sure there's no implementation issues, bring it back next time.
- Gregory Brown: All vote to approve this.
- Josh Morse: Eight approve. One not approve. Okay.
- Gregory Brown: Thank you to our contractor. Thank you for a [inaudible] report.
- Josh Morse: Can we check for...
- Gregory Brown: Oh, yes, the...
- Josh Morse: National Coverage Decision and the guidelines.
- Gregory Brown: So, we are ... the coverage... it says the CMS does not have a national coverage decision to this, but in terms of the thermal ablation techniques, they do. So, we're consistent with that. Then, the other guidelines, NICE is the United Kingdom that considers spinal decompression for sciatica, certainly included there. NAS, discectomy is suggested to provide more effective symptom relief. We're consistent there. North American Pain Society, open discectomy, microdiscectomy for radiculopathy. We're consistent there. So, I think we're consistent with the national coverage decision from CMS and clinical practice guidelines. Okay. Thank you, all. Lunchtime. I have 12:10, so if we could reconvene at 12:40 for our second session.
- Okay. In the interest of time, we're still missing a couple, but we're going to get started. I would like to start by introducing Susan Birch who is the director for the Health Care Authority for the State. Welcome, and tell us a little bit about yourself.

- Susan Birch: I asked to come see this in action, because I have joined what I call the rebel alliance team here in Washington. I came from Colorado where I was bringing up the Obama work for Governor Hickenlooper, and as a nurse with an MBA, I have had just a lot of... I've marveled at the work that has come out of both Oregon and Washington in this arena of evidence-based policy making, and I really want to thank you guys for what you're doing. So, I asked to come see this. I've also spent some time with the BREE Collaborative and also our performance measurement committees, because I just think this work is so valuable, as we tread to drive more uniformity and push towards getting better value. So, one of the things you'll hear from me and some of my comments. I know many of us share this belief, but when I talk about over-medicalization, I don't ever mean that as an insult to any of the provider types, but I do think we've really got to get the appropriate medicalization, as you all do, too, but I also stretch that even a little further and look at what's the right proportionality of social to medical spending. So, I think we're [inaudible] off in the United States, and this State keeps moving kind of in the right direction. So, I love, as we get more appropriate care going and getting things more uniform throughout the state. So, thank you guys for what you're doing. I'm just, as I said, I'm in awe of all that's going on, and I thank the staff that keeps this work going and all the vendors and everybody that participates, and all of you that volunteer to serve on this work. It's really important. Any questions, you all have for me, I'm happy to take.
- Gregory Brown: None right now. Maybe we'll grab you on our break if you're going to be here.
- Susan Birch: No worries.
- Gregory Brown: Okay. Then, our expert for this afternoon, clinical expert is Melissa Hall. Melissa, if you'd like to introduce yourself.
- Melissa Hall: Thank you. So, yes. My background is as a clinical pharmacist in the specialty area of anticoagulation, as well as lipidology, but hey, the reason for being here today is the anticoagulation part. So, I've worked in the area, as a practicing clinician managing anticoagulant therapy for about 18 years now. I'm excited to be here to help with this topic.
- Gregory Brown: Welcome and thank you. Okay. We will start with our associate medical director presentation.
- Charissa Fotinos: Thank you everybody. My name is Charissa Fotinos, and I'm the deputy chief medical officer for the Health Care Authority and instead of turning my back to you so I can see where I am, I'm going to kind of not make great

eye contact. So, this presentation and discussion will be around pharmacogenetic testing for patients being treated with oral anticoagulants. Part of what I'm going to be doing in the presentation is kind of contextualizing the decision making around anticoagulation in light of the evidence. I think that the evidence report that Dr. King will be presenting really gives all the details and information in a really well laid out way. So, I'm going to kind of take a step back and sort of contextualize how we, as the agency medical directors, came up with our recommendation.

So, when thinking about anticoagulation, we anticoagulate for prevention or treatment, and one could argue those are slightly different, but the conditions that we do that for are on this slide right here. In terms of thinking about this, let me get the right... are you doing the slides or am I?

Female: You are. You need to point it at me.

Charissa Fotinos: Oh, at you.

Female: Yeah, because this the computer.

Charissa Fotinos: That makes no sense. Okay. I'm not trying to be rude, guys. Okay. I apologize. Let's try this again. I'll just hold it right there. So, in terms of what we're looking at here, for those of you who have prescribed Coumadin, and probably all of you do, it's a balancing act. It's never a straightforward simple here's a dose and I don't ever have to check you again. Most of us either have developed using clinical algorithms or experience to do it, and what we've learned is that there are at least three polymorphisms involved in the metabolism of Warfarin that can either increase or decrease the metabolism, therefore, effecting our desired anticoagulation outcomes. So, the question really is, can testing improve patient-centered outcomes by both increasing the amount of time or primarily by increasing the amount of time people spend in a therapeutic range of their INR and minimizing undesired outcomes. That's really what we're asking.

We are not concerned about the safety of a blood draw. Efficacy, we are concerned about the ability for this test to guide clinical judgment. In terms of cost, it's medium to high.

These are utilization numbers, and they're quite low. Part of it is because Medicare does not cover this test. Secondly, it often comes as a bundle, and it's not unique just to anticoagulation testing, and it's not paid for uniformly. So, these utilization numbers are low, and that particularly is

what triggered us to ask the question. We get requests all the time for genetic panels for all sorts of things. Anticoagulation is common. We get that request a lot. We currently do deny it but wanted to make sure we are making the right decision.

These are the two codes primarily, the 81227, which is for the CYP2C9 gene, and then the 81355, the VKORC1 gene. Most of what we could pull for diagnoses were related to hypertension, and again, it's not covered so it's hard to get. I was looking up the definitions of the codes in a CPT book. Then, just last year, the 81227 code, 25 million dollars were billed for that code in the U.S. They only reimbursed \$51,000, but it's being used out there.

So, the key questions: What is clinical utility of genetic testing to inform treatment decisions for patients being treated with oral anticoagulants? Does the information obtained from the results of genetic testing change prescriber behavior? Secondly, do those decisions that are informed by genetic testing improve patient outcomes or reduce adverse events? Are there any harms associated with genetic testing to inform oral anticoagulation therapy? Are there key differences among patient population, in terms of harms or benefit? What are the costs and cost-effectiveness of genetic testing to guide the selection? Really, what we're talking about is the selection of Warfarin dosing here. The direct anticoagulants aren't really part of this discussion. So, really, we're talking about Coumadin.

Thinking about the two different genetic polymorphisms, these two CYP2C9 and VKORC1. I'm so sorry. Usually, I'm used to pushing this, and it changes. I apologize. So, these two decrease metabolism, which would lead to an increased bleeding risk. Similarly, CYP4F2 leads to increased metabolism, which would increase the clotting risk.

This slide shows the different variations in terms of prevalence of the different genes. As you can see, the most common type are the *1/*1, and these are the most common. You can see at the bottom, and I apologize this is not easily seen, but certainly the vast majority of people have either the *1/*1 or the *1/*2 with much smaller prevalences here. You can see that there are some differences between Caucasians and African-American populations, but still a pretty reasonable similar distribution. I think these graphs are more interesting. This shows the variation in dose, but if you have these genotypes versus these, you can see the dose difference is about 5.5 to 2.5. So, depending upon the combination of alleles, the dose of Warfarin can end up being different, and this just combines some of the genotypes here. This was a retrospective study that looked at people who

had anticoagulation versus controls and came up with these frequencies and retrospectively looked at the doses and said, okay. Here is what they ended up having, but really didn't necessarily account for any of the other things that related to dosing.

When these are used, two things... there are two ways to use these. This is a clinical algorithm, Warfarindosing.org, and what this shows is... I'm sorry. My slides did not at all match with this. This is what you can put into this thing. Some of the studies used this to guide the dosing, once they had the genetic variation. So, this is a 65-year-old female, non-Hispanic, Caucasian woman, 160 pounds, 5'5" tall. She smokes, is being treated for a DVT. Her baseline INR is 1.2 with a target of 2.5. She is not on a statin or any of those other medications. On the left is just the frequency of the different distributions. If no genetic polymorphism testing was done, the dose that would come out of this without any information on the genes is 7.5 mg. If, instead, you combined the lowest risk versus the highest risk genotypes into this algorithm, the dose range would then be 5 to 11.5 mg. So, it's a significant range, but again, that's kind of what you'd get in terms of dosing based on this algorithm used to incorporate the information about the genetic genotypes.

This is just a reminder to me when I talk about testing that are genetic tests, that these are really things to consider, in terms of evaluating the evidence related to genetic tests. And I think pertinent to this, probably the most important things are, how can we apply this information to patient care? What are the absolute and relative effects, and is the patient better off as a result? Obviously, all of these other questions are important, but I think in terms of patient important outcomes, those are the focus.

Kevin Walsh: Can I interrupt you, Charissa, and ask you a question?

Charissa Fotinos: Yes, you may.

Kevin Walsh: On slide 11, so basically what this is telling me is, if I had done the genetic testing, I'm somewhere between... I'm told give her somewhere between 5 and 11?

Charissa Fotinos: No. You're going to be told that the starting dose is 5. If the genotypes are the most common and not variant. Alternately, if this person has the least common genotypes that are associated with Warfarin resistance, you're going to be told, instead, to start with 11.5. So, this is used to guide a starting dose and subsequent doses after that so you can check in the next day or three days after, plug all this in.

Kevin Walsh: So, is a provider, if I had done that study, I might be told to start at 5, start at 8, start at 11?

Charissa Fotinos: Correct.

Kevin Walsh: Somewhere in that range?

Charissa Fotinos: Correct.

Kevin Walsh: Depending on the allele content?

Charissa Fotinos: Yeah. Exactly.

Kevin Walsh: Thank you.

Charissa Fotinos: Does that make sense? Are we good to keep going? So, I think that it's not just about what kind of genetics are involved in drug metabolism, certainly, there are the pharmacokinetics and dynamics, and I think the other things to keep in mind are there are other factors, that's absorption, distribution, based on body water, disease states, and then drug interactions. Really, but a piece of drug metabolism relates to genetics. I think that's important to keep in mind. From a more practical standpoint, what we're talking about is response to Warfarin, and really, all of these factors influence the way in which Warfarin is metabolized and contributes to the INR; smoking, alcohol, drug interactions, hypermetabolic state, someone has an acute illness, fever, diarrhea, over-the-counter diet supplements, and really adherence, I think, are important. If we overlay the contribution of genetic variants to Warfarin response, it's about 11 to 30%. So, I think we're saying there is a test and it can help us explain about 11 to 30% of the variation, but all these other variables contribute to the rest. So, as I think about it from a clinical decision making perspective, I would venture to say there's a difference in how concerned we are about our initial INR outcome, whether or not we're preventing a clot in someone who might have a-fib versus treating a pulmonary embolus. So, how we... or what we're willing to tolerate, in terms of risks, may differ.

Our decision as to whether or not to incorporate genetic testing, and really the first piece is, is there analytic validity. I think people are pretty good at identifying genotypes. So, that is really not much of a concern here. Then, if we do the test, we'll use some sort of augmented algorithm. We'll put in a lot of variables, put in the genotypes and get something like were shown a few slides ago, or we'll just use that algorithm by itself, or because we've been in practice 20 or 30 years, we'll just do what we always do. So,

really the next step is, we're trying to impact and get to an appropriate range, for as long or as maximal amount of time, the INR. This is really the clinical validity piece. Does this information either change my behavior as a provider, or does it lead to something, which then can lead to clinical utility? Again, I've put the confounders there, because the genetic piece of this explains about 30%, but all the other confounders contribute to what the INR turns out to be. Ideally, we want to reduce morbidity and death, and intermediate outcomes, as you'll hear in the upcoming presentation, really largely are about clots and major bleeding. That's really the clinical utility.

This is just a brief review of the evidence you'll hear in much more detail, and looking at is there is a dose or medication change compared to no test, quality of evidence doesn't apply here. It's built into the algorithms and generally, the changes that are made are in the first week to two weeks of treatment. Then, the genotype is really not used after that to inform future dosing from that. The quality of evidence for whether or not there is an effect on the percent of time in the therapeutic range is low, as is whether or not there's an effect on over-anticoagulation. There is moderate quality of evidence that says there is not a statistical difference, in terms of the effect on thromboembolic evidence, and I put in red what I think is important, and we'll spend a little bit of time talking about is, is there an effect on major bleeding, and moderate evidence says yes, for about every 100 persons tested, there is one fewer major bleed, and I would say... and there's some caveats to that.

Are there direct harms, harms from the test? No. Subgroup differences really, not enough information to make a statement either way, similar to subgroups related to patient characteristics, and Dr. King will clarify that much better. In terms of the cost-effectiveness information, the quality of evidence is low.

Think about people who are at risk of bleeding, and these are probably fairly straightforward. I put a question mark after age 65, because the studies vary in terms of whether it's 75 or 65 or 70 that's used as a cutoff for increased risk. Most of the rest of these probably make sense. Probably the highest contributor or risk factor for bleeding or people with a history of GI bleed. So, I think that still is a consideration when we put all of this information about anticoagulation together.

This slide looks at a group of people who were treated for atrial fibrillation, and the point of this is to show that the risk of bleeding really is in the first 30 days. You can see that people with CHADS scores, which the point of a CHADS score is to better identify those at most risk of bleeding. So, you

can see the rate of hemorrhage is 14 and 17% in the first 30 days versus 4 and 7% overall, or 6%, and the remaining five-year follow-up. So, again, risk of bleeding is most in the first 30 days, and that makes sense with why the dosing algorithm that uses genetics is done the way it does, and this just reinforces the fact that the vast majority of bleeding in this study anyway came from GI bleeding.

This shows going back to the risk of moderate hemorrhage while not using genotype, we're not really talking about thromboembolism here, because that was not a statistical difference in the evidence review. What we are talking about is increased hemorrhage risk and you can see that at the outside INR above 3.5, and you can argue whether or not you're going to kind of coagulate to 3 or 3.5, but this was a study done for nonvalvular a-fib for prevention. The risk of bleeding, cranial bleeding specifically, went up quite a bit after an INR of 3.6. That's why we try to control that, but I think what's also worth pointing out is that if you look at the intracranial hemorrhage that occurs within the normal, what we call, either normal INR therapeutic range, to the upper, there are plenty of cases here, too. So, it's not just the people who have intracranial hemorrhages when their INR exceeds our target value. They have them even at a normal INR.

This is just a closer look at one of the studies that contributed most to the moderate quality of evidence with an increased risk of bleeding, and I think the point that I'd like to make here is that again, the vast majority of major bleeding episodes occurred in people who had an INR less than 4. So, we wouldn't necessarily have been able to prevent those bleeds by monitoring INR, because we'd figure they're therapeutic on most of the bleeds that contributed to the findings in that study were people who were in the therapeutic range.

Current coverage: Regence does not cover, PEBB, or Kaiser. It's considered investigational. Medicaid fee-for-service and managed care is not covered. Labor and Industries does not cover it. Department of Corrections does not cover it.

Other payers: CMS, it's not covered unless it's part of a randomized control trial. Noridian mimics the national coverage decision. Aetna and Cigna do not cover the test.

So, in terms of the agency medical directors' recommendations for pharmacogenomics testing to guide oral anticoagulant dosing, there is currently not strong or consistent evidence that outcomes important to patients are improved, and we recommend no coverage. Any questions?

- Gregory Brown: How long does it take to get the test back?
- Charissa Fotinos: That's a good question. Can you speak to that, Melissa?
- Melissa Hall: I can. I was actually involved in one of the clinical trials. Our Polyclinic was the center several years ago. It took two or three days to get results back. So, you do have to make a dosing decision while you're waiting for those results.
- Tony Yen: Do you see utilization of this test decreasing with the rise of [inaudible]?
- Charissa Fotinos: Our utilization is so low, it would be hard to say if it was for that or another reason. So, we just don't have great utilization numbers.
- Sheila Rege: If I could ask our expert a question. So, you see a patient, you have to do the dosing right away, and this test now comes back three days later. So, what happens then when the test comes back? Then, you change the dose?
- Melissa Hall: In my experience, I didn't find it all that helpful, because we had already had follow-up INRs by that point and were evaluating other variables that you've laid out so nicely.
- Sheila Rege: Alright. Thank you.
- Charissa Fotinos: Dr. King.
- Valerie King: We can get into this, but what I will say is that there were studies where the use of Warfarin was anticipated and known ahead of time, for instance, for surgery, and in those cases, the test was done preoperatively. So, that information was available. In normal clinical practice, you need it before you have it.
- Gregory Brown: So, the example I have is do a hip/knee arthroplasty. You are strong indication for anticoagulation if they've got a personal or family history of a VTE event, then, yeah. If they have a personal history with Warfarin, you can look that up, hopefully. If not, this would be the perfect example. Okay. We are ready for public comments.
- Josh Morse: We have no commenters signed up in advance and none signed up here at the meeting today. We should probably check the phones.
- Gregory Brown: Open the line. Okay. This is Gregory Brown. I'm chair of the Health Technology Clinical Committee for the Washington State Health Care Authority. We are reviewing pharmacogenomic testing for patients being

treated with anticoagulants. Is there anybody on the line that would like to make a public comment? If you are, make sure you're not muted so that we can hear you. Okay. I am not hearing any. If we can mute that line, thank you. Next, we are ready for our evidence report from OHSU.

Valerie King:

Good afternoon. It's good to see all of you. You'll see slides, too. It'll happen. Before the slides come up, I would just say thank you to Dr. Fotinos, because she's covered so much of the background, and I'm just going to whiz through these slides so that you don't have to hear it twice, because she did it better than I would.

There we go. Excellent. So, we'll follow a fairly standard order of service here going from background to methods to results, and then guidelines, payer policies, and a summary at the end. Please feel free to stop me if you've got questions along the way.

So, Dr. Fotinos has basically covered this, that it's a commonly used drug, even with the rise of other kinds of anticoagulants, the direct-acting anticoagulants known as DOAC's. Although this topic was scoped to be any anticoagulant, the fact remained that we only found evidence related to Warfarin, although in the report what you will see is that there are some upcoming or ongoing trials that are looking at pharmacogenetics related to DOAC's.

As Dr. Fotinos told you, there are really three basic ways of dosing Warfarin. The first way is a standing dose or a fixed dose method, and this is a start algorithm that would say give everybody 5 mg, or give everybody 7.5 mg to start, and then base subsequent dosing off of a blood test, an INR. Clinical algorithms, as Dr. Fotinos showed you, incorporate a variety of other things into them, such as other medications, age, gender, smoking status, etc. Then, pharmacogenetic tests basically add to those clinical algorithms. So, it is additional information put forward.

Dr. Fotinos covered this really well. There are basically three genes that have been used, and the polymorphisms in them are what is tested for the variety of ways that they may be expressed. These genes code for enzymes. When those enzymes, which are proteins, are made by the body, then they have an effect on the metabolism of Warfarin. I think that Dr. Fotinos' slides covered this really well, and just to say that the additional information on this slide is that the CYP2C9 enzyme can result... it's the big actor here. It can influence Warfarin metabolism up to 50% if you have a certain combination of alleles. For the VKORC1 enzyme encoded, it's about 25% per allele, and then the CYP4F2 is a minor actor with about 12% per allele variety.

I think that this is pretty much the range that you saw on the prior slides that depending upon the various combination of these alleles that a particular patient has, and I will say that they are really much better studied in populations of European descent than anybody else, but that they can account for somewhere between 10 and 30% of the variation in Warfarin dosing. They don't explain very well variations in dosing for other populations based on other ancestries.

Getting around to methods, you've seen the PICO already. So, this is adults, kids, anybody who needs anticoagulation. Genetic testing applied as an intervention for these kinds of tests to predict a Warfarin dose compared to any other usual care that we've gone over. Then, the outcomes are important because we really tried to concentrate on patient oriented outcomes, things that would matter to you or your mom or your dad. Then, there are some that are, I think, really surrogate outcomes that are used as common clinical measures, but that don't necessarily reflect end outcomes.

So, the patient important outcomes are death, thromboembolic events like stroke, and bleeding. Those are things that you can see clinically. The surrogate outcomes that we found commonly reported across studies are PTTR, which is the percent of time in the therapeutic range, and a high INR. So, an INR basically above 4. Then, we went ahead and looked for any direct harms that might arise from the testing, and economic outcomes, including cost-effectiveness.

The first key question had to do with the clinical utility of these tests. The second had to do with direct harms. The third had to do with subpopulations. The last had to do with those economic outcomes.

We basically looked at randomized trials, because there are a good number of them for this topic for key questions one through three, and then for key question four we looked at cost-effectiveness analyses or other economic studies if we could find them.

We did our general methods of a really comprehensive search going from Ovid Medline to the Cochrane trials register and Cochrane reviews. Then, we looked at a whole bunch of additional sources, including AHRQ, NICE, the VA, and also the reference lists of included studies. The one thing that we did that was sort of our routine method here is that Stanford University operates an NIH database on pharmacogenetic tests called PharmGKB, and we looked there, as well.

We looked at clinicaltrials.gov to see if there were ongoing or upcoming trials for practice guidelines, we looked at the national guideline clearinghouse. We also used Medline to search and looked at the websites of applicable clinical organizations, and per payer policies we looked at all the CMS databases, and then also took into consideration for private payers, Aetna, Cigna, and Regence. This is what we found at the end of the day.

We found about 1200, a few more studies initially. After we winnowed those out and took out things that just didn't meet inclusion criteria, we ended up with 18 studies. There were 13 randomized control trials and 5 economic studies. We used standard methods to assess the risk of bias of each of those studies, and a rating of high risk of bias, moderate, or low risk of bias was assigned based on standard scoring instruments.

Then, we applied a summary judgment using the GRADE system grading of recommendations, assessment, development, and evaluation. That really reflects our confidence in the finding of that particular outcome, ranging from very low to high. This will be a little bit different than the application of the GRADE system you saw in the last presentation. They used the arc modification of GRADE, and that has an insufficient category, and we either say it's none or very low.

So, mortality, major bleeding, thromboembolic events, PTTR, and over-anticoagulation are things that we performed meta-analysis on. I will say that while there were systematic reviews in this field, the most recent of them was not recent enough to incorporate the most recent randomized trials. So, we did de novo meta-analyses on this using RevMan software. Then, we also did some prespecified subgroups on those five outcomes, including what kind of control or comparator they used, what the risk of bias was in the studies, sample size, either greater than or less than 400 subjects. There's a statistical reason why we chose that cutoff, the number of genes that were incorporated into the test, where the study was conducted, the clinical indication for the study. We felt that surgical studies, for example hip and knee replacement, probably had a whole different kettle of stuff around them than did a-fib. Then, we also... to the extent that we could, we looked at the race and ethnicity of the base population enrolled in the study, and for the most part this was not reported to the level of granularity that would be the level you would want. So, we had to sort of look at studies where more than 90% of the population was of a particular race or ethnicity. That's as granular as we could get. Then, we looked at the follow-up period for the outcome, and as Dr. Fotinos shows you, there's a... most of the bleeding events really

occur in the first month of therapy, although they can occur at any point in time. So, we picked that one month of follow-up, as a demarcation.

That's a lot of background. Sorry, guys. Let's get on to the meat of it. So, these are the 13 randomized trials that we included. These are detailed quite a bit in your written report. They really go from around 2007 to last year. You will see just scanning through them that the size of the population enrolled in the study varied. Most of the studies were done in the U.S., but there were some exceptions. The indications, many included populations who were getting anticoagulated because they had a thromboembolic event, usually a deep venous thrombosis, or they had a cardiac arrhythmia, a-fib. Some also included populations that were postoperative. So, they had hip or knee replacements most commonly, or a heart valve, so a mechanical heart valve, usually an aortic valve. They also varied in terms of which genes they incorporated in their genetic algorithm, and then what the comparator was, whether they used just a fixed dose or a clinical algorithm to dose.

I will point out on this slide, and you'll hear this again, there were some what I would call pilot randomized trials. I think Hillman is an example of that with 38 people enrolled. And then, there were some just enormous trials, Gage in the end of 2017, and this is why we ended up doing a meta-analysis, because this is a lot of patients. It's over 1.5 thousand, and compared to all the other patients that were enrolled in all these other RCTs, it's a really substantial number. So, we really had to go ahead and do that.

There were really two that were cardiac valve only, Huang is one of them. Then, Wang towards the bottom of this slide was the other one. Kimmel also a big study, over 1000, but Kimmel and Gage were the only two that really had that many participants. Kimmel enrolled people with VTEs, a-fibs, and sort of a small but smattering of other indications.

So, we're going to get into looking at a lot of these forest plots. So, I wanted to give you a little bit of an orientation here. So, on the left hand side looking at it, you will see that those are the studies by author last name first author and the year of publication. Then, you see the individual data on each of those studies, including the number of events of whatever we're talking about, like a thromboembolic event or a bleeding event, and the total number of patients in either the intervention or the control group. The weight is the statistical weight of that study in the entire meta-analysis, and that weight is based not only on the study sample size but the event rate. Then, for each individual study, that's the result you would get only looking at that study. So, this is a risk ratio for each of those studies

with its 95% confidence interval. Down at the bottom, you get the pooled data. So, if you add them all up together statistically, you get a number of a pooled risk ratio, in this case with its 95% confidence interval, and that's not just a mathematical average of all those studies. It's a weighted average that bases on not only the size of the study, but the event rate in the study, and the spread of the estimate in that study. So, basically, the standard deviation of the event.

Down at the bottom, bottom on the left, you'll see a test for heterogeneity, and the piece that you really need to pay attention to there is the thing that's on the top line in that blue box at the far right, and that's I^2 . So, I^2 is a measure of statistical heterogeneity or how different are these studies one from the other. We basically think that if this statistical heterogeneity is above 50% that you really need to look at that pretty critically, and it may not be a good place to look at the pooled result.

Now, when you get over to that right-hand part with the thing that looks like a bizarre Christmas tree that doesn't have very many balls hanging on it, that's what it looks like. Each of the blue squares represents the estimate of effect for that individual study. Each of these lines is an individual study. The lines that come out of the blue box are the 95% confidence interval for that particular individual study. Then, at the bottom, there's a diamond, and that diamond is the pooled estimate of effect, and the arms of the diamond or the right and left points are the extent of the 95% confidence interval. For a relative risk or a risk ratio, one is the line of no effect. So, if something crosses that line, it's not statistically significant, and you can see that visually. For risk ratios, something that's on the left hand side would favor the intervention or the genetic test. To the right, it would favor the comparator.

With that, let's get to both the narrative and a bunch of those forest plots. Out of the 13 studies, only 12 of them gave data that was able to be included in any of these meta-analysis. One study just didn't report outcomes in that way. We've narratively included that study in the other outcome section within the report. So, essentially, seven out of the 13 reported mortality. Mortality was usually reported as all-cause mortality and was not specifically attributed to the genetic test. Again, attributed to the underlying condition or the anticoagulation. Three of those trials reported no deaths in either of the intervention or control group. In the pharmacogenetic group, there were nine deaths among over 1700 people for a death rate of about 0.5 or 0.5%, and about 0.46. So, essentially, the same in the control group with an absolute risk difference of 0.48 fewer deaths per 1000 people. The relative risk is just slightly over 1 but with a not-statistically significant confidence interval, but it did favor the control

group. The meta-analysis was quite unstable, because of the small number of events that you saw here. If you added a study and it had a lot more or a lot less deaths in one or the other group, it could throw the entire meta-analysis. So, the quality of evidence around this is quite low. It really could be changed by subsequent studies. So, that's what it looks like visually. I think you can see at the bottom, the big diamond is just sitting pretty close to that line.

For major bleeding, there were 11 of the 12 that reported studies that gave you information; however, the definition of major bleeding varied across all of these studies. It generally included bleeding into an important body space, like your head, or things that would require a lot of intervention, like a transfusion or hospitalization. Four of them did not have any bleeding in either group, and the results showed that the absolute risk difference was about 8.5 fewer bleeding events per 1000 people with the pharmacogenetic test. It is a significant confidence interval, and you can see that with the relative risk ratio, as well, and the quality of evidence around this is moderate.

Kevin Walsh: Wasn't there also an absolute risk difference calculated for pharmacogenetic testing versus algorithm?

Valerie King: Yeah. So, I'll get to that.

Kevin Walsh: Thank you. Okay.

Valerie King: So, we did subgroup analysis here, and these are just the main analyses that I'm presenting right now. So, one of the issues with this is that the clinical algorithms that were used, and usually when a study used a genetic test compared to... or an augmented clinical algorithm with a genetic test compared to that clinical algorithm alone, you have to kind of look at what the predicted dose would be. It was possible in the clinical algorithms that were used to get a quite high initial dose in these studies. So, it's theoretically possible, and I think that Dr. Fotinos' example showed this, to get to an initial Warfarin dose of 10 to 12 mg, and it really depended on which clinical algorithm was used. So, I'm just saying that point out that bleeding can be due to a whole variety of things, including the underlying bleeding risk, the CHADS score of that patient, but may also have had to do with the way the Warfarin was dosed in either group.

So, this is what it looks for the main analysis, and I think that this gets to your question about looking at the subanalysis where we divided by the control groups. So, at the top here, you see clinical algorithm dosing, and at the bottom, you see effects dose approach and then the overall is at the

very bottom. So, it's still statistically significant against a clinical algorithm and not statistically significant against a fixed dose. This is the opposite of what we usually see for PTTR.

For thromboembolic events, again, a lot of studies recorded this, but five reported no events in either group. There was an absolute risk difference of five fewer events per 1000 people, not a statistically-significant confidence interval. The results were very heavily weighted by the Gage study. That was the one that was done in an orthopedic surgery population that was very big. It accounted for 81% of the weight in this meta-analysis; however, when we removed Gage as a sensitivity, it really didn't change either of the estimate of effect, or the confidence interval very much at all. The quality of evidence around this particular outcome was also moderate.

So, here you see that big blue box at the top. That's the Gage study, and the size of the box relates to the size of the study. So, you can see it's huge compared to the others, but not statistically significant either with or without it.

We also looked at this one by comparator. I'm showing it to you and again, neither the clinical dosing or fixed dosing was statistically significant. For over-anticoagulation, which was basically defined as an INR above 4, there was one of these studies that defined it as an INR above 3.5, but we lumped it all in together, because they talked about it being... that was what they called over-anticoagulation. They did report... the studies reported this outcome at different time periods. So, I think you saw in the outline of the studies, some of the RCTs reported the outcome at two weeks, and some at 90 days. So, the amount of time that you collect an outcome can relate to the amount of time under this curve. So, if you think that most of the variability in Warfarin dosing happens early on, usually within the first month of dosing, the INR is subject to going up and down and up and down, then if you have more months of anticoagulation that you're looking at, the percent of time that someone is in range will, theoretically, go up with time. That just is both clinical experience. It makes sense. They did report in different timeframes and we found that there was an absolute difference of 18 fewer people with over-anticoagulation per 1000 people who were using the pharmacogenetic test, although the confidence interval is not statistically significant and the quality of evidence of evidence, overall, is low.

Gregory Brown: So, if I understand you right, it's per patient, not patient days. So, there's no way to normalize out the?

Valerie King: Studies reported this eleven ways from Sunday.

Gregory Brown: Okay. Thank you.

Valerie King: So, in some studies, you can pull out a little bit more granular detail, but for the meta-analysis, we had to go with the common thing.

This is the overall. You can see that it's close to being statistically significant, but it's not. This is by control group. Clinical algorithm on the top, fixed dose in the middle, overall at the bottom. Again, close, but not quite.

Then PTTR. So, again, 12 studies reported this. Everybody uses it as a measure in their trials. It's something you can measure. It varies. So, the definition of the therapeutic range differed by population by indication. That's normal. People with an artificial valve need to be more anticoagulated than somebody who is trying to prevent a DVT postoperatively. The length of follow-up for this outcome also varied quite a bit. Again, that curve and the amount of time that you could accrue the outcome was different. There was no statistically significant difference between the groups, although the pharmacogenetic group had 3.1% percentage points more time within the therapeutic range than the control group, statistically not significant. There was substantial clinical heterogeneity in this outcome, so you shouldn't believe it. The quality of evidence is low.

The subgroup analysis is very instructive here, I think. The pharmacogenetic group compared to the clinical algorithm and then compared to the fixed dose, what you see is even though both of these confidence intervals are not statistically significant, the point estimates are really different, one from the other. So, you see about a ten-fold difference, and that should perk up your ears. I think that you can see it really well on the forest plot itself. This is the overall. This is by subgroup. So, at the top, you can see that compared to clinical algorithm dosing, there is really no difference compared to adding genetic information. However, a fixed dose algorithm, this, again, is starting out with usually a dose of 5 mg. It's different. It's different from the top. It's different from clinical algorithms. Neither of them, again, are statistically significant, but they're really different one from the other. I think that what we take away from this is that simply the use of a clinical algorithm accounts for most of the difference that you see here.

So, summarizing all of these clinical utility or clinical effectiveness outcomes, for mortality you see no statistical difference between the

number of deaths with and without pharmacogenetic testing, although our confidence in that estimate is low. For major bleeding, our confidence is moderate that there is a small difference in favor of pharmacogenetic testing reducing major bleeding events. For thromboembolic events, again, we have moderate confidence that there is no difference. For over-anticoagulation, we have low confidence that there is no difference. For the time in the therapeutic range, we, again, have low confidence that there is no difference, and we believe that most of any statistical difference that you see is based on the comparator group.

So, all of these studies had limitations. There were none that were perfect. There were a couple that were at low risk of bias that were really well done, but that's still not perfect. Most of them reported surrogate outcomes quite robustly, and other outcomes not so well. Major bleeding was the only outcome that we saw even a hint of clinical difference with, and there is a statistically significant difference for mean PTTR in favor of pharmacogenetic testing that could be absolutely explained by the clinical heterogeneity of the comparator group.

For harms, those are really reflected in the meta-analytic outcomes. So, is major bleeding a harm or an efficacy outcome? It's both, and there are other adverse events that are reported um, in those randomized trials that we couldn't meta-analyze. Those included things like cardiovascular events, stroke, myocardial infarction, serious infections, way, way, way high INRs or an INR not in the therapeutic range. Then, there were a lot of composite measures of adverse outcomes that combined things like heart attacks, stroke, bleeding, all together and didn't give you a lot of information about how many of each, but there was absolutely no pattern to those other adverse outcomes that would tell you that one thing was better or worse.

For special populations, we were able to do subgroup analyses by race for major bleeding, PTTR, and over-anticoagulation. We did not perform them for the other outcomes, because there were such limited numbers. The studies that reported those characteristics and limited outcome events. So, I think that we need to consider any subgroup analyses by race exploratory and you would need to do individual patient meta-analysis to get a better beat on that. So, the racial and ethnic composition of the populations enrolled in the individual studies is in Appendix C if you want to look at that.

For major bleeding, analyzed by race, they prespecified subgroup. There was not a statistically significant difference for White or Asian subgroups, but for studies with either mixed race combinations, the difference was

statistically significant in favor of the intervention, and for PTTR and over-anticoagulation, there was not a significant difference by any racial subgroup.

For major bleeding by indication in the subgroup analysis, it really didn't give you any statistically significant differences. The two groups that we could really pull out, because of the Gage study, orthopedic surgery, not statistically significant, but again, in favor of the pharmacogenetic testing, and there was a group of studies that were really mixed in terms of the indications. So, kind of a broad clinical application of anticoagulation that you might see in your anticoagulation clinic, Dr. Hall. Again, not statistically significant here.

When we looked at PTTR by the indication for the anticoagulation, this is what some people would call marginally statistically significant, the lower limit of the confidence interval sits right on 1, which is not technically statistically significant for orthopedic surgery. Then, for valve replacement, we saw quite a big difference, but again, that is a very special case where the anticoagulation is more variable at the beginning clinically, and where largely because of the anticoagulants that are given during the surgery. So, early dosing is a little bit... starts lower and is a little bit more variable. When we looked at a subgroup analysis for over-anticoagulation outcome, or an INR above 4 by indication, we did not see a statistically significant difference, and the only group that we could look at there was orthopedic surgery.

For economic outcomes, moving on to key question four, there were five economic modeling studies that were published between 2009 and 2017. Two of those studies were rated as having a high risk of bias, and three a moderate risk of bias. Interestingly, all five of them assumed a hypothetical population of people with a-fib who are having a new start on Warfarin. They didn't look at any other indication at all. Three of them assumed a U.S. perspective. One was U.K. One was U.K. plus Sweden.

These are the five studies. You can see when they were published, what our rated risk of bias was for the methodologic quality of the study. They all reported costs per QALY, or quality adjusted life year as an outcome measure. The one at the bottom, you can see, is reported both in British pounds and Swedish krona, but it's rough. The two at the bottom report in British pounds. So, those both would have a more favorable cost-effectiveness ratio in those particular settings. The three that were U.S. based ranged from \$60,000 to \$172,000 per QALY. They, interestingly, all report... all three of the U.S. based studies were in 2007 dollars. So, they're really easy to look at in comparison. The first two assumed men with a-fib

who were 69 years old. So, really, almost exactly the same analysis, except that the top one assumed a societal perspective, and the second one done by Meckley assumed a third-party payer perspective. The third one Patrick, also assumed a societal perspective and took people up to a year old and took men and women, but kind of similar. It depends on where you want to draw your cost per QALY line. Some people draw it at 50,000. Some people draw it at 150,000. Really, most of the time what you would see in this analysis is that at conventional thresholds used in the U.S., they would not be cost-effective.

Okay, guidelines. There were eight clinical practice guidelines that were published, since 2012, which was our cutoff of five years. Three included active recommendations against the use of pharmacogenetic testing for anticoagulant therapy, both the American College of Chest Physicians [ACCP], the Scottish Intercollegiate Guidelines Network [SIGN], and the Australasian Society of Thrombosis and Haemostasis.

Two guidelines recommended the use of pharmacogenetic therapy. Interestingly, they both come out of organizations that were set up to be in favor of pharmacogenetic testing more broadly. Three really did not give any recommendation one way or the other. CADTH, the ACC, and the AHA, and another taskforce from the ACC and AHA for valvular heart disease, specifically. The first one is for a-fib. I should say that the FDA labeling for Warfarin and its various brand names state that you can consider the use of pharmacogenetic testing.

Dr. Fotinos has covered this already, that neither Medicare NCD or LCD recommend coverage. Aetna, Cigna, and Regence plans covering this area do not cover genotyping for CYP2C9 or VKORC1. The other gene was not even mentioned in any of those particular policies.

So, overall, there were a lot of limitations here, really a small number of clinical events, given the number of patients enrolled in these studies. That's good for them to not have a bad thing happen, but you do see a lot of heterogeneity among studies, study population, for example, the percent of men or the percent of smokers or the percent of African-Americans, etc. The indication of treatment that we've already talked about, the comparator used, and how the definition of the outcome varied and was assessed across studies, and then certainly there was some heterogeneity based on the system in which it was done. So, even among the U.S. based studies and certainly this is even more true when you group in the international studies. What you see is that different hospitals in the U.S. do this differently. Different clinics do this differently. So, there's a lot of clinical heterogeneity around Warfarin management. So, you have

to really consider all of that as a kind of big pool of clinical heterogeneity, as you're evaluating.

I think we've covered most of this. Really, no statistically significant differences, except for major bleeding. Any questions?

Seth Schwartz: This is Seth. So, for the outcome of thromboembolic events, did you guys see any number needed to treat analysis on that?

Valerie King: So, we gave you an absolute risk difference. I can...

Seth Schwartz: I'm just curious, because those numbers, I mean, it's, like, thousands of patients that you're going to test to save to avoid one event or something like that. So, I was just...

Valerie King: Yeah. You are.

Seth Schwartz: ...the difference is, like, six per 1000 versus 15 per 1000.

Valerie King: So, this is per... I've got this displayed as per 1000. So, 5 per 1000, half a person per hundred, yeah. So, at least 200 people.

Mika Sinanan: From an economic standpoint, what's the cost of the test, just simply...

Valerie King: It's actually hard to get a beat on that. These tests were really expensive when they were introduced. They have come down with time, as all genetic tests generally have. I think they center probably around 200.

Mika Sinanan: And this is a focus test to do with things related to Warfarin. Is this information gathered in broader panels?

Valerie King: Yes.

Mika Sinanan: It is?

Valerie King: Yes.

Mika Sinanan: So, you could have a broad panel that dealt with lots of therapeutic agents.

Valerie King: And particular the CYP genes, both of those are involved in lots of other drug metabolism. So, you do see them in other panels that relate to other types of pharmacy products. The VKORC1, that one is much more specific to vitamin K use.

Kevin Walsh: I wanted to thank you for calculating the relative risk into absolute risk.

Valerie King: You're welcome. I'm sorry to put it per 1000. That's a hard frame for our little brains to wrap around, but putting in a frame of 100 is even harder, because you were looking at halves of events.

Kevin Walsh: Can I ask Dr. Hall a question? How common is the use of clinical algorithms in dosing?

Melissa Hall: That's a really good question.

Kevin Walsh: And I would ask, I would say outside of tertiary and academic medical centers.

Melissa Hall: I don't honestly know the answer to that outside of studies where an anticoagulation clinic is not available. Most of my frame of reference is in a very coordinated anticoagulant service situation. Even there, it's not consistent in use of algorithms.

Kevin Walsh: Okay.

Valerie King: The website that Dr. Fotinos showed you with the example of a clinical algorithm is widely available and free. Warfarindosing.org. It's super easy to use. I tried it out for this topic. So, it's not a proprietary weird thing.

Gregory Brown; Do you have the Gage study in your notebook there by chance.

Valerie King: I do. Would you like it?

Gregory Brown: I would like to look at that. Any other questions?

Seth Schwartz: I guess I was just curious, were there ever any instances of targeted use of this testing. So, for instance, in patients who were already high risk using it, like, using it in selected cases, or are there... is it not ever used in that way? Maybe that's more of a question for you, but?

Melissa Hall: I'm not aware of any studies like that, but I think that would be very interesting, because you mentioned the impact of the metabolism on these genetic tests. It is only a small percent of the whole picture. We already know many factors that put patients at risk, particular for bleeding. So, it would be very interesting to see if it's helpful in that setting.

Valerie King: It was not the subject of any trials that even were close to meeting inclusion criteria for this review. I will say that I did read about that

speculative use in some commentaries and some editorials that maybe for... they were saying speculatively maybe for somebody who has a really high CHADS score and still needed to be anticoagulated. I think what you're seeing clinically is that most of those people end up on DOACs anyway, except for people who have got valves.

Melissa Hall: I would agree. I think the clinical area of anticoagulation is really moving in that arena, especially in the high risk patients.

Sheila Rege: Probably more for the expert, so in the orthopedic procedures, I heard, but now in the valves, is that something that's in any way different that we should be considering as a subgroup, or is there data there? I didn't see a lot of data in that at all.

Melissa Hall: Nothing specific in that population.

Valerie King: There's not a lot of data. There were two studies that were really exclusively valve populations, both of them were basically at high risk of bias, both of them were conducted in China. So, different system from zip to nuts, different ethnicity of patients compared to the broad U.S. mix here in Washington. It's why we did the subgroup analysis, and we looked at it, and we still didn't see a difference.

Tony Yen: Can I ask you more about slide number 34 that you have. This is the slide that's most interesting to me about how each of the individual studies in and of themselves don't show really a difference in terms of major bleeding, but the meta-analysis does.

Valerie King: Yep.

Tony Yen: So, can you just comment, like, can you help just remind me personally about what's the validity of a meta-analysis that shows a difference when the individual studies don't.

Valerie King: This is why we do meta-analysis. We think that by pooling studies when individual studies are really under-powered to detect a difference for a rare outcome in particular, and this, fortunately, is a rare outcome, that you can get better precision by pooling. So, as you point out, none of the individual studies show a statistically significant difference, but the pool does, and it's simply because you've got finally enough events compare to the population, and you see a spread between the groups. It's interesting here, I... although I am suspicious that there is quite a bit of clinical heterogeneity among these studies, the I^2 is zero. Okay. In part, that is a statistical artifact, and it is an artifact of having wide confidence intervals.

So, when the confidence interval arms are wide and overlapping, it sort of tricks the statistical program into thinking that there's not much difference.

Seth Schwartz: I also had a question about the cost-effectiveness studies. We always see wide variability, and there's obviously a lot of assumptions that go on there, but those are pretty drastically different, 6000 pounds versus 170,000 pounds. So, I'm curious if you can comment on the differences between those studies and what were the major drivers of the differences between the cost-effectiveness ratios that they reported?

Valerie King: So, I wouldn't, even though it's a doubling of cost per QALY in the two studies that report in British pounds, so the two bottom lines, Verhoef and Pink, part of the difference here is that the cost of the test was modeled differently in those two studies. The profile of the people was a little bit different.

Seth Schwartz: Those two don't bother me so much. The difference between 6000 pounds versus \$171,000 dollars in the first study. So, yeah.

Valerie King: Yeah. Okay. Yeah. It's really different. Part of what you see here is that Verhoef used a lifetime individual horizon. So, talking about the individual person and the rest of their life. Eckman uses a societal perspective, also lifetime horizon, but societal perspective, because in both Sweden and the U.K. healthcare costs are borne differently and less by the individual, that may account for some of those differences. The price, the modeled price was different. So, the price had really come down in both the Pink and Verhoef cost-effectiveness analyses compared to the ones that were done with a 2007 perspective. So, it was factors like that. The perspective, the modeled population, the cost of the test, who bore the cost, and that perspective. Does that answer your question? A little? Not so much?

Seth Schwartz: Well, yeah. I mean, I think we always take this data with a grain of salt, but I think we usually... I think it usually gives us some ballpark where we're within a range. We can sort of say, okay, this is teetering on the edge of what would be considered cost-effective, but 7000 pounds is widely cost effective, and \$170,000 is widely not cost-effectiveness. So, I'm just, it just, it makes me want to just throw out all of this. So, I was just curious if there's some specific factors that could allow us to interpret this data, but it doesn't sound like there is.

Valerie King: I think I'd probably throw it all out. Yeah. I don't think it's very reliable for current decision making. Then again, all [inaudible], mostly men, but that's where the data really comes from. They were completely fair to do that.

It's just a limited perspective when you're trying to apply it to other populations, times, and places.

Seth Schwartz: I guess the one other question I have, which is a broader question. So, these specific tests that we're looking at, so these specific three genes, are there implications for those specific tests on other things, because P450 is obviously involved in the metabolism of a lot of different drugs. So, are we... is this test, potentially, offering us information that would be useful for a lot of other things, or is it really only targeted for anticoagulation?

Valerie King: Both of the P450, the CYP genes are involved in all kinds of other drug metabolism. So, potentially of use in other testing. It was not what we evaluated, but you do see those genes and those alleles more or less represented in panel tests for other drugs.

Melissa Hall: And really, from the AMDG perspective, it's really focused on anticoagulation.

Gregory Brown: Okay. Any other questions? Okay.

Valerie King: Did you get what you needed off Gage?

Gregory Brown: I did. Yep. So, just the event rates for the VTEs seemed really high, but they do what is often done in anticoagulation about total joints is they include asymptomatic DVTs found on venography that nobody uses. If you looked at symptomatic DVTs and PEs, there was no difference. Then, it was only closer to just barely over 1%, which is what you'd expect.

Valerie King: It was a super curious thing with this particular study where they did Doppler ultrasound on every patient at about a month postoperatively. They included those asymptomatic along with symptomatic ones in their overall analysis, but fortunately, they reported it by both symptomatic and asymptomatic. What you saw in the main analysis here was everything all jumped together, but we did do a sensitivity analysis where we substituted numbers for Gage that were symptomatic only to make it comparable to the other studies. We took Gage out and looked at it in sensitivity. It didn't make a difference.

Gregory Brown: The other thing it looks like they did is, they just did it for the first eleven days, I think, so that it... the startup period is where you have the most variability, especially without the genetic testing, and they still had a barely could find some difference, so. Time and range for the first eleven days, I'm not sure that's a clinically useful measure.

Valerie King: Yeah. Again, time and range, the reporting period on that really varied across studies, yeah.

Gregory Brown: Thank you.

Sheila Rege: I have one more question. How much does this test cost? Does anybody know?

Gregory Brown: We asked. We thought about \$200? Is that what someone...

Sheila Rege: I think somebody asked, I don't remember, but...

Gregory Brown: ...yeah. Is that per allele or is that for a panel of multiple?

Valerie King: No. I think that's just per test. They've come down quite a bit, but your agency medical directors may have an idea of what they're paying.

Charissa Fotinos: The one I think we had it as \$140.

Gregory Brown: And that covers all of them, all three?

Charissa Fotinos: Yeah. Well, it was for the...

Valerie King: That's generally per gene.

Gregory Brown: Per gene. Okay.

Valerie King: Yeah, not per allele, but per gene.

Gregory Brown: Okay. So, for three of them, it's, you said 140? So, 3, 420? Anyway. Okay. Thank you. Any thoughts?

Charissa Fotinos: It's been \$140 to \$160.

Gregory Brown: I'm sorry?

Charissa Fotinos: The costs we have range from about \$140 to \$160, and that's just for the CPY.

Gregory Brown: And that was per gene? Yeah?

Charissa Fotinos: Yeah.

Gregory Brown: Okay. Thank you. Break?

Kevin Walsh: Ten minute break time?

Gregory Brown: You getting old and you need to have... the bladder needs a? Okay. There we go.

Sheila Rege: We're good.

Gregory Brown: I think we're a little ahead of schedule, or right on schedule. So, okay. Yeah. Let's take a ten minute break, and we will reconvene.

Well, Carson, this is right up your alley. What are your thoughts?

Carson Odegard: I have a question on utilization. When this came before the agency, was it... what was the highest interest? Was it just the efficacy portion of it or was cost a factor?

Charissa Fotinos: No. It's primarily efficacy.

Carson Odegard: Yeah, because cost...

Charissa Fotinos: It's not expensive. We are getting daily requests for more and more genetic panels to do different things. So, this is a start at trying to have a standardized way in which to look at them.

Carson Odegard: Okay. Yeah, because it looks like the cost has actually gone down from 15 to 17, so yeah.

Charissa Fotinos: Yes. The cost has come down.

Kevin Walsh: That wasn't an opinion. He asked for your opinion. Come on.

Gregory Brown: Dr. Walsh?

Kevin Walsh: No. He has to offer an opinion.

Carson Odegard: What kind of opinion would you like?

Kevin Walsh: Well, what did you think? The same one we vote on every time, Carson.

Sheila Rege: You can use your straw poll things.

Carson Odegard: Can I? Okay. Good. Yeah.

- Gregory Brown: Do you see anything here?
- Kevin Walsh: There is a statistically significant difference in major bleeds, but the absolute, because the absolute rate is so low, I don't feel that the statistical difference is clinically significant. That's the only benefit I see. So, I'm not enthusiastic.
- Gregory Brown: So, did that go away when they did the clinical algorithms, as opposed to just the fixed dosing in the group?
- Kevin Walsh: I think there was a bigger difference in between the pharmacogenetic testing and the clinical algorithm than there was between the pharmacogenetic testing and fixed dosing.
- Valerie King: Yeah. It did not.
- Kevin Walsh: Which was kind of backwards from what you would imagine.
- Valerie King: It didn't go away. You're exactly right. It was in an opposite direction of what you saw with PTTR.
- Kevin Walsh: Right. So, even those two rates, which were the widest rates, the biggest difference, I did not think it was clinically significant.
- Gregory Brown: Okay. Anybody else?
- Laurie Mischley: I agree with Kevin. I'm not terribly enthusiastic about it just based on the small incidence that we see overall in bleeds.
- Mika Sinanan: It's an isolated test. I was querying whether this could be a part of a more generalized assessment. It would be economically feasible in a big range of guidance for different practitioners and different specialties. So, as it stands, I'm not impressed.
- Seth Schwartz: Yeah. I mean, the same thing. I think this type of testing is clearly growing, and we've seen some instances where it has real potential for changing the management for these patients, whereas, in this situation, I think we have fairly good clinical guidelines for handling this. While it's not terribly expensive, it doesn't seem to be helping really that much either. So, I'm not seeing a significant benefit here.
- Sheila Rege: Sheila Rege here. I would agree. I'm not seeing a significant benefit.
- Gregory Brown: Okay. Tony?

- Tony Yen: Sorry. [crosstalk]
- Gregory Brown: Well, pretty much we have a unanimous opinion that we're not seeing much benefit here.
- Tony Yen: Yeah. I don't see much benefit. That's why I was kind of focusing on just one slide that showed a little bit of benefit for a meta-analysis, and that was it. I think meta-analysis data is weaker than individual trial data.
- Gregory Brown: Should we go to our tool? Any more discussion? I don't see a lot of controversy here, I guess. We're all pretty much on the same page. We'll go through our tool. Is it page five there? So, safety concerns? I think we kind of threw out the harms of testing, you said. So, they're not really worried about harms of blood draw or whatever. Cardiovascular events, serious infection. Again, I agree. For the testing, I don't think there's really much safety concern for the actual testing. So, we're more... so I guess we should say any... so I guess if we pose the question correct, is there any... is there a difference in safety issues for anticoagulation based on standard clinical protocol versus pharmacogenetic testing. Any safety issues?
- Josh Morse: So, is this a straw or are we going to the...
- Gregory Brown: No. I think it's... we don't really have any discussion or controversy here. So, we're going straight to our tool.
- Josh Morse: Okay. Alright. One, two, three, four, five, seven equivalent, more, some; more and some.
- Gregory Brown: Efficacy. We talked about major bleeding, small difference, statistically significant but probably not clinically significant. Is that a summary of what others are? Okay. Any?
- Josh Morse: Six equivalent, two more, and some.
- Gregory Brown: In terms of cost-effectiveness, I guess, if it's not effective, how can it be cost-effective?
- Josh Morse: Five unproven, one equivalent, two less.
- Gregory Brown: So, I think we're ready to make our coverage decision. Any discussion over any of those three areas? Okay. So, cover, cover with conditions, or not cover?

Josh Morse: I see not cover.

Gregory Brown: Yep. It's unanimous.

Josh Morse: And for Medicare.

Gregory Brown: So, that is consistent with the Medicare, because they do not cover nationally or locally with Noridian. In terms of clinical practice guidelines, we are consistent with the professional organizations. We're not consistent with the... what the society set up for pharmacogenetic testing, apparently.

Josh Morse: Okay. Thank you, very much.

Gregory Brown: I think you got to be the expert for the most noncontroversial conclusion we've ever made in our lives. So, thank you for your help today. Unless anybody has any other business. Susan, thank you for coming and seeing how we function and operate, and welcome to Health Care Authority, and it's good to have you on board. Thank you, everybody for participating today.