An audio recording of this meeting is available on our website at: http://www.hta.hca.wa.gov/past_materials.html.

Health Technology Clinical Committee Public Meeting
November 16, 2012

Craig Blackmore: Good morning everyone. I want to get the meeting started. If I could have the committee members take their seats, please. It's just a little after 8.

Well, good morning everyone. We have a quorum of the committee members so I'm going to call the meeting to order. This is the Washington State Health Technology Clinical committee meeting and we are now in session. I'm Craig Blackmore, the committee chair. There's a few – just points to be raised before we start. The meeting is being recorded and there are people potentially participating over the phone. So reminder to the committee members to speak into the microphone and reminders to everyone to identify yourselves.

The first item on the agenda is HTA program updates.

Josh Morse: Good morning. I'm Josh Morse. I'm the program director for the Health Technology Assessment Program. Just for facilities we have restrooms down the hall to the right and if there's any emergency in this building we'll all exit out these doors and follow instructions out of the building.

So some quick updates. So today's topics for review are stereotactic radiation surgery and vitamin D screening and testing. Stereotactic radiation surgery will be happening this morning and the vitamin D is in the afternoon. I will give a brief overview of the program.

So the HTA program is located within the state agency called the Health Care Authority. It was created in 2006 through state legislation to use evidence reports and a panel of clinicians, these people here, to make coverage decisions for certain medical procedures and tests based on evidence related to concerns around safety, efficacy and cost effectiveness. Multiple state agency programs participate to identify

these topics and implement the policy decisions that come from this body. The participating agencies include the Health Care Authority, which runs the Uniform Medical Plan and the State Medicaid Program, the Department of Labor and Industries, and the Department of Corrections. The agencies implement again these determinations from this program within their existing statutory frameworks.

So the purpose of this program is to ensure that the medical treatments and devices and services that are paid for with state health care dollars are safe and proven to work. We provide resources for the agencies that purchase health care. We develope scientific evidence-based reports on these medical devices, procedures, and tests, and we facilitate this committee. We staff the committee and these are our practitioners who work to determine which medical devices, procedures meet the tests for safety, efficacy, and cost effectiveness.

Our overall program objective is better health for the citizens of our state. We strive for transparency. We striver to minimize bias, consistency, flexibility and we are cyclic in nature in that we are able to re-review our policies as needed. A very high-level overview of our process. At least annually the director of the Health Care Authority, based on nominations from our state agencies and from the public, selects technologies for review. We then develop project plans and contract with vendors to develop evidence reports. We public draft key questions, draft reports for public comment. This process takes two to eight months to complete. We then bring that information to this committee here in a public meeting for a decision and this committee meets quarterly.

The purpose is to pay for what works. Again, we use transparent processes. We strive to find the best available evidence and we strive for independent decisions from this committee. The key questions for the program are: Os it safe? Is it effective? And does it provide value for the State of Washington? The basis of these decisions: the clinical committee must – decisions must give greatest weights to the most valid and reliable evidence. Objective factors for evidence consideration include the nature and the sources of the evidence, the empirical characteristics of the studies or trials on which that evidence is based and the consistency of the outcomes across studies. Additional factors might include recency, how recent the information was developed; how relevant it is to the questions that we are asking; and considerations of bias.

These are the topics that were selected a year ago that we have been reviewing. The first two, four, six or so topics have been reviewed thus far this year. Today we are reviewing, again, the stereotactic radiation surgery and the vitamin D. Coming up in the spring, in March, hyperbaric oxygen therapy for wound care and brain injury will be reviewed along with cervical level fusion for degenerative disc disease. In May we have scheduled ablation procedures for supraventricular tachycardia. Along with cochlear implants by versus unilateral. And then looking out to next September we currently have scheduled carotid artery stenting and likely cardiac nuclear imaging will be happening in September as well.

This is a public program and we invite people to participate. All of our information is published on the web. Our web address is here. If you're interested in program updates you can email our program inbox there. Public comment is collected on the following here: proposed topics, which will be released for the following year, for next year (we are releasing those either today or on Monday), key questions, reports and draft decisions. All comments are brought to the clinical committee here in those open meetings and the public is invited to nominate Health Technologies for review as well. Thank you.

Craig Blackmore: Thank you, Josh. Craig Blackmore, again. Next item on the agenda is previous meeting business. Before we launch into that I do want to provide one update to the committee. This pertains to recent events relevant to a previous decision we made on bone morphogenic protein. We had discussed bone morphogenic protein at the March 16, 2012 meeting with final adoption of our coverage decision on May 18th. We made the decision to allow coverage for BMP2 with some limitations limited to the lumbar spine only ages 18 years of age and older, and only for primary anterior open or laparoscopic fusion at one level L4 to S1 or vision of lumbar fusion on compromised patient for hematologist bone and bone marrow harvest are not feasible and are not expected to resolve in fusion.

That decision was substantially more restrictive then I believe the prior state was in that there was a lot of off label use of BMP prior to the decision-making – prior to our decision-making process. The recent event is the release on October 25th of the results of a U.S. senate investigation into Medtronic, which is the company that manufactures this product. And what the senate found is – and I'm just reading from their press release. The full senate investigation document is posted on

the web. They found that Metronic without public disclosure of their roles, Metronic employees collaborated with physician authors to edit and in some cases write segments of published studies on its bone growth product of infuse [inaudible] these studies as published may have inaccurately represented in fuse as risks and may have placed added weight on side effects of alternative treatments. And then they report that Metronic made about $210 million in payments to physicians over a 15-year period related to this product. So, you know, I think from the standpoint of the committee our charge is to look at the best available evidence and we rely on the medical literature for that and we, you know, the literature is vetted through a very rigorous process by our evidence vendors. But it still gets down to "is what we read in the literature believable"? Is it a factual representation of what actually happened? And I think, you know, more information I'm sure will be forthcoming on Metronic and this particular product, but, you know, I think we need to be aware of the source and the potential biases and the potential limitations of the information that's being presented to us.

In terms of the decision that we've made, you know, we did substantially restrict the use of this in parallel to the FDA's – the approved indications. Certainly we and Josh and his team will continue to monitor if there's further action by the FDA or anybody else we could potentially re-visit this and of course we can revisit the decision through our usual re-review process as well. But I just wanted to bring that to the committee's attention. Some of this I think we had an idea about as we were having our discussion because some of these allegations and some of this information was available, but there's a little more information available now than there was at the time.

So the next item on the agenda is previous business – previous meeting business and the first piece of that is approval of the minutes. Approval of the minutes is separate from approval or finalization of the decisions that we made. But the minutes are available to the committee members and they are in your handouts and I would solicit comment on the minutes or a motion to approve them.

Man: I move to approve them.

Craig Blackmore: Do we have a second?

Man: Second.

Craig Blackmore: All in favor of approving the draft findings and decision around intensity modulator radiation therapy please raise your hands.

Josh Morse: All approved.

Craig Blackmore: Okay. So that concludes the previous meeting portion. Next is the new topic, which is stereotactic radiation therapy and stereotactic body radiation therapy and the first section of our work on this topic is for public comments both scheduled and open. We have been contacted by several people who wish to address the committee. And we're – five minutes. We've allocated five minutes to each speaker. We also allow people who haven't told us in advance, but are present and who wish to address the committee. If you could just please sign up. There's a sign-up sheet out in the hall and we will, at the conclusion of the previously scheduled comments, we'll have an opportunity for others as well. And finally those of you on the phone when we've completed the public comments from the persons who are present here we'll then un-mute the phone service and see if there is anybody on the line who wishes to address the committee by phone.

The procedure is we would ask you to come up to the microphone, identify yourself, tell us if you have any conflicts of interest, and tell us if you are representing yourself or some other group. I think that's it. Did I miss anything?

Josh Morse So first Dr. Rieke. Do you have slides?

John Rieke: No sir.

Josh Morse: Okay.

Craig Blackmore: Just before you start I think Margaret or Christine, somebody, has a warning sign. So we'll give you some warning when you have a minute left. We'll give you a warning to keep us on schedule here. Thank you.

John Rieke: Thank you. My name is John Rieke. I'm a radiation oncologist, medical director of the Multi Care Regional Cancer Center in Tacoma and I have no conflicts of interest. I'm representing a national organization, ASTRO, American Society for Radiation Oncology. And ASTRO is the largest radiation oncology society in the world with 10,000 – over 10,000 members on oncologists, biologists and physicists. We thank you for

inviting written and open public comments. We've submitted comments in May and another in late September that should be in your packets.

We also support extensive evidence development via our Radiation Oncology Institute and via our support of national cooperative groups such as the Radiation Therapy Oncology Group. We support many Phase I through III studies, all of which are listed on clinicaltrials.gov if – I think that's an important resource that we support.

First of all I'd like to just address our concerns with the report. The report compares radio surgery and stereotactic body radiotherapy with conventional radiation therapy in general. We feel that these technologies have been transformative and are not suitably compared to standard radiation treatment. And we feel that there's ample evidence for safety, efficacy and cost effectiveness in the literature. Important indications for SRS and SBRT are now really standard of care in our state. For example, for stage 1 non-small cell lung cancer treatment in patients who are medically inoperable. And for many brain lesions, for many patients requiring re-treatment, and increasingly for a rapid – very rapid and much cheaper treatment of diseases like prostate cancer.

Surgery compared to stereotactic radio surgery clinical trials will never really succeed in a timely way. For one thing it's very hard to establish equipoise. We have open studies presently for example comparing stereotactic radio therapy with surgery in stage 1 operable patients. A large cooperative group trial opened. It's been accruing very slowly. 45% of eligible patients in that study who've been approved for that study have refused saying that their refusal is based on the availability of a non-invasive procedure.

SBRT and SRS are replacing inadequate standard radiation therapy in a number of cases. The lung cancer case is one in point.

We believe that assignment of many important systematic reviews and cohort studies listed in Appendix G and listed as poor or fair studies involved questions that are really impossible to answer. How will this study – or how was the study done to minimize risk of confounding and show of causal effect? Well, we really think that's probably not a suitable reason for kicking a study out in a technology such as this.

Lastly, and not related to this study we simply like to say that we appreciate the actions of this committee. ASTRO is very much committed

to evidence development. We just would like to make sure that the committee is aware that the actions based on the OHSU report could restrict access of these important technologies to underserved populations and we wish to avoid disparities in regions like mine in Tacoma. That's of particular interest.

We feel SRS and SBRT are safe and effective and are of great transformative value to the people of the State of Washington. Thank you for your attention.

Josh Morse: Thank you Dr. Rieke. We need to take a two-minute technical recess to check our sound recording equipment. I apologize. And then we will continue with public comments.

Okay. It looks like we have the recording corrected. We will continue with the public comments. Dr. Tredway.

Trent Tredway: I have slides today.

Josh Morse: Yes, we will bring those up.

Trend Tredway: Are we still waiting for the technical – great.

Christine Masters: We just had to warm up.

Trent Tredway: And is it going to be on mine up here, or?

Christine Masters: No.

Trent Tredway: My eyes are getting a little bit bad.

Josh Morse: From reading a 414-page report.

Trent Tredway: Great. Thank you. I would like to thank the committee for giving me the opportunity to speak today. I would also like to thank them for not going after spine surgeons directly in this one. Basically, we talked a little bit about the definition of stereotactic radiosurgery. I am actually, Trent Tredway. I am an associate professor of neurosurgery at the University of Washington. I am also here representing the American Association of Neurological Surgeons, the Congress of Neurological Surgeons, and I'm the vice president of Washington State Association of Neurological Surgeons. Stereotactic radiosurgery is very important to me, because…

Craig Blackmore: Sorry. Sorry to interrupt. You have to tell us if you have conflicts of interest.

Trent Tredway: Oh, okay. The conflicts of interest, as you know, are already listed. I have received an honorarium from Medtronic. I've received an honorarium from Escolab, and I've received an honorarium from, I think that's about it. Synthes actually for teaching purposes, and I think that's in the list that I've already sent.

So, basically, we talked a little bit about stereotactic radiosurgery and the actual definition. In 2006, as you can see from this slide, the American Association of Neurologic Surgeons, as well as CNS, also with the support from ASTRO, which we were just represented by, basically came up with a definition of stereotactic radiosurgery, and you could see on this slide, and for sparing time to get to some of the important parts, basically stereotactic radiosurgery is a distinct discipline that utilizes externally-generated ionizing energy in certain cases to inactivate or eradicate a defined target in the head/spine without the need to make an incision. This target is defined by high resolution stereotactic imaging to assure a quality of patient care. Their procedure involves a multidisciplinary team including a neurosurgeon, a physicist, as well as a radiation oncologist. As far as stereotactic radiosurgery background, from a strict evidence-based medicine standpoint, which is what you like to discuss, most of the evidence regarding stereotactic radiosurgery is level 3 or higher. The majority of level 1 evidence in SRS exists for brain metastases and glioblastomas.

SRS was introduced more than 40 years ago in an era that really evidence-based approaches were less of a priority. Today, if a perspective trial of patients with small to moderately-sized meningiomas was designed to randomize patients through SRS, EBRT, or microsurgical resection, it would actually be unlikely to accrue secondary to clinical equipoise issues. While it may seem humbling that the majority of the practice of SRS is supported by class 3 evidence and a small amount of class 1 and 2 data, evidence-based methodologies are useful to organize existing literature to see if there is truly objective data to answer specific questions. However, there is overwhelming evidence derived from a broader way of institutions and hundreds of thousands of patients treated over more than 40 years to support the clinical benefits, cost effectiveness, and safety of SRS in patients who are eligible for SRS.

Now quality of life issues are very important to all of us, as you can imagine. So, from a quality of life standpoint, there is perspective evidence to support the use of stereotactic radiosurgery for patients with brain metastases, acoustic neuromas, meningiomas, and pituitary adenomas. There are a number of randomized perspective trials out there that discuss brain metastases [inaudible] as an excellent paper out. Basically, this defines the significant benefits in terms of neurocognition in patients related to SRS alone over SRS plus whole brain radiotherapy.

There are also studies in acoustic neuromas, as well as medium-sized meningiomas that are listed on this slide that demonstrate the quality of issues are improved. Also, in a non-randomized perspective study of pituitary adenomas, SRS afford neurocognitive preservation, as compared to patients undergoing external beam radiotherapy or being left untreated by pituitary adenomas, and that was published in 2012.

As a spine surgeon, it is very important to my practice, as well. With regard to spinal metastases, patients spinal radiosurgery has been demonstrated in a recently published phase 1 and 2 study to lead to significant reductions in pain and other symptoms and provide a high rate of progression-free survival while at the same time resulting in low spinal cord toxicity.

Other quality of life issues that have been looked at have been well documented in some of the papers that we actually have here.

What about cost effectiveness? Sorry, we've got a little glitch here. From an economics standpoint, SRS has been shown to be cost effective for multiple indications, including brain metastases, acoustic neuromas, meningiomas, AVMs, trigeminal neuralgia, and spinal metastases. In a comparison of surgical and followup costs associated with vestibular schwannomas in patients, radiosurgery has been less expensive than microsurgery, even when factoring in long-term followup expenses. In a cost-effective analysis by the Chang study, SRS alone had a higher average effectiveness than added whole brain radiation therapy. This finding is of high cost effectiveness in SRS and brain metastases patients, it is consistent with other prior publications. SRS has also been shown to be more cost effective in patients with brain metastases from 2012 and a 1995 study, as listed on the slide.

Cho also evaluated socioeconomic costs of open surgery and SRS in 174 patients with benign skull-based tumors. They found shortened hospital

stays, reduced complications, and improvements to return to work, and overall better cost effectiveness with SRS over resection of comparable groups.

There are a couple of other studies here by Leffler and also Papatheofanous, which is difficult to say, that also demonstrate SRS has some cost effectiveness that is very important.

In summary, overall the strength of evidence supporting the use of stereotactic radiosurgery for a diverse group of intracranial indications and spine metastases is high and overwhelming. Some level 1 and level 2 evidence and a myriad of level 3, 4, and 5 evidence spanning 40 years demonstrates efficacy and safety of stereotactic radiosurgery for appropriately-selected patients with malignant and benign brain tumors, vascular malformations, functional disorders, and spinal metastases. At this point, clinical equipoise may preclude some randomized studies. In addition, the higher cost effectiveness and improved quality of life afforded to SRS patients is something we should really take into consideration.

So, in conclusion, SRS remains one of the safest and most effective approaches in neurosurgery and radiation oncology. SRS technologies have resulted in a major paradigm shift, and we should consider this to be appropriate for some of our patients that we are treating. Thank you.

Josh Morse: Thank you, Dr. Tredway. Next is Sandra Vermeulen, please.

Sandra Vermeulen: Good morning. Thank you for asking us to help with some of these important decisions today. My name is Sandra Vermeulen. I have a slight cold. I'm not going to infect anyone, I'm sure. But anyway, I am here because again this is a very important topic. I work at Swedish. I am a radiation oncologist. I am the executive director for the Radiosurgery Program at Swedish. My conflicts of interest are that my professional group, which includes about 13 partners, is in joint venture with Swedish, and we do own a Gamma Knife and a Cyber Knife. We treat about 500 radiosurgery patients a year, and that's about half with Gamma Knife, half with Cyber Knife. I also serve on an international board that represents the Accuray Society, which manufactures Cyber Knife – and to make this go forward.

So, you all know this, and I must commend this audience for the 8,000 articles that have been published and written regarding radiosurgery,

both for SRS and SBRT. It's a lot of data. It's accumulated over 40 years, and you've done an excellent job at synthesizing it.

I thought I would show these slides, partly because I think the concept is hard to grasp. It's easy to read the material and say that there's less toxicity, higher doses, better cure rates, but this shows a conventional radiation dose cloud. This is a dose cloud that would represent treating a pelvic tumor, and you can see all those different colored lines. They represent the amount of dose that might end up in the patient's bowel, the bladder, skin, and that's what a conventional radiation dose cloud does. This is what we're trying to get away from. We are trying to move towards this type of dose cloud. This is an SBRT dose cloud, and it's representing treating a bone met in a person's pelvis. What it shows is that all the radiation doses that otherwise would be including the patient's bowel and the bladder, in this case have been greatly reduced, and as a result of that, we greatly reduce side effects. There is still fatigue. However, you don't see in this case the GI toxicities, the GU toxicities, and these patients, after they are treated, they often can go back to work the same day.

The quality of life is exceptional compared to when we do conventional radiation and some of the morbidities we've been causing, and again, we're trying to move away from those morbidities by reducing radiation to tissues that don't need to be irradiated that are adjacent to our targets.

So, when we look at the advantages, they have been already cited, but if we can increase the dose, spare the normal tissue, we can get better cure rates and less toxicity. And again, this has huge economic impact on the patient, because they are able, in many cases to stay employed and stay working.

So, the areas that we've treated, of course, you know, brain and the body, head and neck cancers, lung cancers, liver, pancreas, prostate, breast, previously-irradiated areas. Most of the data that has been published over the last 40 years is in the brain. There is very few class 1 evidence to support using radiosurgery, and as our last speaker just said, the reason is, it is very hard to tell a patient we want to put you on study, oh but by the way, there's a 10% risk of cognitive change. If you randomize two whole brain versus if we do radiosurgery, and we are going to just go after the lesion or the target in the brain, there have been numerous trials that have been out there. They don't accrue

patients, they finally get closed, and it's because of the lesser toxicity. So, we only have probably less than a half a dozen class 1 evidence data for SBRT and SRS, and it's because of this toxicity issue, and when you explain to the patient what they may be facing with conventional radiation versus these newer technologies, patients don't want to be randomized on clinical trials. Case in point, our lung trial. We now consider SBRT standard of care to treat stage 1 lung cancer. That's changed the standard of care, and yet there's no class 1 evidence. These are not randomized trials, but the data has been so compelling, the control rate so good, they rival surgery 90% controls treating lung without the toxicities. These patients can get off the table, go back to work, no associated economic impact on them, their daily life, their work, no side effects that were seen with conventional radiation, and that's the way we're gonna see it.

We already see partial breast irradiation. We're starting to see this at many of the university settings doing, instead of conventional radiation to breast, which takes six and a half weeks, we are starting to see this one to two-week course, and SBRT is being looked at to treat partial breast irradiation. Prostate, there's emerging data. Again, this is not class 1, but the side effects are little. The control rates are good, and yes, we know the studies still need to be compared and time needs to go by to prove to a group and audience such as yourselves that the data is sound, but in many of our cases when we look at conventional radiation therapy and IMRT, it is cost effective, there is better control, and there is less toxicity.

So, we've gone over cranial indications with the speaker before. Another thing to be said, a lot of times tumors can't be completely resected. So, if there's a residual tumor after surgery, we can use radiosurgery tools. If there are recurrent tumors, if the surgical approach is difficult, if the patient has comorbidities and is not a surgical candidate, this is a terrific alternative. Previously-irradiated areas, we can use the treatments again, and radio-resistant tumors. We also have emerging areas and functional disorders. We have 80% control of stopping essential tremors by burning a very small hole using the Gamma Knife into the lateral thalamus, and those tremors stop, as soon as the hole forms, which takes several weeks to months, and that's all the time I have, and that's all I'm going to say, but thank you very much.

Josh Morse: Thank you. Next is Dr. Patel.

Edward Kim: Actually, I'm Edward Kim. I'm a radiation oncologist. I'm covering for Dr. Patel. He, unfortunately, couldn't make it today. So, I'm just going to review some of his slides.

Josh Morse: State if you have any conflicts.

Edward Kim: Sure. I have no conflicts of interest. I'm a radiation oncologist at the University of Washington. So, sorry. How much time is allotted for these?

Josh Morse: Five minutes.

Edward Kim: Okay. So, not to repeat too much of the information that I'm sure you're all aware of and have reviewed, as well as the information that's been presented this morning, but one of the first things I'd like to talk about is just brain metastases. So, historically, patients with brain metastases have a very poor median survival, although not all patients with brain metastases are identical in terms of their response to radiation. So, oftentimes in studies we tend to lump all patients with brain metastases together, but certainly depending on the primary histology, there can be a variable difference in terms of how they respond to radiation and what the natural history of the disease is. So, there are certain subgroups of patients for whom median survivals can exceed over a year, even though on a whole, when you look at the majority of patients treated with external beam or whole brain radiation for brain metastases, median survivals are much smaller, typically on the order of maybe six to nine months.

So, the development of radiosurgery over the past several decades has allowed for pinpoint radiation to ablate brain metastases while avoiding the rest of the brain and the RTOG randomized trial that has been alluded to and is also described in the evidence report showed improved overall survival for selected patients with brain metastases with a single brain metastases, good performance status. The MD Anderson trial that is also alluded to and mentioned in the evidence report showed that patients had increased neurocognitive decline at four months when treated with whole brain radiation versus stereotactic radiosurgery. This is a small trial of approximately just under 60 patients, but part of the reason for that is actually that it was stopped at interim analysis because of early findings from the study with a preplanned stopping point. So, SRS, or stereotactic radiosurgery, can also be used for benign brain tumors and typically viewed as an alternative to surgical resection rather than

external beam radiotherapy simply because the response of ablative in terms of the response to tissue, it's more akin to surgery substituting radiation for surgery rather than the gradual response of fractionated external beam radiation.

So, again, Dr. Tredway has reviewed several of the series of data that support this approach with meningioma. Multiple series have been published, but the largest was a recent study from Europe with over 4,500 patients with a five-year local control rate in excess of 90% vestibular schwannomas, also excellent local control rates. Gliomas tumors fairly uncommon tumor, but recent series with over 130 patients, again a very large series for a very rare tumor, has shown a five-year local control rate approaching 90%, but also with a low-risk of cranial nerve deficits. Pituitary tumors, excellent control, also with radiosurgery.

So, some of the obstacles to generating randomized control trials comparing SRS to external beam radiation, I think one concept is that SRS is – probably a comparator would actually be surgery rather than external beam radiation. Dose symmetric studies have not been performed, just given the clear avoidance of normal tissue that is possible with SRS compared to external beam radiation. There is equivalent or oftentimes superior local control to external beam radiation when you compare historical series. There is certainly risk of long-term external beam radiation effects, which really have to do with the volume of tissue that's treated with external beam radiation sometimes when compared to radiosurgery, which offers more precise delivery of radiation with a very steep dose fall off, and then there's also just the issues of the amount of time that it takes a patient to go through treatment, typically five to six weeks for a standard course of external beam radiation versus one day for SRS.

Gliomas is also described in the evidence report. I think there is very good evidence that doing radiosurgery up front for patients with glioblastoma actually is not recommended, but there have been retrospective smaller series that actually suggest a role for it in the management of patients with recurrent gliomas, so a highly-selective group of patients who have already undergone standard treatment for glioblastomas but then developed recurrent disease localized at a later time point. Again, I think one of the keys is identifying the subset of patients that benefits the most rather than using a blanket approach.

So, a couple of quick slides on stereotactic body radiation therapy, which extends the same concept but to the body. In terms of biological equivalent dose, this is one of the concepts that is described in the evidence report, but it's critical that when you're delivering 60 Gy with conventionally-fractionated external beam radiation over a period of six weeks, the equivalent dose is very different from when you're delivering over a period of three fractions or five fractions. The far right column is actually the biologically-equivalent dose, and you can see when you see 60 Gy with conventionally-fractionated radiation gives you a BED of roughly 72 Gy. When you give it over 12 fractions, 5 Gy per fraction, it's 90, and again when you're giving it over 3 fractions, you actually have a biologically equivalent dose of 180 Gy, so a very substantial difference.

Looking at SBRT for lung, which is where most of the best data is, I am just going to flip through one quick last slide. So, just a slide from RTGO236, which was a trial of looking at SBRT in a very controlled fashion, which shows excellent local control at 98% and improving overall survival of 48 months, definitely miles above any historical standard. Thank you.

Craig Blackmore: Thank you, Dr. Kim. We will check for any, are there any signups? We'll check the phone. If there are any individuals on the phone who would like to comment, please let us know. Is there anybody on the phone who'd like to comment? Christine, can you mute the phone, please? Were there any signups?

Christine Masters: I didn't see any on the list, but…

Josh Morse: Okay, thank you.

George Larimore: I'm George Larimore, chair of the Department of Radiation Oncology at the University of Washington. My department offers stereotactic radiosurgery and stereotactic body radiotherapy to patients. We have no equity interests in any facility.

What I'd like to do is…

Josh Morse: Sorry to interrupt. Do you have any…

George Larimore: I have no conflict of interest. What I'd like to do is step back. You've heard a lot of individual data on different studies looking at how SRS and SBRT work. I'd like to step back and maybe take a look at the forest

rather than focus on specific trees. Radiation therapy has been used in the treatment of ionizing human malignancies, almost since its inception and discovery by William Conrad Rankin in 1895. These early beams were very poorly penetrating. We had poor imaging, and so we tended to use large fields. Over time, people evolved what's called standard radiotherapy giving 1.8 or 2 Gy/fraction five days a week to a total of about 60 to 70 Gy. We found that worked fairly well. We could do it with sort of acceptable side effects, but it wasn't really scientifically based. We now have a much better understanding of the radiobiological processes and much better understanding of the imaging. It's clear that this so-called standard fractionation scheme does not work as well as we'd like in many cases. In many cases, we can improve outcomes, as you've seen by some of these studies, if we give larger amounts of radiation each day and go to smaller total doses. It's more biologically effective.

In stereotactic radiosurgery, very high doses of radiation are delivered in a single treatment. We don't play on differences in response between tumors and normal tissues. We try to ablate all cells within that target, so we have to have very precise control of where those beams are located. This is more akin to a surgical resection than standard radiotherapy. When a small number of treatments are used over a shorter period, we call this stereotactic radiotherapy. It's a hybrid between surgery and standard radiotherapy. These shorter time courses offer much less stress in this location to the patient and their family than a prolonged course of radiotherapy. We also can then complete the radiation therapy part of an overall course of treatment much more quickly so it doesn't interfere with chemotherapy or other types of modalities as part of the overall treatment. The radiation fields we use must be exquisitely tailored to the target volume to keep side effects to a minimum. This requires both precise imaging and treatment delivery and a sophistication of these that causes more resources to be expended per treatment than compared to standard radiotherapy. It's made up economically of the fact that you have many fewer treatments. These techniques evolved to fill treatment needs that were not being met by standard radiotherapy. As you've heard, stereotactic radiosurgery gives a nonsurgical option of treating many intracranial disease processes, some of which are benign, such as arterial venous malformations, acoustic neuromas, trigeminal neuralgias, as well as various types of malignancies. The treatments are safe, and very few patients are going to be agreed to be randomized to this type of noninvasive treatment versus an invasive surgical procedure with prolonged recovery period.

Stereotactic body radiotherapy offers a safe and effective treatment of metastatic disease adjacent to spinal cord, treatment of early stage lung cancer without outcomes that are very akin to a surgical resection, again without the invasive procedure or the prolonged recovery period. So, I think you need to think about these techniques as more akin to surgery than to standard radiotherapy and keep that in mind when you look at their efficacy. Thank you.

Josh Morse: Thank you Dr. Larimore.

Craig Blackmore: That concludes the public comment period of this morning's discussion. Next, we have the agency utilization and outcomes.

Kerilyn Nobuhara: Good morning. I'm Kerilyn Nobuhara. I'm the senior medical consultant at Washington Medicaid, and I would like to thank the committee for their consideration of these topics. I think that you've already discerned that stereotactic radiosurgery and stereotactic body radiation therapy have very different levels of evidence supporting the two different technologies, and I'm sure that you'll ascertain this, as you go through your deliberation this morning.

Just a brief background about the technology in general. Stereotactic radiosurgery, again, is referring primarily to treatment of intracranial pathologies, stereotactic body radiation therapy is pertaining to treatment of other areas of the body. Again, the evidence levels supporting these two different technologies are vastly different, and I think that you will actually find your deliberation a little easier if you consider them quite separately.

The reasons cited by providers for their rapid dissemination of SRS and SBRT include academic centers in order to perform clinical research, to gain a competitive advantage in the marketplace, the ability to deliver much higher fractions of radiation therapy, and to allow for retreatment in certain select patients.

Stereotactic radiosurgery was also designed to treat inoperable intracranial pathology, and it really did start as a disruptive technology for neuro-oncology providers. However, the technology has disseminated very rapidly to other areas of the body, so we would recommend the completely separate considerations of SRS and SBRT.

You'll note that there's been widespread adoption without adequate comparative clinical trials to other radiotherapies or to even surgical resection. Also, keep in mind that there is no absolute consensus in terms of the number of radiation fractions, the radiation dose per fraction, or the maximum number or size of lesions, which should be treated at each session. Also note that there haven't been any comparative effectiveness studies of SBRT to IMRT, which is one of the reasons why we actually elected to separate these topics on different days.

An area of increasing controversy in the literature is the treatment of early-stage prostate cancer and also for GYN cancer treatment. So, we actually kind of avoided any kind of comparison for your deliberation this morning.

Remember that SRS and SBRT are treated as hypo-fractionated therapies, so this means from one to five sessions per patient for a treatment session and keep in mind that's actually much more convenient for the patient, as opposed to say IMRT or conventional external beam radiation therapy, which also often requires 20 to 30 sessions.

From the director workgroup perspective, the primary criteria ranking for safety were a medium concern, efficacy high concern, and cost a high concern. Current state policies: PEBB has a very detailed policy for both SRS and for SBRT. The PEBB Regence policy includes treatment of essentially all malignant and benign intracranial neoplasms provided that the patient is actually of a good functional status, so these set a Karnofsky Performance Scale of greater than or equal to 70 and a life expectancy of greater than six months. They also consider treatment for spinal or vertebral body tumors, as medically necessary, trigeminal neuralgia, and for stage 1 nonsmall cell lung cancers, also again in patients who have a relatively good performance status.

Washington Medicaid uses Hayes, NCCN, and LCD draft for considerations. All SRS and SBRT treatments are on prior authorization. L&I presently has no published criteria for SRS or SBRT, and the Department of Corrections follows NCCN guidelines.

There is no national coverage determination published by Medicare. There is an LCD determination published by Wisconsin. The Noridian LCD is presently still in draft form. To note, for the Wisconsin LCD, in reference to SBRT, they actually treat SBRT as a secondary treatment

consideration following other forms of radiotherapy, primarily IMRT. So, they actually kind of prioritized IMRT and EBRT over SBRT for a number of different neoplasms, and you can see lung, liver, kidney, and pancreas. So, while the indications are quite broad, again, they are trying to actually prioritize use of IMRT over SBRT. For SRS, for the LCD, SRS is actually considered medically necessary in this LCD, again for treatment of just about all malignant and benign intracranial neoplasms. The Karnofsky Performance Scale isn't quite as stringent as the PEBB Karnofsky scale where they are asking for a score of greater than or equal to 50% or an ECOG performance status of 2 or less.

SRS is also kind of merging into what's called SRT in this LCD meaning that while SRS classically referred to a single treatment session using a skeletal fixation device during the treatment, now that the technology has improved, cranial radiotherapy can also be hypo-fractionated meaning between two and five sessions. So, in this LCD, treatment of certain neoplasms and AV malformations falls under what they're calling as cranial SRT, meaning hypo-fractionated treatment.

From the workgroup perspective, again safety was a medium concern, and there were two primary issues that came up in our discussion of this topic. There was the safety concern because of the higher risk for toxicity because of the higher dose delivered per fraction. The second consideration is that SRS, in particular, and perhaps SBRT in some respects, allows for the treatment of a new population of patients who previously wouldn't have been treated otherwise, because they would have been considered inoperable.

So, as our radiation oncologists who spoke earlier this morning have described, it may or not have been more appropriate to choose a surgical comparator, as compared with EBRT for our topic, but we actually ended up choosing EBRT as the comparator for this discussion, but that also does raise a different type of safety concern, and that's why the Karnofsky Performance Scale and ECOG were placed into both the LCD and PEBB criteria, because although you are selecting a patient who is considered surgically unresectable or medically unstable and not fit for general anesthesia, in order to address the safety concerns, they do need to meet a certain performance standard.

So, the key questions that emerged are, what are the potential harms of SRS and SBRT compared to conventional EBRT? What is the incidents of

these harms? And what is really the necessity in terms of duration of treatment?

Efficacy was a high concern from the workgroup perspective. As you'll see, there is limited evidence to support the therapeutic effectiveness of SRS or SBRT versus EBRT, again, although I think you'll ultimately find that the evidence supporting SRS is much, much higher in level than the evidence supporting SBRT. There is even less evidence to support the therapeutic effectiveness of SRS/SBRT as compared to surgical resection and as alluded to earlier by our providers, that study probably could never be conducted.

In your deliberations, we request that you separate the CNS tumors from the non central nervous system cancers. Again, that way we can make final determination for SRS as opposed to SBRT.

Cost was a high concern from the workgroup perspective. This is a costly technology. Of note, however, keep in mind that the CPT and the HCPCS codes associated with SRS and SBRT are actually compensated per treatment course rather than per treatment session, as they are in IMRT. So, the CPT and HCPCS codes include treatment sessions from one to five, and therefore we are actually compensating per treatment course rather than per treatment session.

The agency utilization data from PEBB and Medicaid, you can see that the average paid per patient is varying quite a bit, between $16,000 and $29,000 for the PEBB population and for Medicaid the average amount paid per patient receiving SRS or SBRT treatment is between $11,000 and $16,000. Also note that over the past few years, the total number of patients receiving this technology has increased over time.

When separated out by age and gender, not surprisingly, the number of patients who are receiving this type of treatment goes up with age, which is what you would expect for any type of cancer-related treatment. The Medicaid population is reflecting Medicaid becoming the secondary payer for older patients and also reflecting a few of our pediatric clients who have received SRS treatment and these are all for CNS tumors.

Our utilization data: These are allowed charges from both PEBB and Medicaid. You can see that the maximum facility fee allowed from the Medicare population is $60,000. Essentially for professional services, the maximum amount allowed is about $5,000. The professional charges are

separate from the other breakdowns, which are for planning, navigation, delivery, and other associated costs. Sometimes, there's a collimator build or imaging studies, which are included in the total costs per treatment.

The diagnoses in the PEBB and Medicaid populations reflect what's in the national literature. The most common indications for SRS and SBRT treatment are intracranial pathologies. There are a few spinal indications, and the others would be primarily for lung, pelvic, and some GI and liver indications. Medicaid shows the same kind of diagnosis distribution with cranial indications being the most common diagnoses, which are referred for SRS or SBRT treatment.

So, again, the agency considerations, in general, the evidence supporting probable SBRT moreso than SRS is actually of low quality. The RCTs, which we will hear about from our vendor, address brain metastases and glioblastoma multiforme. The radiation morbidities associated with this treatment are quite mixed in terms of reporting, and the cost analyses studies are essentially nearly impossible to do because of the myriad of treatment options and the difficulty in choosing appropriate comparators for SRS and SBRT therapies. Some of the comparators, which are in the literature, include IMRT, EBRT, surgery, and palliative care.

So, the workgroup recommendations would be to cover with conditions for the following diagnoses: Those include medically inoperable or unreceptable primary brain neoplasms or metastatic disease for patients with a Karnofsky's score of greater than or equal to 70, a life expectancy of greater than or equal to six months, and limited tumor volume on presentation, for medically-inoperable or unreceptable early stage nonsmall cell lung cancers, also for patients with a Karnofsky's score of greater than or equal to 70, and a life expectancy of greater than or equal to six months. For symptomatic primary or metastatic spinal or paraspinal tumors with histories of previous radiation treatments to the areas or who have a requirement of high-dose radiotherapy, we would also ask that all other diagnoses be subject to agency discretion.

Craig Blackmore: Thank you. Are there any questions from the committee on the details of the presentation we just heard? Obviously, we'll have an opportunity to revisit.

Man: I have a question. The last slide. Dr. Nobuhara, you were saying and, and the wording in here is or.

Kerilyn Nobuhara: It should be and.

Man: And?

Kerilyn Nobuhara: Yes.

Man: Thank you.

Craig Blackmore: So, next on the agenda is the evidence report from our colleagues at OHSU. As they are preparing, I am going to take an opportunity to introduce Dr. Martin Fuss who is rejoining us as our clinical expert. So, thank you for coming back. The role of the clinical expert, as you know, is to help us to understand the clinical context and the technical details of the procedure and the committee members will, I'm sure, have questions in the course of this morning's deliberations. So, again, thank you for joining us. Are we ready?

Martha Gerrity: Thank you. I'm Martha Gerrity. I'm from the Center for Evidence Based Policy where I work about half time. The other half of my time I'm a general internist at the Portland VA Medical Center. I have an MPH in epidemiology and a Ph.D. in education. I have no conflicts of interest. We're delighted to be here and privileged to participate and contribute to the work of the HTA. This describes how the presentation will be chunked and the flow of the presentation starting with the background section ending with limitations of evidence. With your permission, I am going to go quickly through the background section, since much of it has been presented already.

We have already heard about radiation therapy, in general. This is a figure depicting where the comparisons we will be talking about today fit in. We're dealing with the center column, external beam radiation therapy, and specifically with the comparison of stereotactic radiosurgery and body radiation therapy with conventional EBRT. This, again, is another depiction of conventional radiation therapy in figure 2 where you can see possibly two beams delivering 1.8 to 2 Gy to a tumor affecting the normal tissue surrounding the tumor. The depiction of SRS radiation field where you have a number of different beams that can deliver 1 to 2 Gy. If you're going from different directions, the normal tissue would receive that lower dose while the target would receive a much higher dose, as indicated, up to 60 Gy.

I want to give you a little bit of clinical background on the various cancers that we'll talking about today, since we are cutting across a number of different cancers. These data are from the NCI. They're based on the surveillance, epidemiology, and end results database. They include the incidents between 2005 and 2009, as well as five-year survival. We've ordered them basically in the way we will present the data. First is lung, and I'm going to point out the incidence is relatively high, 62/100,000. The five-year survival specifically for localized stage 1 cancer is 52.2% and that's 2002 through 2008. Next are brain and spine tumors primary, and the incidence is much lower survival, five-year survival is lower across all of those conditions. I am then going to skip down to prostate, since that's been brought up a couple of times. Obviously, very high incidence in our populations, 154.8/100,000, but I also want to draw your attention to the five-year survival rate in 2002 through 2008 being 99%. Similarly breast cancer very high incidence 2.4/100,000, 89% five-year survival rate.

So, a little bit about SRS and SBRT and how the devices are approved by the FDA. The devices are approved for sale through the FDA 510K approval process that does not require there be comparative studies on efficacy or safety. This report provides a broader analysis of the evidence than is required by the FDA. SRS and SBRT use is growing in the U.S., as already indicated in the previous talk. Radiation oncologists in a survey reported their use of SBRT up 65% in 2010 from 30% in 2007.

So, the PICO and key questions for this report, the population is adults and children with malignancies where treatment by radiation therapy is appropriate. The intervention, as we have discussed, is SRS or SRT for the brain or SBRT for the body. The comparator is conventional external beam therapy, although we recognize that surgery and/or chemotherapy may be used for specific cancers. The outcomes I've listed by the key questions we'll be addressing. The first key question is related to the efficacy and effectiveness, and the outcomes include survival, various tumor control rates, quality of life, functional status, and other measures related to quality of life. Key question 2 is related to harms including radiation complications. Key question 3 is related to subpopulations. I am going to call out here pediatrics, although it's considered a population. We will report the evidence as part of key question 3 to call it out, since there were so few studies dealing with pediatric patients. Key question 4 deals with evidence around cost and cost effectiveness.

So our methods – for the evidence part of the review, we used best evidence systematic review methods. We started with a search. The search strategy was to look through Medline, Cochran, the AHRQ databases to identify recent good quality systematic reviews and technology assessments published between 2002 in April of 2012. Once we identified those, we looked at the last search date, and we updated that with Medline and Cochran's searches for subsequently published individual studies. We also did a Medline search for studies if there were no SRS or technology assessments, again through 2002 to April of 2012. We also looked at the 124 references from the ARC technology assessment of SBRT and then finally, we looked at the references from public review of the key questions and, again, from the references submitted in response to the draft report.

The inclusion criteria for the studies follow from the PICO. We had some additional inclusion criteria besides the fact that it had to be in English, since none of us read foreign languages. These, in general, we restricted sample sizes to greater than 50, except for the following cancers where we were expecting either a high incidence or a low incidence of those cancers. So, for key questions 1 and 3, efficacy and subgroups, for the central nervous system, we dropped the sample size to 20 and looked specifically for comparative studies because of the effectiveness and subgroup question. For non-CNS tumors, the more common cancers, we use the sample size of 50 to look specifically for comparative studies or included specifically comparative studies. For non-CNS cancers other than the ones listed above, we dropped the sample size to 20, and we also included some noncomparative studies, since there were very few studies to begin with but didn't want to miss any important information.

For key question 2, which was about harms, the sample size we used for inclusion was 50 for comparative and non-comparative studies, except for pediatric populations. We used a sample size of 20, and if there were studies that seemed to indicate there were serious harms. For key question 4, we looked at all comparative and noncomparative studies about cost and cost effectiveness and of note, we excluded dose and dosimetry studies. We next took each study that was included, and we used the grade method to rate the overall strength of evidence, and this was a two-stage process. First, we did dual ratings of study quality looking at risk of bias for each individual study, and these studies were rated as good, fair, or poor quality, and if you look at the table in the first column, we established the initial strength of evidence based on study design where randomized control trials, the initial confidence in the

estimate of the effect reported as high. For observational studies, those start out with an initial estimate of being low. The second stage is to consider lowering or raising the strength of evidence based on a number of factors here. For us, the biggest factor was the risk of bias in the individual studies, so we tied in the ratings of good, fair, and poor, and for many of the studies we dropped the quality ratings because of the risk of bias and ended up with the final strength of evidence that you will see in the report.

So, the next step, we looked at guidelines and policy. The guidelines, we looked at national and key specialty organizations for guidelines published after 2006. Again, we did do a ratings of methodological quality using the appraisal of guidelines research and evaluation or AGREE instrument. Again, provided summary ratings of good, fair, and poor quality for the guidelines. We also looked at selected PARE policies, as was presented, the Medicare and national and local coverage determinations, which you have already heard about. We also looked at Aetna, Blue Cross, Blue Shield, and Group Health.

So now, we will move to the results. We identified 3,034 citations and reviewed them for inclusion, 959 were submitted during the public comments on the key questions and 48 for the draft reports, 253 studies met inclusion criteria. These are all listed in Appendix F, 12 systematic reviews and technology assessments were identified, 141 individual studies of which only seven were randomized control trials. There were two case series that included only pediatric patients. There was an additional 51 case series that included pediatric patients, but we couldn't comment on them specifically, but – because they weren't stratified based on age.

Subsequent Medline and Cochran searches were done for randomized controlled trial after received public comments just to make sure that we didn't miss any very recent studies, and we did this for April of 2012 throughout October 10, 2012, and we identified no new randomized control trials.

So, for the findings, the overview. I am going to call your attention to the table that hopefully you have with you. It's the very high level summary of evidence. It's Appendix E in the full report and you can either follow that or just follow the information in the slides. So, this is the overview. Findings are grouped by cancer and strength of evidence starting with comparative studies. So, we will first be talking about brain metastases,

including subgroups and then primary brain tumors, including glioblastoma, glioma, and pituitary. I have italicized brain metastases and glioblastoma, because these are the cancers that have data from randomized controlled trials. We will then move to head and neck, which were primary craniopharyngioma studies. We then move into noncomparative studies. We will go into a little more detail with lung cancer, specifically inoperable stage 1, nonsmall cell lung cancer. We will describe the evidence for spine and then list all other cancers.

There were only two case series that focused on children. One was a case series of children with ependymomas and the other was a case series of children with glioblastomas. These are the abbreviations that you will see in the slides. On the left are the standard overall survival, local control. EBRT, when that term is used for radiation in the brain, it's referred to as whole brain radiation therapy, WBRT, and I will describe recursive partitioning analysis when we get to studies that use that information. On the right are the symbols that we'll be using for the very high level of evidence summaries. The comparison will be between SRS or SBRT to EBRT. A horizontal arrow indicates that there was no statistically significant difference in outcome between those two, an up and down vertical arrow means that the arrow was inconsistent across studies, an up arrow means that there were better results with SRS or SBRT. A decreased arrow means that there were worse results or reduced results with SRS or SBRT compared to EBRT.

Brain metastases, as everyone knows, are common, which is why we are going to start there; 40% of cancer patients have them. Of those with brain metastases, 30% have single metastases, lung, breasts, melanoma, colon, and renal cancers commonly have brain metastases. You've already heard in the background that steroids and whole brain radiation have been the mainstays of treatment. Surgery has been considered for some patients with single metastases, good performance status and stable systemic disease.

There were multiple comparisons of SRS and WBRT in the literature. We're focusing on three of them, SRS and WBRT versus WBRT alone. In the report, you see adding WBRT to SRS but that wasn't really the focus for today, so it's not going to be in the slides. We also looked at SRS alone versus WBRT and then SRS for recurrent or progressive brain metastases. These were case series only, but we included them here just to do all of the brain metastases at once. The overall evidence base across all of these comparisons, we identified seven systematic reviews.

Two were actually by Sow, one in 2012 that updated the 2011 publication. Those identified six randomized control trials. We also identified 12 cohort studies and 25 case series, and remember these are across all the key questions.

So, for the first comparison, which is SRS and WBRT versus WBRT alone, the overall evidence base included three good quality systematic reviews. These identified three randomized control trials. Only two were published. The third one was a small randomized controlled trial published in abstract form alone and no statistics were done for the comparisons. So, the systematic reviews and us, we did not include that in the evidence base.

The first RCT is Andrews from 2004, fair quality RCT including enrolled 333 adults but 2 dropped out before randomization. Patients had to have one to three metastases and good performance status. [inaudible] was of poor quality RCT including 27 adults, two to four metastases, good performance status. There were no cohort studies.

This is our summary table of the evidence. On the left will always be the strength of the evidence by key question and then the findings. You'll see arrows only for studies where we have comparative data. So, for key question 1, which were outcomes, it turns out that there was no statistically significant difference in overall survival. I have given you the hazard ratio from the Patel meta analysis of 0.82. You can see that the confidence interval just barely crosses 1. Some might call this a trend towards improved overall survival, but technically it's not statistically significant. For local tumor control, the combination of SRS and WBRT had improved local tumor control. The hazard ratios are listed there.

For key question 2, there was moderate strength of evidence that there was no difference between these two approaches in acute and late toxicities for key question 3, which was subgroups. The quality of the evidence was low, and I am going to call out, again based on the Andrews randomized control trial, single brain metastases compared to multiple brain metastases and the recursive partitioning analysis class 1.

Let me just take a minute to describe RPA. It is a way of identifying prognosis. People with class 1 have a median overall survival of about seven months compared to class 2 with four months and class 1 with about two months, well done study of this predictive model. So, the first comparison for single brain mets, there was increased median survival for

individuals with single brain mets. If you used the combination therapy compared to WBRT alone, it is 6.5 versus 4.9 months. For RPA class 1, again, if you used SRS and WBRT versus WBRT there was some survival advantage, 11.6 months versus 6.9 months. These were all statistically significant differences. There was improved local tumor control for these comparisons, and there was also a decrease in the number of patients with a worsening performance status using SRS and WBRT compared to WBRT alone. This has already been alluded to.

The next comparison is SRS versus WBRT. The overall evidence base, there was one good quality systematic review. This systematic review did not identify any RCTs. Linsky identified six cohort studies. One was a fair quality prospective cohort study. There were three retrospective cohort studies with concurrent controls. As you will note, there were two that were of fair quality, one poor quality. There were two poor quality retrospective cohorts with historical controls, and this is the summary of the evidence from those studies. For key question 1, the strength of evidence was low with suggestion of increased overall survival with SRS compared to WBRT and these were reported as narrative summaries of the four cohort studies. For key question 2 for harms, there was low strength of evidence that there was no difference in acute and late toxicities. For key question 3, there were no studies.

For brain metastases, the use of SRS for recurrent or progressive brain metastases, I am going to remind you that we're including it here, even though these are just case series, so no comparative studies. There was one good quality systematic review. They identified no RCTs, no comparative studies. They only identified 12 small case series, and the harms across these case series were very inconsistent.

For key question 4, we are going to cover economic studies altogether across these various comparisons. There was one fair quality systematic review that included two poor-quality economic studies that address the various comparisons of SRS and WBRT. There is actually a third poor-quality economic study, but it's that comparison of adding WBRT to SRS, which is in the report but not described here.

All studies took the perspective of the healthcare system. This is important, because the healthcare system was often a local hospital that was doing SRS at their facility. There was great uncertainty and any estimates of cost effectiveness for SRS due to the assumptions and the model was the conclusion of Chang, and we are going to provide you with

the comparisons that we looked at. It turns out that the quality of the evidence is very low for SRS alone. It's uncertain the next statement, but the suggestion is that SRS alone is more cost effective than WBRT alone or in combination with SRS. You can see for the comparison of SRS and WBRT versus WBRT, the incremental cost effectiveness ratio was $12,289. The incremental quality adjusted life years was about $10,000/$11,000. When you looked at SRS versus WBRT, which was a separate study, this study only reported cost per quality adjusted life years for SRS, and that was about $17,000, and then the cost for quality adjusted life year for WBRT was $10,381, so about a $7,000 difference.

Now, we are going to move onto glioblastoma multiforme. The overall evidence base for glioblastoma included one RCT, two cohort studies, three case series. Souhami has already been mentioned. It's a fair quality RCT. It included 203 adults with newly diagnosed tumors that were less than 4 cm in diameter. Patients to get into this study had good performance status, as defined by KPS of greater than 60. SRS was followed by EBRT plus carmustine, a chemotherapeutic agent, versus just EBRT and carmustine alone. There were cohort studies included, Norkedi, which was poor quality, 61 newly-diagnosed patients with glioblastoma and Kong, a poor-quality study with 114 patients with recurrent glioblastoma, so a mixed group.

So, for the results, strength of evidence for key question 1 was low, suggesting no difference in overall survival for SRS compared to whole brain radiation therapy. No difference in overall quality of life. For key question 3, harms low. Again, the quality of evidence or strength of evidence was low, that there was some increased symptomatic radionecrosis, which was the most discussed serious harm for SRS. This occurred in approximately 3 to 5% across the studies. It sometimes led to surgery for mass effect. There were no studies related to subgroups and no studies on cost or cost effectiveness.

Next is glioma, so a lower grade glial tumor. For a little bit of background, it's the most common primary tumor of the brain. It's classified by histology, astrocytes and pathologic grade low versus high. We use the categorization you will see in the report that authors used for the various brain tumors. We decided not to try to parse them, we'd just go with what the author's reported, so we classified them by the types of tumors. These are all the studies that were classified as just general gliomas. The overall evidence base included one cohort study that was poor quality, including 114 patients with recurrent malignant glioma

treated with salvage SRS compared to 360 historical controls, eight case series, one was fair and severe were poor quality, and I'm going to call out here the one pediatric study, Marcus, which was a prospective case series involving 50 pediatric patients with progressive low-grade glioma.

Strength of evidence and findings. For key question 1, very low strength of evidence. So, these findings are quite uncertain and, as you can see, there's inconsistency in median survival comparing SRS with WBRT. Key question 2, harms, there's suggestion of some symptomatic radionecrosis, occasionally leading to surgery for mass effect. Key question 3, this is one of the few pediatric studies, and it is a case series, so we can't give you any comparative data, but based on this case series, the overall survival across the case series was 89% at five years, 82% at eight years, 4% of patients progressed to anaplastic astrocytoma, 8% developed Moyamoya syndrome, which is a constriction of the arteries in the Circle of Willis, which is at the base of the brain and supplies the brain with blood and can cause cardiovascular accidents and seizures. There were no cost studies.

I'm going to move on to pituitary adenomas. Overall evidence based, two cohort studies, 13 case series. The cohort studies included Kong of fair quality cohort study with 125 patients with primary pituitary adenoma. [inaudible] is a poor-quality cohort study including 72 patients with both primary and recurrent pituitary adenomas. The case series included four fair quality and two poor quality studies.

So, the results – the strength of evidence, as you would expect, is low and very low, so for key question 1, low strength of evidence. No difference in overall survival between SRS and WBRT. No difference in local tumor control. Again, these are just suggestions that this might be the case, very low quality. This is a very uncertain result but with the suggestion that there's a decrease in the development of new hypopituitarism. These were the numbers that were provided: 61% of the SRS group, 72% in the WBRT group, but no statistical test was reported. Some of the side effects included headache, nausea, fatigue, edema, visual deficits, cranial nerve palsies. There were no studies involving subgroups or cost.

So, head and neck is next. Overall evidence base. There is one cohort study, poor quality involving 51 patients with primary or recurrent nasopharyngeal carcinoma, six case series all poor quality, three involve patients with primary and recurrent nasopharyngeal carcinoma, two involve patients with squamous cell carcinoma of the head and neck, one

was a case series of patients that had a variety of different cancers in the head and neck region. So, as you might imagine, the strength of evidence is very low. For key question 1, no difference in overall survival. No difference in local tumor control. For key question 2, harms, there was the suggestion that with SRS there is a decrease in serious, in other words greater than grade 3, late complications. The numbers they have provided, there were 20% of those getting SRS versus 40% of those getting WBRT. These included death, cranial neuropathy, carotid blowout, radionecrosis, trismus, xerostomia. There were no studies addressing subpopulations and no studies on cost.

Now, we are going to move into lung cancer, and I'm going to point out again that there were no comparative studies for lung cancer. A little bit of background, and I want to point out this background is for stage 1 nonsmall cell lung cancer. The three to five-year survival rate with surgical resection is estimated to be up to 60 to 80%, depending on the tumor size. So, that's with surgical resection for stage 1 nonsmall cell lung cancer. The five-year survival with EBRT is estimated again from case series of being 15% to 3% compared to with no treatment the estimates were around 5%, five-year survival. The overall evidence base, there is one poor-quality systematic review that included 35 case series of patients with inoperable stage 1 nonsmall cell lung cancer. From our Medline search, we identified an additional 33 case series. The majority of the studies focused, as I mentioned, on patients with inoperable stage 1 nonsmall cell lung cancer, although there is a study out of Japan that included people with operable cancer.

So, for the findings and evidence, for key question 1 the strength of evidence is very low, because these are case series. It suggests, although very uncertain, that three-year overall survival is 38 to 59%, five-year overall survival is 45%, and I put an asterisks there to just remind you of what it was for EBRT from case series done in the '80s of 15 to 30%. Overall survival for stage 1 tumors less than 3 cm being better than stage 1b, which are larger tumors. For key question 2, harms, very low strength of evidence. For serious acute toxicities, the ranges given were 2 to 5%, for late toxicities, such as fatigue, pneumonitis, esophagitis, dermatitis, chest wall pain, the estimates range from about 2% to 10%. There were no subgroup studies. For key question 4, there is very low quality of evidence, and the evidence was inconsistent across the studies related to cost and cost effectiveness.

Next, we're going to move to the spine. The overall evidence base, there is one fair-quality systematic review that included 29 case series. We found an additional 13 case series and one poor quality economic study and the strength of evidence for key question 1 was very low, involved local tumor control, pain, quality of life we couldn't even estimate because of the type of evidence and again, for key question 2 the harms are listed there, as described in the studies. There were no studies of subpopulations and for key question 4, there is very low strength of evidence that SBRT costs are greater than EBRT costs.

Now, the rest are all listed here. There are a variety of abdominal cancers, primary brain cancers, head and neck cancers, and prostate cancer. They were all case series, and I am not going to continue to bore you saying there's very low quality of evidence across all of these. They're all described in the report, and the details are in Appendix F. The only thing I'm going to call out is the second bullet point. There was only one fair-quality case series that focused on children. It included 21 children, mean age 7, who had resection and SRS for ependymomas. The median survival after SRS was described as 27.6 months with a confidence [inaudible] of 12 to 36 months, one-year overall survival is 85%, two-year was 53%, and three-year was 23%.

So, we looked at the mod database to see if there were any serious harms reported to mod. It was not particularly helpful. There were three reports of serious adverse events, two patient deaths, one from metastatic lung and one from metastatic stomach cancer, one patient had a portal vein thrombosis and hepatic artery occlusion. More serious adverse events have been reported in the lay press than in the mod database.

For guidelines, we identified 16 guidelines related to SRS or SBRT. One was good quality. It was the Australian Cancer Network and involved primary melanoma. Two were fair quality from the American College of Chest Physicians dealing with stage 1 and stage 2 nonsmall cell cancer. One was from ASTRO related to brain metastases, and there were 13 poor-quality guidelines. Those are listed there. I want to just point out that many groups use the National Comprehensive Cancer Network guidelines. We made multiple attempts to try to identify their methods via phone calls and e-mails, and other than a very high level description of how they develop their guidelines, we could not get specific information, in particular, how they did their evidence review to support their guidelines, so I want to make note of that. We found 11 ACR

appropriateness criteria. All of those were rated as fair quality. They did a bit better job of transparency and providing the evidence that they used. Recommendations varied by malignancy, and you're going to see this in this massive table. On the left column, these are cancers where SRS or SBRT is usually not appropriate or not recommended. You can see bone metastases up here. The brain metastases from ACR are the multiple metastases to the brain and large brain metastases, and you can see the rest listed here. The stage 1 nonsmall cell lung cancer are patients who are operable, and a variety are listed as maybe appropriate, and there are a few that are listed as usually appropriate, and you can see there brain metastases and thyroid cancer.

So, policies, as described, no NCDs, two regional LCDs were pertinent to Washington, as already mentioned. LCD 30318 covers SRS and SRT for intracranial tumors. The specifics were the tumor had to have image-distinct margins, had to be hard to reach, unusual shape, or near a vital structure. There had to be five or fewer metastases. The patient had to have a good performance status, which they defined as a KPS of greater than 50, which we might want to discuss, or an ECOG performance status of less than 2, whereas SRS as boost treatment for larger lesions treated with WBRT or surgery, and they list some of those. The other LCD covers SBRT for tumors of the lung, liver, kidney, pancreas, and low to intermediate risk prostate cancer. They indicate only when aggressive treatment is justified, other forms of radiotherapy or focal therapy cannot be safely or effectively utilized, the tumor can be targeted with acceptable risk to surrounding critical structures. The patient has had previous radiotherapy to the same or adjacent sites, and there were some specific ones for germ cell and lymphoma, if effective chemotherapy regimens had been exhausted or not feasible. That same coverage determination for SBRT explicitly does not cover SBRT under the following conditions: Treatment is unlikely to result in clinical cancer control and/or functional improvement, when there's widespread cerebral or extracranial metastases, the patient has a poor performance status, there are lesions to other sites, those are listed there, are generally not covered, but may be in cases of recurrence after conventional EBRT.

So, the overall summary, believe it or not, we're close to the end. This is the summary for brain metastases. This is the comparison of SRS plus WBRT versus WBRT alone. The outcomes with moderate strength of evidence was no difference in overall survival, increase in local tumor control with the combination, no difference in acute or late toxicities, of

note WBRT doses often adjusted when SRS is used. Low strength of evidence for single metastases and for RP8 class 1. There seems to be, for the combination therapy, increase compared to WBRT. There seems to be increased median survival, increased local tumor control, and fewer patients have worsened performance status at six months. For SRS versus WBRT, there is some low strength of evidence suggesting increased overall survival and no difference in acute and late toxicities.

So, glioblastoma multiforme, SRS versus WBRT, there is low strength of evidence. That there is no difference in overall survival but noting that radionecrosis can occur in about 3 to 5% occasionally leading to surgery. Gliomas there is very low strength of evidence for all outcomes. Pituitary adenoma, low strength of evidence that there is no difference in overall survival or local tumor control.

Head and neck, very low strength of evidence for all outcomes. Inoperable stage 1 nonsmall cell lung cancer, these were noncomparative studies, so very low strength of evidence with a three-year survival of about 40 to 60%, five-year survival of about 54%, overall survival of the smaller tumors being better than the larger tumors. The serious acute toxicities range from 2 to 5%, for the acute late toxicities 2-10%, spine was very low strength of evidence for all outcomes, and then all other studies had very low strength of evidence for a variety of cancers and tumors.

Then the limitations. As you've heard already, there's a limited number of comparative studies, in particular, randomized controlled trials and cohort. Many studies did not adjust for confounding variables, such as other treatments, patient age, tumor stage, change in standards of care over time, or radiation dose. The vast majority of studies were case series were small sample sizes, and I am going to stop there.

Craig Blackmore: So, I am sure there are a lot of questions. Thank you, by the way. It's just about 10:00, and I think given the time, we should take about a 10-minute break and give the committee an opportunity to assimilate all of this information and then we'll resume with questions for our vendor and our other presenters and then launch into the discussion. So, we will reconvene at 10 after.

I'm going to ask the committee members to resume their seats so we can restart the meeting. Okay, we are back in session. The next period of time on the agenda is really designated for the committee members to

ask questions related to the presentations, either to the agency directors or to the vendor or to our clinical expert. So, are there any questions from the committee?

Man: I want to kick off by asking about the incidence of radionecrosis, as a harm factor. The development of SRS, by my understanding is a learning curve. People have improved their awareness of its utility in a different number of treatment scenarios. So, we have seen the wide range of conditions being treated. What sense do you have on reviewing the evidence in the way that you have done that the incidence of radionecrosis was a part of the learning curve, and by that I mean have people learned to avoid the frequency of – or reduce the frequency of radionecrosis in terms of looking at where the tumor particularly is cited? Will it be vulnerable to a mass effect there? Is it near to an eloquent area, etc., etc.? So, I mean, is there any sense that there is a diminishing frequency of radionecrosis, as people learn to use SRS in a more quotient fashion?

Martha Gerrity: I'm going to start out. From the evidence we reviewed, they were predominantly case series, and you can see that our search was 2002 through 2012, so the more recent case series, but when you look at when those patients were treated, they range back into the 1990s. So, it's difficult to say from the literature that there is a learning curve, and I think I'm going to turn this over to Dr. Fuss, our clinical expert, since it's really difficult to determine from the literature. If this was just part of the learning curve, then the incidences dropped.

Martin Fuss: Yes, my name is Martin Fuss. I'm a radiation oncologist at OHSU. In radiosurgery, SRS and SBRT are a significant part of my practice. This is actually a great question. I think you have to answer that in two different ways. First of all, yes there was a significant learning curve, predominantly in the 80s and 90s. Initially, there was this perception that you could treat almost any intracranial tumor, as long as it was reasonably localized with significant and high doses of radiation, as long as you stayed away from surrounding brain. So, specifically lesions larger than 3 cm were treated by SRS and increased rates of radionecrosis were subsequently observed. Today, the general recommendation is that radiosurgery be reserved for smaller lesions in the brain in the upper accepted diameters, mostly about 3 cm, and as such, the rate of radionecrosis has significantly dropped, but radionecrosis is not just a technical issue. It also comes as a factor of time. So, it's beneficial survivals after the administration of radiosurgery come along with a

higher risk for the development of delayed radionecrosis, and so patients who live one, two, and three years and longer after radiosurgery are actually the ones that are at risk for the development of radionecrosis. So, to some degree, this is just a price to pay for survival, and in those patients we, in fact, see an incidence rate that is still probably about 5% predominantly in patients with favorable outcomes, and it is just a factor of depositing a significant radiation dose even with steep dose gradients, meaning the radiation dose falls steeply off to what are surrounding brain tissues that will be related to some residual risk for radionecrosis.

Martha Gerrity: I actually would like to ask our clinical – is that dependent on the type of brain tumor at all?

Martin Fuss: Yes, there would probably be a higher necrosis rate in primary brain tumors, but then one of the pathologic features of the glioblastoma multiforme specifically is suppressants of necrosis. So, it is often very difficult to discriminate between treatment effect and recurrent tumor, because the inherent feature is necrosis. Long-term survival in glioblastoma has improved but is still hard to come by these days, so this would predominantly refer to brain metastases specifically in patients who have a solitary metastases. We now see a subset of patients surviving long-term, fortunately.

Man: I suppose I was asking the question, in part, just by reading the report and some of the emphasis placed on changing patterns of fractionation. So, that's what I was really wondering about. Has fractionation actually reduced the incidence of radionecrosis?

Martin Fuss: Well, the fewer the number of fractions and the higher the dose, in those few fractions, probably there's an inherent higher risk for radionecrosis. We don't have good data to say that while moving from whole brain to radiosurgery survival may improve but at the cost of a lower rate of radionecrosis. Now, if you changed the radiosurgery, let's say, to a 2-fraction/3-fraction/4-fraction/5-fraction stereotactic treatment, thus the rate of necrosis would drop again. There's just no data to support that at this point in time.

Man: Actually, I have a couple of questions. I will start with one and then see where things go, but it was on slide 19 looking at brain metastases, SRS, and whole brain versus whole brain alone, and there's, under the third key question, the comments about performance status that said that

they have decreased performance status presumably in the SRS plus WBRT group at six months.

Martin Fuss: Actually, I think that's the other way around.

Martha Gerrity: And again, for those of you who are doing due diligence in looking at these slides ahead of time trying to keep things down to a somewhat manageable number of slides, we used abbreviations and these arrows. What that arrow indicates is that for individuals treated with SRS and WBRT compared to WBRT alone, the individuals treated with the combination therapy, fewer of those patients had worsened performance status compared to SRS. So, they actually did better. Their performance status was better. It's a double negative. We tried hard to get around that, but it was the way some of it was presented in the study. It's the Andrews 2004 study.

Chris Standaert: It makes sense. You can't say they're getting better. You're saying they're not as worse.

Martha Gerrity: Yeah, they're getting less worse.

Chris Standaert: Yeah, whatever. Getting less worse, yeah.

Man: Okay, and along those same lines, I guess on that same slide and then the one looking just at SRS versus WBRT alone, which I think is probably more interesting a comparison, on key question 2, in terms of toxicity, they found no differences, and I'm just curious about that, because in our public comments the whole point about SRT versus WBRT was the fact that they thought there was less toxicity and less complications, but what I'm seeing is that none of the data showed that point.

Martha Gerrity: This, again, is slide 19 for the comparison.

Man: Or 21. It's 19 and 21, but more germane in 21, because it's a direct comparison of SRS versus WBRT.

Martha Gerrity: Right. These were comparative studies. The overall strength of evidence was low, suggesting that there might be no difference in acute and late toxicities.

Martin Fuss: May I comment on that?

Man: Please.

Martin Fuss: Because this is a very – this comes down to many of my physician-patient discussions about the use of SRS or whole brain radiation. The dose start is typically a reference, chronic, and irreversible side effects, as they may be related to whole brain radiation or SRS alone. There's an obvious and very distinct acute toxicity profile difference between radiosurgery and whole brain radiation. A typical radiosurgery patient undergoes a single treatment, goes home, and goes about his life the next day. A whole brain radiation therapy patient may undergo 10 to 15 days of treatment, so that's a factor that they have to come to the hospital for two to three weeks. They will lose their hair. You could say this is not a big deal, but it's fairly stigmatizing, if you're diagnosed with cancer. Those patients will experience significant fatigue, as they undergo their course of whole brain radiation to the degree that they spend at least more than 50% up to more than 70% of the day's hours in bed and asleep. Nausea is a frequent occurrence with whole brain radiation. We call those acute side effects and we classify acute side effects that occur under radiation treatment and within 90 days of treatment, and obviously that fatigue resolves largely within 90 days of the completion of radiation therapy. The hair loss does grow back somewhere between three and eight months after radiation therapy. So, the acute toxicity profile is distinctly different. We don't list those as toxicities, because they are actually expected. You know that you're causing the hair loss. You know that you're causing fatigue. You know that you're often causing nausea, and as such, to some degree, we, in our field, make the mistake of not classifying that in those publications, because it is unavoidable if you administer whole brain radiation.

Man: Not to downplay the significance of those on the quality of life while you're going through treatment, I'm just trying to – the sense I got from the public comment and when we see the descriptions of these therapies, it seems that there's a pretty significant toxicity difference that they're trying to avoid, and I'm not seeing that in the literature that was presented. So, maybe you can tell us what acute and late toxicities they did include and didn't find a difference in.

Martha Gerrity: We can pull up some of the specific ones. There was some mention of nausea, fatigue, in general with radiation therapy, and those in the studies reported were no different. Some of the more – what some of the public commenters have said about quality of life coming to the hospital once, twice, or three times compared to a dozen or more times,

some people consider quality of life, which was not reported. The late toxicities…

Martin Fuss: While you're looking in the paper, I want to make two more comments. What we have to recognize in those patients, they have an extremely limited lifespan, actually, measured in a few weeks to a few months. Having a patient come for three weeks out of their remaining 12, 16 weeks of their lifespan is a significant impact on their quality of life. Also, there is the concern of a decline in neurocognitive function with whole brain radiation, and again, this is a two-sided sword. Cognitive decline may be related to delayed small vascular changes in the brain and is an effect that manifests itself over, let's say, 6 to 12, maybe 24 months after radiation therapy, and it's always a concern. Predominantly, attention span, short-term memory, it's kind of an early aging of the brain, but neurocognitive decline is also related to in-brain tumor control. So, having an active tumor process in the brain and that likelihood is higher with whole brain radiation than it is after radiosurgery. It's directly related to a decline in neurocognitive function. So, local control actually here translates into a quality of life benefit. There are very few trials that have systematically included neurocognitive functioning, and the only one that was referenced earlier today is actually an MD Anderson comparative trial. We, as a field, have become cognized enough of the fact that we have not included this type of data, but it's difficult to do, because neurocognitive test batteries are elaborate and to have your patient undergo a two to three-hour neurocognitive test battery is exhausting. So, few patients in that situation actually agree to doing it. I've been part of several trials, and it's very difficult.

Martha Gerrity: And we found two studies that reported neurocognitive outcomes and again very few with quality of life measures, and they weren't the widely-accepted quality of life measures. I'll read you directly from one of the studies of SRS versus WBRT. This is the fair quality rate study, and this is all they say. The rates of grade 3 acute toxicity, according to the common toxicity criteria, were 4% in group A SRS and 2% in group B. The rates of grade 3 or greater late toxicity, according to the RTOG criteria, were 4% for both groups. That's the only information they provide, and that's similar for the poor quality cohort studies.

Man: Can I ask just a natural history question? We're looking at the differences in weeks to months between these two treatments if we think they are effective. What's the natural history of untreated brain mets in terms of survival? Is there any knowledge of that?

Martin Fuss: Yeah, there's knowledge. There's relatively good data, three to six weeks average, and that obviously depends on the volume of disease that presents when we see those patients. If you have solitary metastases, even untreated, the life expectancy is probably more than six weeks. If you have multiple left untreated, it may be less than six weeks.

Man: Yes, I have a question for Dr. Fuss. You know, being a rapidly-evolving field and the complexities of the equipment involved, it's kind of a hardware question. Are there differences in toxicities when you're comparing the different types of equipment? Or another part of this question, are you phasing out certain types of devices and using some of the newer technology or newer brand names just because of what you're finding with toxicity or other outcomes?

Martin Fuss: That's another great question, but we have never tested technology platforms prospectively against each other. We, as radiation oncologists see them as toolsets. Surgeons have never tested the choice of their scalpels or knives against each other. It's a preference. At the same time, this preference is based on technical parameters. So, yes, we select technologies that are appropriate for those stereotactic treatments in brain and body. Brand names like Gamma Knife, a pretty dedicated toolset for intracranial lesions. CyberKnife, brain and body. I personally use what's called a Novalis TX, again a tool that's suitable for brain and body. Common to all those devices, and there are others, this is not an exclusive list, is the ability to collimate or shape small radiation beams so that you generate a beam that is sized appropriate to that small and complex-shaped lesion that you're wanting to treat. Some of the older technologies that are still in the field and are very viable in use for more conventional radiation therapies just don't have those high-resolution beam-shaping capabilities. So, those may not be as appropriate for treatment of stereotactic concepts, unless you add on additional add-on devices that then collimate or shape your beam down to a smaller size.

Yes, there are significant technology requirements behind it, but I would submit that today those of us offering SRS and SBRT have all invested into appropriate technologies that allow us to deliver those quality treatments.

Man: Thank you.

Martha Gerrity: I might add onto that, I alluded to there were more horrible adverse outcomes reported in the lay press, and those that have been reported in the New York Times and other places were situations where there wasn't great care taken in assuring that you are targeting the right target. So, the story in the New York Times was about a hole burned in a woman's chest wall, because the targeting missed the tumor and targeted the chest wall. So, adhering to the ACR standards for operation of these devices and everything else in assuring that you're really getting the tumor, as opposed to a normal structure is incredibly important.

Martin Fuss: This is closely associated to the hardware question. At the end of the day, I believe it comes down to user expertise, and to the team treating, and the team treating is - when it comes to brain as was alluded to earlier a neurosurgeon or radiation oncologist or medical physicist. A medical physicist is the safety net in all of that. We bring the brains, these physicians, and we entirely rely on the physics team to assure that we safely deliver what we want to. So, the cost is clearly in the effort and in the technology.

Chris Standaert: I have a bit of a multi-pronged question. So, one, I didn't see studies of SRS or SBRT compared to surgery. So, for some of our benign tumors we're talking about, acoustic neuromas, pituitary adenomas, those are surgically resected. Meningiomas are surgically resected, and I assume a logical comparator would be surgery, but we don't have any studies looking at that at all, do we?

Martin Fuss: We do not.

Chris Standaert: That's helpful.

Martin Fuss: I think this comes down to preference.

Chris Standaert: Right, but those become very different outcomes, too. People don't usually die from an acoustic neuroma in current Western care. So, our outcomes become very different in those, but we don't have any data on that, at all.

Craig Blackmore: Just to be clear, it's not that there is no data, it's that it was excluded from our technology review. So, we don't actually know if there's anything.

Chris Standaert: Why was it excluded? Because you didn't look for surgical comparators?

Martha Gerrity: We did not, and the reason being is we were asked – I call this the vertical slice. So, you look at an intervention and comparators as you guided us to across a number of different tumors, and that's what we did. We could have taken a vertical look at any one of these cancers and said, for brain metastases let's look at all different treatments and any comparative data related to all different treatments. This report was fairly complex.

Chris Standaert: We didn't guide you to do anything. Just to correct. So, we, the committee didn't guide you.

Craig Blackmore: That's not entirely fair. We had the opportunity to provide feedback on the key questions and what everybody thought, so.

Chris Standaert: But this creates a dilemma for us, because then we have, we're supposed to comment on coverage, but we have things for which we're not really considering. We didn't really look at the treatment of acoustic neuromas, for example. I mean, how, the search didn't cover the data we need to comment on that.

Martha Gerrity: We could have spent three days here if we had done it that way.

Chris Standaert: I understand, I just don't – so I'm getting it in my head and trying to understand coverage issues, which is what I'm trying to get at, and that creates a dilemma for me. That's one. The second is this issue of a lot these coverage policies talk about a life expectancy of greater than six months. They talk about Karnofsky scales, which you mentioned briefly, but I didn't hear in your presentation, I didn't hear data stratifying patients by life expectancy and by SRS versus WBRT for example. I didn't hear this.

Martha Gerrity: There was only one randomized controlled trial that did that.

Chris Standaert: So, one, is there data that you have found that helps with issues of treatment outcome versus life expectancy as an independent predictor, and can you help us with this Karnofsky scale, and is there data on trues – again, functional levels as an independent predictor of outcome.

Martha Gerrity: Okay. For all of the randomized controlled trials and the better quality cohort studies, to get into those studies, you had to have good performance status, and the most common cut-point was a Karnofsky

performance scale of 70 or greater, and that indicates that patients can take care of themselves, are out of bed at least 50% of the time, but are unable to do normal work or other activities. So, there's some limitations in their function, but they're at least able to get out of bed and do their own self-care and activities of daily living. And those cut-points are usually used for entry into any of the NIH funded oncology trials.

Chris Standaert: Those are typical entry criteria…

Martha Gerrity: Those are typical entry criteria, yeah.

Chris Standaert: Okay.

Martha Gerrity: And so, as you're indicating, this is a highly selected group of individuals with better performance status.

Chris Standaert: And the life expectancy issue, was that factored in somewhere, or is that not?

Martha Gerrity: That gets folded in, and the one study, the Andrews 2004 study was a randomized control trial. That looked at RPA class, recursive partitioning analysis class, and there were three classes. Class 1 there were specific criteria: A KPS score of greater than 70, age less than 60, controlled primary tumor, and no extracranial metastases, and the study that developed that, this is a predictive instrument, so there was an initial develop what goes into this predictive instrument, and then they validate it in a population of about between 1,000 and 2,000 patients, but it turns out with class 1, the median survival is about seven months; class 2, four months; and class 3, two months. So, it's a prognostic indicator.

Chris Standaert: Of outcome.

Martha Gerrity: Of outcome, right. And people do better with SRS plus WBRT or SRS alone if they have the better prognostic indicators.

Chris Standaert: So, they use that, and they stratify it by one, two, three…

Martha Gerrity: That was the Andrews.

Chris Standaert: …in that one study.

Martha Gerrity: Yeah.

Chris Standaert: And found that to be class 1 did better.

Martha Gerrity: And it's the only study that did it that way.

Chris Standaert: It had a better…

Martha Gerrity: Yeah.

Chris Standaert: Okay.

Man: Just to clarify, what do you mean they did better? Everyone did better, or they did better in one group or the other?

Martha Gerrity: So, what it was, was class 1 patients, so those patients in the Andrews study that were class 1, so overall they were going to do better no matter what. They were randomized in their strata to receive SRS plus WBRT versus WBRT alone. So, if they got both treatments, their overall survival was better by, I believe it was a month or two.

Woman: And that was in the subgroup that had a single met, increased survival.

Martha Gerrity: There was also, they had two subgroups that were [inaudible]. The other was individuals with a single metastasis. If they got the combined treatment compared to just getting WBRT alone. They also had better overall survival by a couple of months. This is slide 19. Let's see if I can get 19 up here again. That's this slide. It's key question 3. So, there was better median survival, so people with single metastases that received the combined therapy had an overall survival of 6.5 months. Those that only got WBRT had a survival of 4.9 months. So, patients with RPA class 1, those that got the combined treatment had a survival of 11.6 months versus 9.6 months for patients who only got the WBRT. So, that was within a class. So, that would imply, and it's not up here, that those who had multiple metastases did not have the survival improvement, and those who were of lower RPA class did not achieve that type of survival improvement. Maybe Dr. Fuss would like to comment on that from a clinical perspective.

Martin Fuss: So, in general when we discuss radiosurgery with our patients, generally recommended cover for the use of radiosurgery is the presence of five or less in some studies, four or less in other studies, three or less brain metastases. So, three, four, or five it has to be a limited number.

Currently, in some perspective studies assessing the validity of using radiosurgery in patients who have five and more metastases, and that is particularly interested in indications that are considered radio-resistant melanoma, renal cell cancer, sarcoma patients, because they had a response to whole brain radiation therapy. It's just extremely poor. So, there may be a subset of patients who are high in number of metastases that may be appropriately treated with SRS, but in general, it would be a limited number, five and less, being acceptable for SRS.

Woman: We are trying to make decisions on the kind of data that is here, which is case studies and cohort studies mainly. Am I understanding correctly that most of what we have here are those two types of data?

Martha Gerrity: Yes, and actually in the body, it's case series. There are very few cohort studies. So, we can't give you any information about compared to external beam radiation or other information.

Craig Blackmore: So, I'm struggling with the cost question, and obviously the SBRT and the stereotactic techniques require a more sophisticated level of equipment and perhaps training. There's going to be a greater up-front cost, but then the fractionated treatments, external beam, multiple visits, there's going to be indirect cost to the patient, etc. Perhaps the agency medical directors, perhaps Dr. Gerrity, can help me to understand the relative trade-off and the short-term costs of one versus the longer-term cost of the other.

Martha Gerrity: That's a wonderful question, and I wish I could provide you with evidence related to this, but these studies are very poor. The models derive their outcomes data from case series. In one situation, one was an internally done small series of 47 patients that they used. Most of the studies use the charges incurred by an individual hospital to estimate costs. Some allowed additional treatments to be included in their cost estimates. Say, for example, someone had SRS initially but it recurred. They could have surgery, and sometimes that was included, sometimes it wasn't included. So, I would be doing you a disservice to even estimate what the cost impact is.

Craig Blackmore: Do the agency directors want to take a stab at that, or not?

Woman: From the Medicaid perspective, the average costs for treatment alone, or actually average cost per patient [inaudible].

Craig Blackmore: I'm sorry, I missed what you said. I'm not sure the mic's on.

Woman: So, from the Medicaid perspective for average cost of treatment per patient, both IMRT and SRS and SBRT are actually very comparable.

Craig Blackmore: But not standard fractionated external beam. We don't…

Woman: Both are more than standard fractionated external beam, yes.

Man: Sorry, I missed the last comment there. Can say what your question was in response to external beam radiation therapy. I missed the answer to that.

Woman: Both SRS and SBRT, as well as IMRT cost more per patient, as compared with standard external beam radiation therapy.

Craig Blackmore: From the standpoint of the payer. From the payer's perspective.

Woman: Yes. So just cost, average cost per patient.

Man: And that's a cost per course of treatment for the patient's whole sequence of treatment?

Woman: Yes, for course of treatment for radiation therapy only.

Man: Alright. And by how much more, do we know?

Woman: That, I can't tell you, because it's very diagnosis dependent.

Man: Okay, is there any sense by what kind of factor? Double the cost? 25% more?

Woman: Again, it depends on the diagnosis that's being treated, so that's really difficult.

Man: But considering the diagnoses that we've actually been asked to deal with here, you can imagine it'd be useful information for us to know.

Woman: We could probably pull that, but I don't have that data right now.

Man: And along these same lines for the vendor. Just looking at slide 24, I'm a little confused at what I'm seeing, because in terms of the conclusion,

you say that SRS alone is more cost effective than WBRT alone or a combination, but if you look down at the third row and you compare the two, SRS is actually more expensive or has a higher cost-effectiveness ratio or cost per quality than WBRT. So, I'm confused at your conclusions there.

Martha Gerrity: It probably should have stated maybe, just to imply that there's a lot of uncertainty, because it's low quality, but what you're seeing in that final row with the numbers, when we talk about cost effectiveness, it doesn't mean that it's cost savings. It means that it's more costly but potentially more effective or improves quality adjusted life years.

Man: That's inaccurate, because qualities actually take that into account. So, when you're looking at the cost per quality of each intervention, so it is simply more expensive for the same quality.

Martha Gerrity: Right.

Man: That's the exact opposite of what you say as your conclusion.

Woman: Actually, in the text, it's the opposite of what's in the slides. So, page 65, the lower section in systematic reviews, it has the opposite of what's on the slide.

Martha Gerrity: But that first sentence might not be accurate. That might have been a reversal.

Man: So, which is it then? Which is more cost effective?

Woman: In the text, it says that the SRS is more cost effective, but $10,000 is assigned to the SRS.

Man: I still don't understand.

Martha Gerrity: So, the last line is flipped. I apologize for that.

Man: So, $17,000 is for WBRT and SRS is more…

Martha Gerrity: Right.

Man: Thank you.

Martha Gerrity: Sorry about that.

Chris Standaert: Just – I just…

Craig Blackmore: Go ahead.

Chris Standaert: I just want to say in terms of these numbers, I mean this is very low level evidence and data on cost per quality has big error bars, and I personally have a great deal of difficulty saying $10,000 versus $17,000 per quality is substantially different with the level of evidence that we have. I know they're taken out to the last dollar, but if you went to sort of your most reasonable estimate, it's nowhere near that finite, and I personally look at these and kind of go…

Martha Gerrity: Yeah.

Chris Standaert: They look relatively similar to me. One isn't $180,000 and one isn't a million, one isn't that same order of magnitude.

Craig Blackmore: I would echo that. There are few types of studies more easily manipulated and/or unconsciously distorted than cost-effectiveness analyses to the point where the New England Journal, for example, won't publish a cost effectiveness analysis that's funded by a drug company or manufacturer, because you can make the numbers look like anything. So, given that these are listed as very low quality, I would not consider this reasonable at all to consider. The question I was trying to get at is simple cost. How much does it cost? And then we would have to make our own inference about cost effectiveness. These guys are making huge assumptions about effectiveness. If you conclude it's effective, it's fairly easy to say it's cost effective, but even the simple question of does it cost more was my question.

Martha Gerrity: Along that line, we looked hard for any estimates of just cost within a single system and couldn't find any. Or unit cost for each part of the process, but couldn't find any.

Man: Do we have any of the cost effectiveness trials? Can we just look at how they did their cost estimate, see them?

Martha Gerrity: We could, and I did, and they were all over the board. They did them differently, often based on charges, which, as you all know, vary quite a

bit. Hospital A doesn't charge the same thing for the same procedure as Hospital B.

Man: I have a question for Dr. Fuss. We're seeing data on SRS versus WBRT, and then we're seeing combination therapy versus WBRT alone, and when you're treating a patient are there specific criteria you would use to determine whether you'd use combination therapy or SRS alone as an alternative?

Martin Fuss: Yes, and here comes a significant personal bias. So, you have to take what I say with a grain of salt. Personally, in a patient who has three or less brain metastases at presentation and is referred to me for consideration of brain radiation treatment, I try to avoid whole brain radiation therapy. The duration now for that is that less than 30% of my patients were initially treated with radiosurgery alone require an additional treatment, either an additional radiosurgery or the combination with whole brain radiation for at least 4.5 months. So, there's two followups. Within two followups, only one out of three patients will require an additional treatment. So, I am deferring the whole brain radiation treatment, the potential radiation treatment and its impact on their quality of life for a significant amount of time. Well, I judge this to be a significant amount of time. So, the bias today is increasingly to spare patients, appropriate patients, the impact of whole brain radiation.

Craig Blackmore: Any other questions?

Woman: I have a general question for the agency medical directors. They showed data from 2008 to 2011 over 200 PEBB patients and about 250 Medicaid. Can they give us just a guess as to – because these were covered with no conditions. If we were to apply the conditions that they have recommended, what percentage of these cases do they think would not be covered? You may not be able to answer that question.

Kerilyn Nobuhara: I think that it wouldn't impact our SRS authorization rate in any way honestly right now, which is actually very close to 100%. It would alter our consideration for SBRT.

Chris Standaert: Another question. With regard to SBRT versus IMRT versus whole body radiation, we went through IMRT last time, and one of the things we talked about was spine and paraspinal mets using IMRT, but is there data comparing, I mean, is the difference between IMRT and SBRT for

paraspinal or spinal metastases? Because that was one of our criteria under IMRT, but again, there's no comparative data you gave us. So, I mean there's similar conceptual models between these two in a way. One's more ablative, but it can – any feedback on that, or no?

Martha Gerrity: I'll let Dr. Fuss talk about the conceptual model. There were no comparative studies.

Martin Fuss: I want to clarify one thing. So, IMRT is just a planning and delivering modality. You want to get the airport, you take your personal car, you take a bus, or you take a cab. So, this is the modality that gets you there. If we talk about external beam radiation 3D conformer, IMRT, those are just increasing sophistications of a technology that you are using to get radiation to a certain location. SBRT is a concept. You're treating a small lesion so inherently it is size, 5 cm or smaller. It's not a limitation for external beam radiation therapy in general. Where you benefit from creating a gradient of radiation dose within the target to the area outside the target, so implied is a risk to the structures that are surrounding. Then, you use a planning modality, and that could be 3D conformer radiation therapy or IMRT to deliver your treatment concept. So, SBRT can utilize IMRT planning and delivery techniques. So, there is a significant overlap. SBRT is a treatment concept, less than five treatments to a small lesion 5 cm or smaller, where you have a need for steep-dose gradients. So, let's say you treat a bone metastasis in the middle of a femur. There's not a lot of risk around it, even if it's only 2 cm in size, so there's not a good justification to use SBRT as a treatment concept. Now, to the topic of spine, we would treat a larger lesions or a complex-shaped lesion, just because it's a better planning modality, with IMRT techniques, but you could still treat it under the SBRT paradigm and deliver five or less high-dose radiation treatments.

Chris Standaert: And would that be termed IMRT or would it be…

Martin Fuss: It would be then be the term SBRT.

Chris Standaert: Because you have less than five, or five or less.

Martin Fuss: Yes, that's five fractions or less, and you're using specific…

Chris Standaert: So, if you did six or ten, you'd call it IMRT?

Martin Fuss: It would be IMRT. And that's unique to the U.S. This is a – I mean, the challenge here is that the cutoff for SBRT is five fractions or less. Once you go to six, you can't call…

Chris Standaert: You can't call it SBRT anymore.

Martin Fuss: You can't bill it as SBRT.

Chris Standaert: Because you're not – you can't bill as SBRT. Okay.

Martha Gerrity: Although I would note in the literature they fudged that, and…

Chris Standaert: This is an extension of the conceptual model of IMRT in a way. I mean, it's a…

Martin Fuss: Yeah, it utilizes our advancement, our technology advancements to create a new treatment paradigm.

Chris Standaert: Right. You're getting a tighter feel, but you can do it with the higher doses.

Martin Fuss: You have the capability to do that now. You also possibly have the capability of increasing the radiation dose for each one of those fractions, so don't trickle it in a two-grade per day but use a massive dose, which has a different biologic effect on the tumor.

Chris Standaert: Right.

Martin Fuss: This is having technology and then using it the right but almost more expensive way.

Female: I have studied that. I mean, how would you, given that process, collect data that would help make decisions about that?

Martha Gerrity: So, the ideal study would be a randomized controlled trial where you randomly assign patients to different groups, but if you are unable to do that, although I would argue that in some situations you probably still could do it even though people have suggested you can't. You would want a well-done prospective cohort study, a large database registry study. The other place where the technology sounded good was metal-on-metal hips. We thought they're going to last longer. People aren't going to require recurrent operations and low and behold, it was a large

well-done registry out of the UK that demonstrated that we were actually causing harm to people. They were requiring surgery for hip replacement earlier than with the older version of the hip replacement, and I could see doing something similar if there was the wherewithal to do that where you collect data prospectively. Say you have all the markers to control for potential compounders.

Craig Blackmore: Just to sort of get back to reality, because that's where we are. Just to sort of sum up, and this would be an opinion of one committee member and not the whole committee, but it seems to me we're in this situation where we have advancing technology, and we have a pathophysiologic model that drives that technology where we believe that focusing the beam better and irradiating the tissue around it less is good, and I think we can all get on board with that. That makes a lot of sense, and there's perhaps some data and there's some experience that tells us that there might be fewer side effects in some people, but the drive is always to take the new technology and apply it with broader and broader indications, and it seems inevitable that as you take this new more focused beam and apply it to lesions in places other than the brain and in places other than adjacent to critical structures, that the value of any of that technology is going to decrease, and unfortunately, our job is to – we can either say we're not going to cover it at all, we can say cover it without limitations, or we need to draw the line in the sand and say these are the areas where we think there is benefit to this technology despite not overwhelming evidence, and these are the areas where we think maybe there isn't benefit, and I think from my perspective, we rely a lot on our intuition and on the clinical judgment of the people that do this, because the evidence here is really not overwhelming, but at the same time, I'm not sure I'd want my brain radiated in its entirety if I had a single metastasis. So, that's sort of how the problem lays out to me, and I'm not saying that makes an obvious answer, but I'm hoping to use that to direct us now to the next phase of the conversation, which is the committee trying to work towards a decision.

Man: Craig, just to clarify. We've been doing a lot of talking about this for brain mets, but we haven't talked at all about SBRT, and that's obviously a totally different level of data and has a lot more hand waving in terms of where we are with that. I guess I think maybe if somebody were to poll us and see where we are, I think I could see myself leaning towards the conceptual decision for SRS, but I'm having a harder time knowing how to handle SBRT, and I'm curious if anyone on the committee has any thoughts.

Craig Blackmore: So, just in terms of framework, what I was going to do, and you can give me input, is to deal with, you know, sort of go by body part and start with SRS and have a discussion among the group about whether we want to just consider SRS as a unit or if we want to focus on brain mets or meningioma or whatever and then move on to the SBRT and have the same idea of are there specific areas we want to call out or do we want to treat this separately, but I definitely am proposing at this point that we divide the SRS and the SBRT if that resonates with everybody.

Woman: That's fine. I'll wait.

Craig Blackmore: So, where are we in terms of starting with SRS? What is – who can help us start the discussion here? Should we have more coffee and then start the discussion.

Chris Standaert: I guess one way to start thinking about SRS is do you look at specific conditions? So, brain metastases, which frankly is lumping a bunch of things together, because all brain mets are not created equal, I wouldn't imagine. Brain metastases versus primary tumors, and you have sort of the malignant tumors versus the benign tumors, and are we talking intracranial or brain, and do we lump them all together as one thing, or do we sort of break them apart? I think we have data on metastases. We have some data on primary tumors, the best on glioblastoma. I have a bit of difficulty of what to do, how we phrase this, and what we do with the wording when we start talking about things like acoustic neuroma, because our review cut out the comparator to what is the other standard of treatment, which is surgery. So, how do we even comment on whether you should be doing this or not when we didn't look at the – for those tumors I'm not – I have a bit of dilemma in how we address that. I'm not sure we looked at the rational comparators.

Man: Well, yeah, but I don't think surgery is a rational comparator. There are conditions clearly with surgery.

Chris Standaert: No, no, no – for [inaudible] so like acoustic neuroma, for example. That would be the rational comparator, I would think. We didn't look at that data.

Man: Well, I don't think we should. I think that we should be looking at this in regards to these are either – consider – we should be looking at inoperable conditions, whereby there are some metastases, for example,

that you can resect surgically and achieve a good result. So, I think that the way we should be approaching this is not from metastatic versus primary brain tumor, because I think that we could get ourselves into a lot of difficult problems there when we start to subdivide tumor types by their kind of radiosensitivity, etc., etc. Maybe we should actually consider ourselves to a more kind of an anatomic basis and just say okay, is this actually surgically resectable without – what I mean to say is, consider only tumors on the basis of whether they are amenable to surgical resection or not, and the ones that are not are the types that we should be considering in this.

Chris Standaert: I guess I have some trouble with this. We didn't talk about surgery one iota, so how we determine that is very hard, and I suspect there's a discussion you must have either with the patient or in your head at times where is this a better choice than surgery? I mean, that becomes the choice. So, it's not that it's not, you know, that it's inoperable. It's that perhaps this has less morbidity than trying to operate on it. And we didn't look at that data. So, determining something – I'm not sure there's a clear line. I mean, you can – a clinical expert can help clarify this for me and make sure I'm not out of line, but I'm not sure there's a clear line between operable and inoperable and there may be certainly circumstances where this is the debate where is this a different – the relative cost and benefits of this versus surgical approach so they may be operable theoretically, but, you know what I mean?

Man: Well…

Chris Standaert: Does that – am I?

Martin Fuss: Yeah, and I think you're touching a good point. The treatment team for SRS brain consists of a neurosurgeon and that is the surgical capable, and the radiation oncologist. So, implied in the decision making process to recommend radiosurgery, obviously is the neurosurgeon's decision to not pursue a surgical approach.

Chris Standaert: Right.

Martin Fuss: So, I think the advantage here is that you have two parties, two relevant parties on the table.

Chris Standaert: Right. It doesn't mean that surgery isn't a consideration or an option. It's meaning that in the aggregate, the neurosurgeon isn't recommending it

in this circumstance after discussing with his radiation colleagues that radiation be pursued, as opposed to neurosurgery, as a primary treatment.

Martin Fuss: Yes.

Chris Standaert: But that's different than saying it's inoperable.

Man: And that's also another assumption because oftentimes there is no – we haven't looked at the data at all, but a lot of times, particularly for acoustic neuroma, there is no difference in terms of the treatment outcomes, at least based on the survival or whatever the big outcomes are, and it really becomes a choice issue. So, it's not even necessarily an indication. It's a patient choice issue, and I don't know if that's true or not for brain mets.

Martin Fuss: Yes, there's a certainty less true for brain mets. Yeah, because technically there is no inoperable brain mets. Let's not forget that. The question is, what's the cost? The cost in terms of patient function.

Man: Well, I suspect we may be just getting confused in terminology, when I'm saying inoperable, I don't mean – I'm talking about more than the aggregate there. Maybe I chose that word wisely, but it's more the aggregate surgical decision not to proceed, because you're just adjacent to an eloquent area, etc., etc., but I think that we can – my concern about going down the avenue of individual tumor types is that we can spend an awful lot of time on levels of discussion. I think few around the table are actually – who would feel comfortable in pursuing, and I think that there's some level where we actually have to leave it to the judgment of the treatment team, as to which course to go to whether it should be surgical or whether this should be radiotherapy. So, having made that distinction, then the choice before us at this precise moment in time is what avenue of radiotherapy do we think the public part should cover? I mean, that's essentially what we're being asked to do.

Craig Blackmore: I guess I would endorse not trying to break into tumor types, because I think our charge is to rely on the evidence, and I don't think the evidence is there to allow for the differentiation. There may be clinical judgment that allows for that, but that's not our job, which I think is just echoing what you're saying.

Man: As far as SRS is concerned, I think through the process of what we're going to go through and think about, okay, what are our options? We either cover this, don't cover this, or cover this with conditions, and I think it's going to be, at least where I am, I think I have a hard time saying we're not going to cover this to some degree, and then I'm trying to think okay, if we're thinking about conditions, are there any conditions that we could identify, at least for SRS where we'd say, well you shouldn't do that. It's not clear to me that I could come up with any. I'd kind of be curious if anybody has any thoughts of where they're going to be, so in my mind at least I'm leaning towards for SRS for brain mets and these types of conditions to cover without conditions at the discretion of the team making the decision of what's going to be offered.

Craig Blackmore: There are conditions that other organizations have used, other guidelines and the current – there's one of…

Man: Certainly in terms of like performance status and some of those types of things, but I mean, in terms of…

Craig Blackmore: They're evidence based, because I haven't seen evidence to drive it, but they exist.

Man: That's less on whether or not you should do it and more on okay, who should we be doing it in, though, as far as the conditions that I've seen. I haven't seen the condition so much as we shouldn't do it for this tumor type. It's more about the patient. So, I think we can argue about the patient types whether that's evidence based or not, but as far as this discussion about tumor types and us making a distinction about okay, we're going to offer it for two metastases but not three metastases, or we're going to offer it for glioblastoma but not for X. I don't know that we're going to make any headway doing that at all. So, I don't know if you want to poll us or if people have different opinions than I do. I'm happy to listen, but I'm not – I don't feel like we're making any progress.

Chris Standaert: I mean, based on a tumor type, I didn't see much to help us very clearly either, and then we get into issues sort of the patient characteristics. So, this sort of Karnofsky scale, do you – if the majority of studies are already excluding everybody with a performance level of less than 70%, then maybe we have a cutoff there, and then we have to deal with a lot of these things they're talking about, life expectancy and that sort of thing, and do we deal with that, as well. I mean, are these reasonable conditions to put in this or not?

Man: I have a bit of a problem with rigidly adhering to the same criteria that were used in studies. Studies will adopt population characteristics, so as to arrive at a definable result. The reason they choose that particular population is so that they don't get lost, perhaps, in the complexity of patients who are, for example, really ill and may die from other causes, and I think that that doesn't necessarily justify the adoption of those criteria when you're looking at treatment decision across the population. I'm thinking, for example, there are many diseases in which we say okay, let's not include those ones in the study because, they've got a high risk of dying and I wouldn't be able to see whether or not that's a treatment effect when doing the study, but that does not necessarily invalidate applying that once you've derived the confidence in the treatment, then it does not imply that you shouldn't actually apply that treatment across a population. Do you see what I mean?

Chris Standaert: Oh, I see what you mean. It gets difficult because if you go by, you know, if you follow the evidence side of it, you say the evidence for this population, but if you go – if you looked at studies on, my field is in back care, if you took the exclusion criteria, we would have no spine care whatsoever for people who have had prior surgery or workman's compensation, because every study excludes them from every treatment. They assume they're not going to do so well, and they don't want them in there. They don't think it's going to be a – they are going to have a hard time finding it, I guess. It does get tricky if you're trying to then go by, and especially something like this, you're trying to go by thin evidence in terms of where to start drawing lines. It gets kind of tricky, but what do you do with patients who were totally not included, so people who really have very poor functional status, you know?

Craig Blackmore: I have less problem with functional status than with life expectancy, to be honest. I think life expectancy is hard to predict. It's hard to define, and if you look at our limited data on brain mets, the life expectancy is theoretically 6.5 months if you get the SRS, and it's theoretically 4.9 months if you get the whole brain. So, are we looking at expected life expectancy based on your treatment or are we looking at – I don't know where you get that information from, but in terms of functional status, I'm more comfortable with having some defined criteria for that if the committee wants to go in that direction.

Chris Standaert: I would assume there's some correlation. Does that scale you talked about include functional – I forget the name of that scale.

Martha Gerrity: The Karnofsky?

Chris Standaert: No, the other scale. The one, two, three category.

Martha Gerrity: RPA. Recursive partitioning analysis?

Chris Standaert: Does that factor in function as part of its…?

Martha Gerrity: Yes. It includes the Karnofsky Performance Scale, as well as age and active disease outside of the brain.

Chris Standaert: Right. I assume the performance scale is partially predictive of survival, I would imagine.

Martin Fuss: The only challenge with RPA is that is has age, and age, as a cutoff to provide a certain type, I just want to caution, is somewhat exclusive. This may not be so relevant for your population, because you're largely caring for 65 and younger, or providing care for 65 and younger, but since your policies are highly respected and looked at in other states and by other policy makers, I would suggest using maybe an ECOG scale of three and better, and that's a person who can still care for themselves as a performance status, and that is also a prognostic factor and has no age cutoff in it.

Man: But do we have any data on that in our report?

Craig Blackmore: I mean, we have studies that used 70 as a cutoff and the Karnofsky. We have existing guidelines in other places that use similar cutoffs. Do we have data? No.

Martha Gerrity: I might remind you that in brain metastases, there is that subgroup analysis that suggests that those with a better RPA class do better with a combined treatment versus WBRT alone, and this is for brain metastases. I also want to remind you that brain metastases are going to be your most common tumor of the brain, as opposed to the primary tumors.

Craig Blackmore: I stand corrected, thank you.

Man: I suppose I actually need to ask the medical directors again about this. The current standard at the moment is a Karnofsky scale of 50, am I correct?

Kerilyn Nobuhara: We used 70 in one [inaudible].

Man: Okay, but some agencies use 50.

Kerilyn Nobuhara: The [inaudible] is in the LCD [inaudible].

Man: Okay. That was it, alright. I mean the difference between a Karnofsky scale of 50 and one of 70 is where, you know, at 50 you require frequent medical help and basically, you're not self-caring. I'm just wondering what would be – why was 70 picked? I suppose when I look at somebody who might need medical help, does that, you know, what was the transition between that degree of medical help and then somebody's whose self-caring, which is the 70? I mean, what's the rationale for making that filter?

Kerilyn Nobuhara: The 70 was picked just because the minority of evidence that was available, limited the study population [inaudible] 70 or greater, and that's how we ended up at 70 at Washington Medicaid.

Martha Gerrity: What might be helpful is to listen to the descriptions of the KPS of 60 and 50. So, for KPS of 60, the patient is unable to work, able to live at home, care for most personal needs with varying amounts of assistance. So, for 60 he or she requires occasional assistance but is able to care for most of his personal needs. At 50, requires considerable assistance and frequent medical care.

Man: So, by applying the 70 filter, we would be denying treatment to those who need occasional assistance. So, that's why I'm just trying to understand why the limitation came into being.

Man: Is there any correlation between outcomes of treatment for those different groups? Like the differences between 50 and 70? I guess I'm just trying to think about this functionally. So, if you have a patient who's essentially functional and doing well but is likely to die within three to six weeks if you don't treat them, it makes a lot of sense to offer them treatment. If they're, regardless of what you're going to do, going to die within a month or two months, it doesn't make a whole lot of sense to spend the money to prolong their life by two weeks if they're already debilitated. At least I'm – I mean, if it's my mom, I might feel differently, but in terms of making these decisions, in terms of conceptualizing it, I

can understand – I see differences. So, I'm curious as to if there's any data looking at those different groups.

Craig Blackmore: Can you just refer us to the actual slide data on that subgroup analysis?

Martha Gerrity: Okay. That is…

Martin Fuss: Maybe I can make a comment in the meantime. This Karnofsky, the cutoff probably is somewhere between – is probably around 50. A patient who is less than 50, so dependent on care, typically institutionalized or in a hospital or in a skilled nursing facility or something like that is not a radiosurgery candidate for a number of reasons. Those patients have to be immobilized, and they have to be compliant. Someone who is – often those patients no longer fulfill the criteria, and that's a safety criteria, as much as a quality criteria. So, I think from a judgment standpoint, it would be very unlikely that a team of capable neurosurgeon and a radiation oncologist who is engaged in radiosurgery would offer this type of a treatment to a patient of a Karnofsky of 40 and lower. I have offered – I certainly have offered in coordination with my colleagues in neurosurgery SRS to a patient of 50 and higher, because this is a very variable scale, but that's the degree of assistance mean. But at that level, that patient can be – there's an expectation that we sent this patient home, and I think that's a reasonable cutoff, probably medically.

Man: Karnofsky wouldn't follow one from that, then again, how immutable is that Karnofsky scale? Is this a patient who may have a Karnofsky scale of 50 now, but there's a chance that in two or three months' time, with good treatment allowing steroids to kick in, which may be delivered concurrently as well, that their Karnofsky could improve to 70?

Martin Fuss: Yes.

Man: So, it's variable over time?

Martin Fuss: That's the challenge with all of those. The ECOG between two and three is the same.

Chris Standaert: I assume there are other comorbidities that are difficult to factor into, bad hips and bad knees and other things that affect care and all this sort of thing. I mean, going by data, the only data we have is that this is the

typical cutoff, and we have the RPA thing where people who have a higher RPA, which correlates to sort of function and survivability.

Man: But the things that bothers me is that a lot of these patients will get started on steroids at the same time as somebody's considering the start of their radiotherapy and steroids, themselves, will produce an improvement in somebody's functional basis.

Martha Gerrity: This is the slide that you asked for, and if anyone's interested in looking at the survival curves from the original Andrews Study, I'd be happy to send this around. What you see here is brain metastases, the subgroup of single metastasis, so that strata only. It's SRS plus WBRT versus WBRT alone for single metastases. If you look at the survival curves for multiple metastases, those survival curves almost exactly overlap in the article. For RPA class 1, they didn't provide the survival curves but just the data, so it was class 1 only that there was improvement with the combined treatment versus WBRT alone. They suggest that for class 2 and class 3, they did not see that difference with adding SRS to WBRT.

Craig Blackmore: I guess in terms of the Karnofsky or whatever sort of functional measure we use, I am comfortable with such a cutoff if we believe there's evidence that treatment effectiveness is different, and I'm comfortable with the cutoff if there's medical reasons that it might be more dangerous to do the procedure in somebody with a lower functional status, but I'm less comfortable with us determining who is eligible for some treatment that we may believe is effective based on our judgment of their functional status.

Richard Phillips: I have one comment. It seems to me, as we make this decision, we're being asked to make a decision on technologies, which don't always hit the nail on the head when it comes to the selection of the surgery, radiation therapy, alternative forms of radiation therapy, and I agree with, as it has been said, that we really need to address the issue that is in front of us, but what I'm concerned about is that we're getting to the point where we might be micromanaging well-informed radiation therapists and neurosurgeons involved, sometimes tumor boards, and I'm concerned that we're going to be imposing regulatory recommendations on them that really make no sense for us to make based on the information we have. So, I guess what I'm really getting at is, it seems to me that it's getting very difficult for me to do anything else other than just say let it stand as is. The Karnofsky score, for example, I mean, those are decisions that those decisions are going to make. I

mean, the fact that they get steroids here or they might vacillate, that has to be a dynamic decision made by the healthcare providers involved, it would seem to me, and I'm just a little bit – I have a problem, myself, of trying to impose something based on limited information. So I'm sort of leaning in the direction of more of a laissez-faire.

Craig Blackmore: Any other comments?

Michelle Simon: I hear you, Richard. I understand your position. I guess I view our position here as this committee a little bit differently in that it is our job to look at new emerging technologies and look at the evidence basis for that, especially if they're expensive, which this one seems to be based on agency utilization data and consider whether it's safe or effective. That's what the report was from the Medicaid person. So, I think we should take it seriously and not have the laissez-faire attitude and look really at the evidence hard, so, that's my opinion.

Man: In all due respect, Michelle, I think we heard that it's expensive, but we didn't hear what the comparator cost was, the EBRT. That information isn't there in front of us. So, we're asked to make a decision of SRS versus EBRT but without knowing how much EBRT costs.

Michelle Simon: What we heard was a relative cost, that's all. You're right. There's no specific numbers on it. We just heard it was relatively more expensive. So, then it comes down to effectiveness. Is it effective? And that's really what the discussion here is about, I think.

Craig Blackmore: Okay. So, I think we're at the place where we start to think about what decisions we're going to make, and I sometimes like to sort of get the sense of the committee to direct our decision-making process and usually we have two of three choices that we're sort of between. My sense here is that there probably isn't a lot of enthusiasm for a no cover decision in the brain, and also – well let me back up. I'm thinking, at this point, that the committee is heading in the direction of including all brain tumor types, etc. as one decision. Does that resonate? Okay.

Man: Metastases?

Craig Blackmore: All intracranial tumors. So primary and metastatic.

Man: So, you're talking primary and metastatic?

Craig Blackmore: I am. I'm asking the question, but I thought that was the sense of where we were going? Is that not where we're going?

Man: I'm more comfortable with metastases. That's the bulk of the information that was provided to us.

Craig Blackmore: That is true.

Man: So, to include primary is making another decision without any evidence, it seems to me.

Craig Blackmore: The evidence is limited all the way around. I mean, I think whatever we want to do we can do. We can consider metastases separate. There are a number of clinical tumors and scenarios that we could consider, and I guess I'm asking for a straw vote, if you will, about whether…

Man: Well, can we agree so if we're going to go beyond metastases, can we at least say medically inoperable?

Chris Standaert: Medically inoperable? Is that – I just – is that what you said?

Man: Yes.

Chris Standaert: No, I mean I have the same – I have the issue that I brought up before. There is no tumor in the brain that is technically viewed inoperable.

Man: We've been down this road before, Chris.

Chris Standaert: I know, so that's where the language is really difficult.

Man: I know, but nobody else is supporting your position about that. At least nobody's saying anything.

Chris Standaert: If somebody can define inoperable for me, then I'm totally comfortable with the word, and that's the dilemma.

Man: I think we got a definition the last time we went down this, and it's the decision of the team that it's not a place where people want to go with a knife. Yeah, it's a relative decision, yes.

Chris Standaert: So, that's the definition.

Craig Blackmore: So, on some level it's implied. I mean, if somebody – if the physician and the patient are saying this is the treatment we want, then that implies that there's been a discussion of alternate treatments and for whatever reason, this one was recommended. So, I mean, do we need to somehow put that into words or do we assume that if we're being asked to pay for something, it's something – that choice was made. The problem is, if we try to dig into that choice we get into an area where we don't have information. If we try to say this is a situation where you should or shouldn't do surgery, because that's outside of our realm. So, that's the struggle.

Chris Standaert: That is my difficulty, yes.

Martin Fuss: But could you, since it is a team decision, there will be a statement by a neurosurgeon, as a guidance. I think it would not be unreasonable to expect that statement by a neurosurgeon so that you don't have someone who's advertising a certain type of treatment without involving the surgeon who gives input, and I think that's not unreasonable, because this should be a team approach to management of intracranial diseases, and you would ask for a neurosurgical opinion regarding the probability and the appropriateness of radiosurgery.

Martha Gerrity: I might add if you look at the National Institute of Health and Clinical Excellence guidelines for the lung, inoperable stage 1 lung cancer, they also suggest that there be a thoracic surgeon involved to verify that this is truly inoperable. So, that notion of the team is there and having that statement available.

Craig Blackmore: That said, does that resonate with…

Man: It really does, Craig.

Craig Blackmore: So, that might be considered a condition, I think?

Man: Yeah.

Chris Standaert: That there be neurosurgical input?

Craig Blackmore: That there be – yeah. Is that the issue that you are concerned with. Is that the sort of approach that would…

Man: Well, I think that limits the field a little bit beyond primary. Your proposition was that any brain tumor we would cover.

Martin Fuss: Any brain tumor…

Craig Blackmore: I mean, at this point, I'm trying to get us to two or three options, so what I was looking for is first do we consider everything together, meaning we make one decision that covers everything, and we can have conditions or not, or do we have a separate decision on, you know, astrocytomas and a separate decision on metastases and a separate decision on IAC tumors, meningiomas, or whatever? So, I mean, it's semantics on some level, but I'll back up and ask the unbinding straw poll, unofficial, is there anybody who thinks we should have a noncoverage decision? So, I think if we can kind of table that one then we can go in the direction of what would conditions look like or not, and then that allows us to circle back to what it looks like, and I don't think I'm seeing enthusiasm for no coverage. So, then we move into conditions, and conditions might be we're going to cover these tumor types or conditions might be we've heard about having surgical input or multidisciplinary team. We've heard about functional status. We've heard about life expectancy. Are there other types of conditions that we should be considering?

Man: Functional score.

Craig Blackmore: I'm comfortable with the Karnofsky Scale. Okay. So, I think at this point we should have Margaret or Christine or somebody get us a piece of paper and we should start this.

Man: Okay, are you assuming that nobody – I mean, Richard almost implied that we should just cover without conditions, and I mean, I'm not happy – I wouldn't want to go that way.

Craig Blackmore: Yeah, I mean, I think we haven't made a decision yet in terms of cover. We've sort of, I've got a straw poll that says we're probably not heading down the no coverage realm. So, I'm trying to figure out what conditions might look like and then we'll have a vote.

Man: Yeah, I was just trying to help you by saying can we have a straw poll of – is there anyone in the room who thinks we should just cover unconditionally? I hope the answer is no.

Craig Blackmore: I think that's a fair point. Is it – so before we spend time trying to come up with conditions, do we, are we all heading in the direction of covered without – unconditional coverage, in which case we can save some time. So, who would be leaning in the direction of unconditional coverage at this point? Okay. Now, nonbinding, of course, at least now we're at the place where defining what conditions might look like would be of value. So, I think what I would like to see is some of the types of criteria put up on the board, and this isn't going to be exact, but at least to get an idea of what some of the options are for us to consider. So, one would be functional status, which is probably going to be Karnofsky, I'm thinking. The next one would be…

Woman: Medically inoperable.

Craig Blackmore: Yeah, so sort of surgical input, I guess.

Woman: Medically inoperable or unresectable.

Richard Phillips: Operable status or something.

Craig Blackmore: I don't know that it's inoperable or unresectable. The judgment thinks that the patient made an informed, hopefully, choice between these options, and it doesn't mean you couldn't do the surgery, but surgical input. Another one we heard was life expectancy. That's come up. What else has come up?

Man: Metastasis.

Man: Tumor size.

Craig Blackmore: Tumor size.

Richard Phillips: Number.

Craig Blackmore: Number of tumors. Anything else that we might start to think about here?

Chris Standaert: The LCD talks about – Medicare LCD talks about image-distinct margins. So, do you actually sort of zero down on these things. It says distinct margins, so you have a finite tumor.

Craig Blackmore: Okay, finite tumors.

Michelle Simon: That would probably get covered under surgical input, but. Do you want to do primary versus metastatic, either or both?

Craig Blackmore: Tumor type?

Michelle Simon: Yeah.

Craig Blackmore: Tumor type. Okay, so now I'm soliciting discussion around which of these are criteria that the committee wants to pursue.

Joann Elmore: Karnofsky and surgical input.

Man: These are the big ones. I mean, the thing that really struck me with the various public comments are, people love this. It's gee-whiz technology. We're getting so good at it, we can take out tiny little lesions in really obscure places. Why not use it in the prostate, because we technically can where I think it left for-profit centers who have got – are already invested in the machine. It's technically possible to use SRS or SBRT in all sorts of places. I think our job is to do some kind of line in the sand and say we just – I like – I think we need to say something about functional status, something that we require, as a team, including surgical input that they have deemed that this would be the best approach.

Craig Blackmore: This is SRS, though. We're not into the body yet.

Man: Well, it – all of us – my thinking would be similar in that other than – those are the main ones. For us to get too tiny about tumor size, distinct margins, tumor type. I think that's in the realm of what a balanced medical team would come up with. They'll decide this would be better done surgically or it would be better if this was done nonsurgically.

Man: In many ways, tumor size is entirely dependent on where the tumor is.

Chris Standaert: Yeah.

Craig Blackmore: And who measures it.

Martin Fuss: Yeah, but not for radiosurgery. I mean, there is good data that asks you exceed 3 cm in size, that the complication rate increases significantly, and I think this is globally accepted. You may consider that a size exceeding 3 cm requires special justification. I would, as a physician, always put very

specifically down why I'm addressing a disease larger than 3 cm by radiosurgery.

Craig Blackmore: I personally haven't seen great data. Maybe I missed it. Do we have great data that says that 3 cm is the cutoff?

Martha Gerrity: There isn't specific data of subgroup analyses looking at tumor size. However, the vast majority of the studies restrict based on tumor size of less than 3 or less than 4 cm.

Martin Fuss: There is actually good data. There's RTOG 90-05. It's a dose escalation – it's a dose finding study for radiosurgery including close primary and secondary tumors. They're obviously not randomized trials. It is truly dose finding and dose recommendations for maximally tolerated doses were made for tumors smaller than 3 cm, this is commonly – 2 cm is the best indication group for radiosurgery, between 2 and 3 cm, and then larger than 3 cm, and at the larger than 3 cm level, the doses that are – again, this kind of defines the cutoff for suitability. So, again, I think this would be appropriate and a justification for treatment of lesions larger than 3 cm, and that would be seconded by probably everyone involved in radiosurgery.

Man: So, my intentions of saying that, that tumor size is larger than where it is, is that I would regard tumor size as being a function to be determined by the surgical team or by the tumor team in that respect. So, I'm not arguing with you on the 3 cm size. I was just saying I don't think we should actually consider that, because I would hope that the treating team would be using that type of data in their considerations. I think it's – we don't need to get into that level of weeds.

Richard Phillips: And since this cutoff was embedded in those studies anyway, it wouldn't apply to our decision making.

Michelle Simon: We just don't have the evidence to say it. I mean, maybe it exists, but we didn't look at it, so we can't really use it.

Chris Standaert: Well, it's like the Karnofsky. We have the same issue with that. That's the cutoff. We don't have studies comparing different levels of the Karnofsky scale. We have that as a cutoff for entry into the RCTs, and can you tell me what did they use this criteria for those RCTs typically? So, it's the size of tumor, Karnofsky, and?

Martha Gerrity: Number of tumors.

Chris Standaert: Number of tumors. Those were the prime determinants?

Martha Gerrity: Those were the common ones.

Chris Standaert: And the number of tumor limit is typically 3, 5, 1?

Martha Gerrity: Usually, either 2 to 4 or 1 to 3.

Chris Standaert: Okay.

Joann Elmore: It seems like to maintain, we ought to put team decision making or team analysis, including surgery.

Man: Yep.

Man: I think some wording currently is going to be our best sort of guard – what I want to guard against is just allowing, let's say, for-profit centers to – this is what they do. They don't want input from a surgeon. They – I mean, I want to give the Health Care Authority some defense that if it's not – if there hasn't been a joint decision by a multidisciplinary team, including the surgeon, then they can either say no or we need to do it on an individual basis. I think requiring that would probably be pretty sensible.

Chris Standaert: I mean, is that we're putting things like tumor size? I mean, you can make a legitimate argument that, you know, the only evidence we have, which is what we're supposed to be using is on patients with tumors of 3 cm or less with a Karnofsky of somewhere of 70% or 50% or higher, whichever one you want to pick, and four or less lesions.

Man: Right.

Chris Standaert: And that's the data we have, and so that may be the only thing we could really say.

Man: See, and if it's outside of any of these criteria, they are welcome to argue their case, but we're not comfortable with it.

Chris Standaert: Others at agency discretion.

Craig Blackmore: Okay, I'm trying to parse the lists. Tumor type? Yes or no? I'm seeing some nos.

Group: No.

Craig Blackmore: Alright. Get rid of it. Distinct margins?

Group: No.

Craig Blackmore: Alright. Get rid of it. Life expectancy?

Chris Standaert: We don't have any data or independent predictor. We have the RPA scale. We don't have studies on…

Man: Well, you know what the natural history is. We've heard the natural history.

Man: It's bad.

Chris Standaert: It's bad, yeah. So, the recommended cutoff from the state is saying six months, but we don't have a – we have the RPA data, which says people who, in fact, are in that have a potential life expectancy as a metric of it. The people who are sort of doing better overall have a more robust response to the treatment, and maybe we capture that in Karnofsky so we don't have to get into life expectancy.

Man: In that recommendation of six months, is that six months with treatment? Is that what we're…

Chris Standaert: It doesn't tell.

Michelle Simon: Yeah, or is that without treatment?

Man: I mean, because like none of these patients have a life expectancy of six months without treatment.

Chris Standaert: Some of them do.

Man: Obviously, for the meningiomas and other things they do, but…

Chris Standaert: Some do.

Man: Because that's a very different – I mean – you see it's a very different point, right? If they're saying, if you're not going to live six months, we're not going to treat you, period, then we're not going to treat any of these people with mets.

Craig Blackmore: Alright.

Man: I thought it meant if you looked at the patient as a whole.

Michelle Simon: Without treatment.

Man: It doesn't matter what the patient looks like if they have brain mets. I mean, if the life expectancy is three to six weeks…

Man: They can have other things that would shorten their life expectancy even more.

Man: I mean, I suppose you're right, but we certainly aren't going to be able to use this fine of a microscope to separate patients who have a life expectancy of one week versus three weeks. I mean, there's no way we can make that determination, I don't think.

Michelle Simon: Even with treatment we don't really know what the life expectancy is, because the data is not that robust for that, either.

Man: The point is I think, to Craig's point, I think this becomes a very, very difficult thing to determine.

Craig Blackmore: Yeah, I just think it's arbitrary. I mean, you can always – there aren't life tables that are precise that we would have some…

Chris Standaert: No, it's a judgment call.

Man: Those are very subjective bars we're giving people to put on there, so it's probably best not to have it.

Craig Blackmore: Should we get rid of the life expectancy?

Group: Yes.

Craig Blackmore: Okay. Get rid of it. Functional status? Are people comfortable with some sort of Karnofsky cutoff or not?

Man: I'm not comfortable with using a cutoff. I'm just not that comfortable with using a suggested level of 70.

Craig Blackmore: Okay. Let's start with the general question. Are we comfortable with some sort of functional status cutoff? I'm seeing nods. Are they shakes? Are they all…? Okay. I'm seeing nods. Okay. What's the threshold then? 50 has been suggested. 70 has been suggested.

Man: Well, I would like to ask Michael. So, 70 was what most of all these studies use as an inclusion. So, on – we can, I mean maybe they all just flipped a coin and got 70 or maybe there was a reason they chose 70. So, what's – expand on your interest in using 50.

Martha Gerrity: There were some that did use 60 and some of the case series and cohort studies went down to 50.

Man: Besides the Wisconsin LCD?

Martha Gerrity: Right.

Man: The Wisconsin, that was a coverage decision. My, it's kind of already outlined as the imprecision around taking a study filter and applying that to a population for a treatment decision. I would – it just makes no sense to me.

Man: And again, Mike, as you said, often in a study, they will pick a higher functional stage just to make sure everybody gets in the study, can do it safely, and we'll see if this is effective, but it in clinical reality you might well use it on people at a lower functional status.

Man: Especially given the fact that their functional status could very well change over time with a concomitant addition of steroids.

Man: Well, I would just remind you that the Karnofsky scale was developed by oncologists, wasn't it?

Martin Fuss: Yeah, and maybe I can give you just a little bit more guidance. Once you get into a 40% range, some of the language has that the disease may be progressing rapidly, and you took out the life expectancy, but in 40, it is implied that this is very limited. So, 50, again, my expectation for a patient with a Karnofsky of 50 would be that I send him home after

radiosurgery with some degree of care, but to send him home to his environment.

Chris Standaert: Is Karnofsky a 10, 20, 30, 40, 50 or is it a 51, 52, 53?

Martin Fuss: 0 to 100.

Chris Standaert: But based on 10s or you can be a 53?

Martin Fuss: Yes, 10s.

Chris Standaert: Because the Medicare LCD says greater than 50. It doesn't say 50, so it'd be 60 or higher is what they're saying, and the studies are mostly 70, but some go down to include 50s in some of the case controls.

Martha Gerrity: There is one.

Martin Fuss: So, they grouped in 100, 90, 80.

Chris Standaert: Right, by 10s.

Martin Fuss: So, this is grouped in 70, 60, 50 is a group, and then 40 and below.

Chris Standaert: And below is another grade – another stratification.

Michelle Simon: So, I don't know enough about this, but who applies the Karnofsky score? Who decides that?

Martha Gerrity: It would be the treatment team.

Richard Phillips: Medicare uses greater than 50.

Martin Fuss: It is a quality care in your charting, electronic charting, to determine the performance status of a patient, and as such, we are encouraged to use either ECOG in oncology or Karnofsky score and grade every patient at their incoming consultation.

Craig Blackmore: Okay. I guess we're looking at 50, 60, or 70. That's where we're converging, and we need to pick one. So, 50, yes or no? Shows of hands. Just out of curiosity 60, shows of hands. 70 shows of hands. We've got a nice split.

Man: Take a committee average and come out at 58.9.

Chris Standaert: Can we read 50, 60, and 70?

Martin Fuss: Yeah, I have it right here.

Chris Standaert: Thank you.

Martin Fuss: Let me read you the 50% before it dropped down. So, the group 70, 60, and 50, this is one group that has one common language, unable to work, able to live at home and care for most personal needs in a varying amount of assistance, and then the assistance that amount breaks down to 70, they barely need any assistance, 60 requires occasional assistance but is able to care for most of their personal needs, and then 50% means requires considerable assistance and frequent medical care. That applies to many of our oncology patients, but again, they are able to live at home, and the distinction and then the next group 40, 30, 20, and 10 group unable to care for self and then also implied that they are no longer able to live independently.

Group: Okay.

Craig Blackmore: Okay. Does that affect the choices here? I'll have people raise their hands again. 50. There it is. Could we write a 50 please on the board?

Chris Standaert: 50 or greater. Greater than or equal to 50.

Craig Blackmore: Alright. And then – so we'll need wording around team analysis including surgical input is that a criterion, however we word it, that the group is comfortable with including?

Chris Standaert: I would do multidisciplinary…

Craig Blackmore: We like that. Some sort of team – I'm looking at the second one down, team analysis including surgical input so the decision – okay. So, there seems to be a…

Man: Should we specify neurosurgical input or does it not matter?

Craig Blackmore: Well, I mean yeah, let's get some wording on here that we're comfortable with. So, the condition would be that…

Chris Standaert: At this point, assessment including neurosurgical.

Man: The only multidisciplinary sort of thing is if for some of the benign tumors their neuro-otologist and other surgeons that are involved.

Man: I would – yeah, I would leave it.

Man: Just leave it as surgical.

Craig Blackmore: Surgical? So, multidisciplinary team evaluation, including surgical input. Is that fair?

Group: Sounds good. I think that's fine.

Craig Blackmore: Okay. Tumor size?

Man: Less than 3 cm.

Chris Standaert: Less than or equal to 3?

Craig Blackmore: I have a proposal for 3.

Chris Standaert: Inclusion with less than or equal to 3? Is that what they were? They were less than or equal to 3?

Martha Gerrity: Most of them were, but there were a couple that were less than or equal to 4.

Craig Blackmore: Okay. Do we want 3 or 4?

Man: Three. If somebody's got a bigger tumor, they can always argue their case.

Chris Standaert: They can, yeah. And then we can put this thing at the bottom saying…

Craig Blackmore: Does that resonate with the group?

Man: I don't know what we're polling.

Group: Right.

Craig Blackmore: Alright. Let's just ask one more time. I want a show of hands whether we should include a criterion for tumor size or not. So, if you think we should include a criterion for tumor size, let's have hands if we want a limitation based on tumor size. I've got three, six. Alright, so we've got a majority.

Man: Can I hear from the people that do not want – we had clearly from Dr. Fuss about there's general consensus of people who are saying they don't want a tumor size assuming that the multidisciplinary treatment teams are smart enough to figure this out.

Group: That's what we're saying.

Man: I'd be fine with that if we think…

Woman: We didn't review the literature. We're not able to…

Craig Blackmore: Okay. Is that – I'm getting a lot of nods on that. Okay.

Group: Yes.

Craig Blackmore: Let's get rid of tumor size. It's the same hold for number of tumors? The same logic?

Man: Yes.

Craig Blackmore: So, is the group comfortable then with a functional status of the Karnofsky score of greater than or equal to 50 and a multidisciplinary team analysis including surgical input as the two conditions that we would use?

Group: Yes.

Craig Blackmore: Is there further discussion? I don't want to shut us down. Okay. I'm going to move then to the decision tool. So, this is in your packet. It's the HTCC coverage and reimbursement determination analytic tool and defines the best outcomes and values for the state and the patient. The HTA program focuses on the questions of is it safe, is it effective, and does it provide value? We've all been through this before. I'm not going to read it in detail. The process consists of a nonbinding vote, and I'll have you grab your yellow cards please. Then, this is our first voting question, and the question is, based on reviewing the technology

assessments and information, etc., we will make a determination is there sufficient evidence under some or all situations that the technology, and the technology here is SRS, so we're talking about the brain and cranial contents. Is there sufficient evidence that under some or all situations it is effective, and your choices are that it is unproven, that it is equivalent in effectiveness meaning equivalent to external beam fractionated treatment…

Woman: [inaudible].

Craig Blackmore: No. You're comparing it to conventional radiation therapy. Is it less effective or is it more effective? Let's see some cards.

Josh Morse: Nine more, one unproven, or is that? It must be 10 more.

Craig Blackmore: Yeah, there should be all 11 of us.

Josh Morse: One unproven.

Craig Blackmore: Okay, and then the second nonbinding question is, is it safe? And again, the choices are the same. Okay. This is going to be all over the map.

Josh Morse: Let's count equivalents, one, two, three, equivalent; unproven three; one, two, three, four, five more.

Craig Blackmore: The third nonbinding question is, is it cost effective?

Josh Morse: Eleven unproven.

Craig Blackmore: That was easy. Any further discussion at this point? I'm going to move on to the binding vote now, and again, this is for the SRS only and based on evidence about the technology safety, efficacy, and cost effectiveness, it is not covered, covered unconditionally, or the third choice is covered under certain conditions, and the conditions we have laid out on the board, functional status with a Karnofsky score of 50 or greater and multidisciplinary team analysis including surgical input. I would like votes.

Josh Morse: It looks like 11 cover with conditions.

Craig Blackmore: We are required to determine if our decision is in line with Medicare and national coverage decision, and I think I am right that there is no Medicare national coverage decision.

Josh Morse: That's right.

Craig Blackmore: So, that is fine. The next piece of the decision making is related to SBRT and we're back to where we were in having to make a decision about whether we consider all of the potential uses, tumors, and body parts or if we drill down on specific indications and treat those differently, and I guess we need to have some discussion. Who would like to start us off? David, do you want to start us off, since you've…

David McCulloch: Is this for SBRT?

Craig Blackmore: SBRT.

David McCulloch: Yeah. I mean, I think for the nonsmall cell lung cancer, I'd be comfortable with something very similar to that.

Craig Blackmore: And the rest? Prostate, breast, everything else?

David McCulloch: The other is the paraspinal tumors, and I think that where there is a question of being near sensitive important structures, like the spine or the spinal cord, and those are the two that HTA wanted us to comment on and for all the rest just say no, you've got to argue your case on an individual basis. So, both of those, paraspinal tumors, primary or mets, or nonsmall cell lung cancer, I'd be comfortable with something similar to that.

Craig Blackmore: Do I have some other thoughts?

Joann Elmore: When we went through the list, it seemed like there was less and less data on other…

Craig Blackmore: That's a fair statement.

Chris Standaert: That's a fair statement, yeah.

Man: I was wondering whether we could use just similar language to that, which we were using with IMRT that essentially said was to spare adjacent critical structures to prevent toxicities within expected life span.

We came up with that and what seemed to be very similar constraints than brain mets.

Chris Standaert: Right. I tend to go the same way. I mean, this is – we have a lot less data on SBRT than we had on SRS, which wasn't phenomenal, but to me it's the same theoretical construct as IMRT, and our expert sort of said, well if you do four that's SBRT, if you do six it's IMRT. I mean, that sort of – you kind of go how do you cover IMRT but not SBRT even though it's sort of – you know, it's the same theoretical thing. So, there's that idea of critical structures and lifetime toxicity exposure that we talked about in IMRT for us to go with, and that would include head and neck tumors and paraspinal tumors.

David McCulloch: That makes sense to me and excludes the likelihood of it being expanded into just because it's technically possible. We'd like to use our cool new tool.

Craig Blackmore: Does it?

Michelle Simon: So, are you suggesting we limit it to just that, the spinal tumors? Or are we saying that category applies to all tumors? So, they could be used for prostate, as well?

David McCulloch: Right.

Michelle Simon: I'm not as keen on that, I guess.

Joann Elmore: We had that discussion last time.

Michelle Simon: I know.

Man: I mean, we're already – we've already covered prostate with IMRT in those circumstances. That's already withstanding, so as Chris said, it's the difference between six doses or if we do it in less doses, it's now four doses, and now it's SBRT, so we say okay, we're not going to cover it if we use two less doses.

Martha Gerrity: I might remind the committee there was comparative data for prostate and IMRT, and there is none for SBRT.

Michelle Simon: Yeah, and the data we have on prostate, it wasn't about efficacy, it was just about side effects, I think. Isn't that right? There were like four case series and that was it.

Martha Gerrity: Right. For SBRT, it was case series. For IMRT, the evidence suggested that IMRT there was less adverse effects to the rectum and bladder.

Chris Standaert: I guess SBRT, I mean – they're not totally identical. I mean, SBRT you're trying to essentially kill everything within the field, right? You're trying to – it's a destructive process, and the issue that you brought up early on of radiation necrosis, that sort of thing, isn't as prevalent in IMRT, I assume. It's not quite the intent.

Martin Fuss: Yes, the intent to SBRT is ablative, you're right there, so to kill all tumor cells within a given defined target.

Chris Standaert: It kills everything within the target, essentially, right? Not just tumor cells.

Martin Fuss: Then you want to – that's why you have to restrict your target to the actual tumor, like in SRS.

Chris Standaert: Right.

Martin Fuss: Because, that is ablative, as well, whereas IMRT the implication would be that despite the fact that you necessarily may have to include some normal tissues, but you're still taking advantage of the superior organ at risk sparing concept. Let's say you treat a larger area right next to the kidneys, which are explicitly radiosensitive, and you're still able to preserve the renal function with IMRT. Now, with SBRT you go that one step further. You maintain all the protection but your treatment intent becomes truly ablative.

Chris Standaert: So, in some tumors where sort of the tumor is actually not so clear margined and more infiltrative into sort of healthy tissue around it, you may not think about SBRT, because you can kill a lot of healthy tissue, too. You may actually want IMRT and try and get the tissue that is more radiosensitive. So, prostate, for example, you may not want to fry the whole prostate. You may want to – I mean, I don't know.

Man: But that is again where we might rely on a multidisciplinary team analysis.

David McCulloch: Absolutely. I want that phrase in here, as well.

Chris Standaert: And we have no specific data on prostate like we did for IMRT, but…

Craig Blackmore: So, I guess there's kind of two pathways that I'm hearing here. One pathway is to mimic the IMRT decision that we made, and the other pathway is to sort of mimic the SRS decision that we've made, potentially limiting that to specific body parts or types of tumors. I mean, what does the group think? Can I get more input on other people's opinions? Carson, what do you think?

Carson Odegard: Well, I'm okay with what's stated up there right now. I don't know if you'd want to get into the specifics of the organ itself. For example, the lung, and we don't have the data on prostate, so we can't really address that.

David McCulloch: So, one thing we've said in – we've put language in, in some previous decisions, to say requiring developing a registry of documentation to get the data. My worry is that we already do too many prostate surgeries, and we intervene way too often in prostate cancer anyway, and here we've got a relatively safe tool, so we'll start doing it in smaller and smaller incidental tumors. I would love us to be able to at least restrict it by saying if you're going to do it, you need to at least be part of our whatever our language was – a registry.

Chris Standaert: I mean, you could – there is the other issue with this. If we do this, really we have no data – we have very little data on SBRT, and we are giving an awful lot of authority to a multidisciplinary team that is going to have no data and probably owns the Gamma Knife or whatever, you know, and so you wind up with the same dilemma that we give them a lot of authority in this one with very little, you know, guideline or restraint or anything else. So, do you say it's for paraspinal sort of things, because they are clearly more difficult? Do we get into tumor types? Do we leave it and give the agency more discretion to sort of say we will review a multidisciplinary plan, but we don't let them just – we give the agency the right to sort of dispute the plan if they don't agree with it? I mean, or do we draw the lines ourselves? Those are the things we – either we let the team draws its lines, we draw them, or we give the agency more discretion to do it.

Craig Blackmore: I guess I'm struggling with, you know, we had bad data on SRS, but at least we had some. We've got a little bit of bad data on the lung, but you know, I'm seeing nothing for most of this stuff, and I think our job is to say what data is there and I'm just not seeing it.

Man: I guess, I mean, it goes back to the question of what's our charge? Is our charge to allow anything, unless there's data? Or is our charge to make decisions on things, and if there's no data, they're not covered. I mean, is the onus on us to prove that you can't do it, or is the onus on the technology to prove that there's evidence that it's worthwhile? And I thought our charge was the latter, but I'm not sure that I'm in the majority.

Craig Blackmore: I think our charge is the latter, and I think, you know, what constitutes evidence, and in the SRS, personally, I was willing to rely a little more on the pathophysiologic model of not wanting to radiate brain, but brain is much more radiosensitive than other structures in the body, and I'm not seeing evidence that using this in the prostate is going to decrease complications, and I'm not seeing evidence that it's going to improve outcome, so I think, you know…

David McCulloch: I thought there was, imperfect though it was, there was enough in nonsmall cell lung cancer to say for the tumors near sensitive structures, this is becoming a pretty reasonable option. I'm given that we've said the IMRT thing for paraspinal, I would think for those two conditions we could leave it at this and for everything else we see argue your case. But even for nonsmall cell lung cancer and paraspinal, I think we should put in the language to say that you have to be collecting data on this.

Chris Standaert: We had this same discussion on data last time. I mean, we chose "or" at the end of it. We didn't say and, and the trouble with saying and you have to be collecting data is, you know, so now you have people saying, you know, for nonsmall cell lung cancer this is sort of in a very delicate site. This is the standard of care. As soon as you say and, people won't get it, because you don't have the infrastructure to collect data, it is not there, and we can't make that happen. So, I worry about the and. I like the idea, I really do, but in the operability of it all in the current healthcare environment, it's challenging to mandate that.

Craig Blackmore: And again, to reiterate, the agencies have the ability to pay for anything regardless of our decision if it's part of an IRB approved research study.

So, we don't have to say that for them to cover things that are in research trials.

Martin Fuss: And, can I make a comment? Registries for IMRT, the last time, that was difficult because such a registry does not exist. However, there do exist registries, big registries for SBRT, and it's not limited to organ site. There is actually the Radiosurgery Society, and I'm a board member there, so I have to disclose that, we hold a registry of over 11,000 enrolled patients. So, you can – it's a very straightforward process. You can, once a patient is identified as being appropriate for SBRT, you end up under an IRB, your data into that registry, and this data gets tracked and so we are currently out of this academic society mining some of those data to answer some of those questions on a larger scale where you're not restricted to the 100 patients that you treated yourself, but you have access to 5,000 lung patients that are enrolled in the registry. So, there's a significant acceptance of entering such data into registries. Some insurance providers stipulate that in order, for example, to cover SBRT for prostate, and it's not terribly expensive to be able to enter data into the registry, so I think it's reasonable.

Chris Standaert: So, there is an existing registry?

Martin Fuss: Yes. Actually, there are multiple – and there is an effort to unify them at this point in time for the United States so that it is becoming one big database, something like SEER.

Chris Standaert: So, that is an option here, then.

Michelle Simon: That's awesome.

Man: I agree with what David suggested then, actually.

Man: So, that would be critical structures, team agreement, and entering data.

Craig Blackmore: I don't like critical structures, as much as I like paraspinal and specifying spine. Critical structures, I know we've used that, but it…

Man: No, it was me that came up with the critical, trying to make it like IMRT, but I actually bow to let's consider lungs, spine, and paraspinal structures and then everything else, if it's in a registry.

Man: Although we've seen no data on spine or paraspinal either. The only thing we've seen data on is lung and that's poor, but at least there's something that we have to go on. Spine, there is nothing.

Man: But I don't think it's the same reasoning as we're using for SRS for the brain. I mean, it's neurological tissues.

Craig Blackmore: It's an extension of the, again, pathophysiologic model that the neural tissue is more sensitive to the…

Chris Standaert: I'm fine using the IMRT rationale. If you have a paraspinal tumor and, you know, either you – you're radiating the cord or you cone it down somehow and then do you do that in one, two, six, or ten treatments becomes the decision.

Man: Well, I agree with that, and I think, you know, when we look at what's the reason for restricting them, I think you, if the reason for restricting – you know, the treatments are not that dissimilar. The toxicities are not that dissimilar, but maybe a little bit less. The only real reason I can see to restrict this is cost, and what we've heard is that it may be more expensive than EBRT, but it's probably…

Chris Standaert: Compared to IMRT.

Man: Compared to IMRT, which is the alternative, which we've essentially already approved, we don't know if there's any difference. We're operating without data anyway, so if we're going to say – you know, I think it makes sense to call out lungs, because I think with lung we can at least say there's some data to says that there's an improvement, and it's twice the life expect – or twice the control. That's reasonable, but for – even for paraspinal. I mean, I don't disagree with it, but I think even just to call out paraspinal relative to prostate or relative to something else, I mean, I don't know that we're standing on firm ground there.

Craig Blackmore: Any other thoughts? Joann?

Joann Elmore: Candidly, I was pondering whether to say that we would leave all the SBRT to the discretion of the agency, but if the agency approves it we would require two things, one that a multispecialty team analysis with surgical input be included and two, that the patient be enrolled in a registry. I'm getting at this issue of it's challenging with the lung, and it's definitely challenging with the lack of data.

Craig Blackmore: I think we have to be careful with leave it at the agency's discretion. I mean, the agency has asked us to help them.

Joann Elmore: Well, and I wondered about saying we discourage it due to the lack of data.

Craig Blackmore: Yeah. So, I mean, I don't have – if the group wants to go with the conditions you've detailed, that's fine, but I don't like saying, you know, the agency has asked us to look at something and we say no, you do it. I think we should at least make an effort to make a decision based on the evidence as best we can without…

Joann Elmore: And I think you're hearing us say that we didn't see a lot of data on the paraspinal, so we're all hesitant making yes or no binary decisions.

Man: No, not all.

Woman: Where is the data on the frequency of which it could be in the financial – from the agency that – frequency of which all of these others occur?

Woman: They didn't break it out for us.

Man: Do you mean the incidents of the tumors?

Joann Elmore: Oh, they do have spinal. I take that back. Four spinals in Medicaid, one in PEBB. The other sites, it's definitely increasing, so this is where they do need our input.

Chris Standaert: You know, I get the vagueness of letting the agency decide. I mean, they sort of asked our discretion at the end, but every policy they have out there says that – basically gets to the issue that this is yet another thing in the spectrum of radiation and oncologic therapy, and every [inaudible], but we have to consider in the scope of lifetime exposure and risk and tumor recurrence, and all these sort of factors that go behind when you do this and when you're doing the math about radiation exposure. If you start specifying body parts, it gets really hard, because you may have somebody who's had prior radiation for lymphoma who now has a paraspinal met who now needs, you know, and you're doing the math and you go we can't do this to his tumor – his cord, unless we do this, and that's what we're – do we restrict that or do we let that go through an

appropriate analysis between the state and some reasonable multidisciplinary team?

Craig Blackmore: I think it's a hard job we have, and I think making decisions is always hard, and there's traps that you can fall into in trying to make those decisions, and one of those traps is to say, I can't decide so I'll just say we'll do it if it's a research study, and the other trap is I can't decide so I'll leave it to the agencies. I'm not saying there isn't a role for each of those, but I think it's kind of like being a radiologist, and say, we cannot exclude and consistent with, and you know, you have to do your job, and your job is to make a decision using those other tools only occasionally. That's my opinion.

Woman: So, the options are paraspinal and that leaves out the prostate or include?

David McCulloch: Well, as I've read it the way it's written up there now is that we're saying for spine and paraspinal and nonsmall cell lung cancer, that's covered, as long as it's a multidisciplinary team with surgical input. For all other places, the justification needs to be to spare additional critical structures in the context of clinical – well maybe we say all of the others leave to the agency, but what you said, Joann, leave it to the agency, but if they're going to say yes, it should at least be with these other two things.

Woman: Did you guys want to add the Karnofsky in there under the conditions?

Woman: Brain tumors are different in terms of disability, although with lung you have COPD disability, but…

Craig Blackmore: I mean, you're doing it because they have COPD disability, right?

Martha Gerrity: Can I ask a clarifying question? When you say nonsmall cell lung cancer, the evidence was primarily for stage 1 inoperable. Are you adding that in, because I read that as being all nonsmall cell lung cancer patients.

Chris Standaert: We hadn't gotten there, yet.

Craig Blackmore: Absolutely. Okay, so in terms of process, I think, again, if we try to narrow things down, I'm thinking that the committee is not leaning towards a no coverage decision. Can I get some nods to confirm that, and we're moving in the direction of a cover with conditions or an unconditional coverage, and so we are going through the process of

defining what those conditions might look like, and it sounds to me like there's a reasonable consensus in the group that nonsmall cell lung cancer stage 1 inoperable is something we're comfortable covering, is that…?

Group: Yes.

Craig Blackmore: And we've been discussing cancers of the spine, paraspinal structures. Can I get some nods about yes we want to cover those? So, informally I'm seeing mostly enthusiasm around that. We can't always get to 100%, and then we've got multidisciplinary team analysis including surgical input. Do we wish that as a requirement for all, so including, is this in addition to being a cancer of spine and paraspinal or nonsmall cell, you also have to have this team?

Group: Yes.

Chris Standaert: Because you can't decide inoperable if you don't have a surgeon.

Craig Blackmore: Okay, and we're pretty comfortable with these. Then, so now, the rest of this would apply to other cancers, cancers at other locations, and we're trying to figure out what we're saying around those other cancers. That's where we are. And so, one proposal is to use language similar to what we did with the IMRT, which is to say spare adjacent critical structures to prevent toxicities within the expected lifespan. Can I get some discussion around that language?

Michelle Simon: Are we also saying this is under the agency discretion, this last section?

Joann Elmore: I would want to. I wouldn't want to just give it a blanket like this.

Craig Blackmore: I mean I guess I would sort of – I almost see this as an or. Either we say to spare adjacent critical structures, prevent toxicities, or…

Woman: No.

Woman: That would probably…

Man: I almost think what we're saying is don't cover, but cover it…

Chris Standaert: No.

Man: …but if they're doing data acquisition then cover it, which is basically saying the same as don't cover.

Chris Standaert: No, this is saying if they enroll in a registry they can treat other structures provided their math sort of states that this is the thing they should be doing.

Craig Blackmore: And the agency's…

Chris Standaert: We haven't said that. Right now, we don't have to say the agency has anything to do with it.

Joann Elmore: I would want it to say at the agency discretion.

Craig Blackmore: What does that look like to the agencies? Can I get input from – if – what I'm hearing from the committee is we want to, I think, one proposal is that we would only allow treatment of these other areas and other tumors if there were some potentially unusual circumstance where there was an adjacent critical structure and would you guys be able to operationalize that?

Woman: It would be easier to operationalize if you state that it's noncovered, because even a non-covered condition could be evaluated as an exception to rule for agency consideration of that authorization request.

Craig Blackmore: So, if we just said non-covered, you would have the ability to rule on exceptions? We're getting some debate I'm getting conflicting information.

Man: Just to clarify amongst the committee, are you guys thinking like that they would require some sort of preauthorization to do this?

Richard Phillips: So, basically just subject to agency discretion.

Man: If you say non-covered and there's a trial, that's an exception.

Craig Blackmore: Right. But otherwise, if we say non-cover, they can't…

Man: That's my interpretation.

Craig Blackmore: Whereas if we said subject to agency preapproval would that be – could you operationalize that?

Man: And what are we expecting them to make that decision based on?

Craig Blackmore: Based on…

Man: I mean, because we're saying turn it back over to the agencies, but the agencies have the same data that we just looked at. So, what's going to make, I mean, presumably the individual clinician team can basically make an argument that it's better than....

Craig Blackmore: They would have to make an argument that it's sparing adjacent critical structures. I don't know if that's helpful or not. I don't know.

Man: Could we just put the multidisciplinary team analysis, including surgical input, and then subject to agency approval and leave it at that? Then that way, they'd leave open to a lot of judgments and we don't get into the particulars.

Craig Blackmore: I'm not sure that's restrictive enough to meet the committee's desires.

Chris Standaert: This is just a question of how tightly we draw the circles. All we've said now is that the fundamental distinction is that if you go in to use it for something other than those two conditions is that you're trying to spare critical structures of excessive radiation dosage, and you're part of a registry or some study, and you go to the agency and have them give you their blessing.

Woman: And you have a multidisciplinary team. You have the three ands.

Man: You know, what I'm struggling with here is I think that ultimately what it seems that we think is that this may not be any better than IMRT or whatever else is approved, and what we really want to know is okay, well, maybe we should revisit this because if there is some data that shows that it's better, and we'd accept limited data, because we seem to be willing to accept it for lung, but anything that shows it's better than something else would be reasonable, but right now we're not seeing anything. I hate to say this, but this seems like the situation where we say don't cover it, because there's nothing to say we should cover this.

Craig Blackmore: I'm having trouble figuring out why we could cover this.

Man: I mean, if we're going to come up with so many restrictions.

Woman: If we say don't cover, they can always come in and ask.

Craig Blackmore: They can always enroll in a trial. If they're in a trial, then they can do it.

Chris Standaert: You can say all other indications are subject to agency approval, which essentially says there is no other condition that somebody can do this on their own without clearing it.

Craig Blackmore: Yeah, but…

Chris Standaert: If you say not covered for other indications. Nobody can get that cleared. That's the only difference.

Craig Blackmore: Unless they're in a registry.

Man: Can I read you the AMD recommendation that we started with?

Craig Blackmore: Yeah.

Man: All other diagnoses subject to agency discretion. So, they're saying they'll decide all the others. That was their proposal.

Craig Blackmore: So, how would you operationalize that, agencies?

Woman: A prior authorization process.

Craig Blackmore: Based on what criteria?

Woman: It would depend on the diagnosis. That's all we have to work with. We're working with the same evidence you are.

Craig Blackmore: I mean, isn't that our job? Isn't our job to look at this and say is there any data that it works? And if there isn't to not pay for it, and then if there's – because it's experimental. We don't know if it works, and if it's involved in some sort of research process to acquire that data, then the agencies will support that, because that's their job, and then we'll learn something.

Man: As part of – we've already talked about this, as part of a clinical trial, does a clinical trial, does that definition include that of a registry? A well-run observational registry?

Craig Blackmore: That's a good question. So, agency directors, if there were a registry and a patient were to be enrolled in that registry, and it was something that we didn't cover, would that be something that you would pay for?

Man: If it was an IRB approved registry, which you'd probably want it to be, it's just like you said before. That's in the law that we can cover anything if it's part of a study, an IRB approved study, and if the registry is part of an IRB-approved study, then yeah, we'd cover that.

Man: I would just like to…

Chris Standaert: IRB.

Craig Blackmore: Registries aren't necessarily under the auspices of an IRB. Registries aren't IRB approved necessarily. That's a reasonable way to accumulate this kind of data, because you're not going to get an IRCT very readily.

Craig Blackmore: In the past get an IRB to rule that it was exempt.

Chris Standaert: You could, yes.

Craig Blackmore: Or expedite, perhaps.

Man: In the past, I remember when we talked about autism and behavioral therapy. There wasn't really an alternate treatment, and there was some indication that it might be useful. We weren't comfortable enough to cover it without conditions. So, we attached the trial or registry to it in hopes that more evidence could be gathered to prove whether it was helpful or not. None of these other body structures have shown that there's any evidence. So, I'm not personally willing to grant them the same pass that we gave behavioral therapy, because they haven't shown anything. If they had, we would be seeing it.

Man: Well, the other thing we're hearing is that there already exists a registry with 10,000 patients in it that just hasn't published anything yet.

Martin Fuss: Can I comment on something? I see where you're struggling, and I'm struggling with the same thing. Our field has gone through a host of phase 1 and 2 trials, but they obviously don't make into this evidence review. Carefully analyzing what doses can be delivered, to what organ structure and where should you stop. So, there's good guidelines there,

and they apply to organs like the liver. They apply to organs like the lung, and there is reasonable data for prostate, as well, but none of them are evidence-creating. So, it is not that we do not know it doesn't work. It's not that we don't know that it's safe. I think there's a lot of guidelines around it. What we have not yet done are those perspective randomized trials or big cohort studies. That's the challenge, and I think this is the data that you do not have in front of you, because this is not qualified data for this review.

Craig Blackmore: I don't think we're – the committee's not expressing a lot of concern about safety. There's no data that it's better than using another approach.

Chris Standaert: And I guess I have the same – this IMRT sort of dilemma gets me, and I hear what everybody's saying. There's no data and true clinical trials, but there clearly are going to be circumstances where again you can do the calculation about tissue toxicity and decide you really have to focus this beam down. You're going to be – somebody's going to have to say that at some point, and we used this idea for IMRT to spare adjacent critical structures, and that was our rationale at the time that you're not going to study all these things individually. We're not going to get that data, but we have tissue toxicity data that exists that says you really can't expose various adjacent structures to the kind of radiation you need to get to this tumor, and that was the whole rationale for what we said on IMRT, which is that, and this is similar to that. This bothers me more, because we have even less data than we had for IMRT, and we don't have specific things called out like prostate and other peripheral soft tissue tumors, but the idea of not covering anything else, period, and not even giving the agency the authority to do that, I think there are going to be cases where this may well be the best thing to be doing for people with peripheral tumors, based on the math.

Man: Chris, I'm struggling with that. I totally agreed with the concept for IMRT. I mean, I think what we were saying is the difference between, you know, just sending a big beam of radiation into your whole pelvis versus focusing it pretty precisely makes a lot of sense, but to what point do you take that argument? So we now know, we basically approved IMRT for that situation. So, I think for the brain it's pretty easy to say okay, like we've talked about, well, you know, whether you remember what happened yesterday or not may be a millimeter away whereas for your prostate, with IMRT, they have already shown you can cone the beam down pretty much and what I'm struggling with it's hard for me to

envision what the data is going to look like that's going to show a big difference between IMRT and SBRT for – I mean, I think there's a bigger assumption. It's harder to make the assumption that it's going to be a significant difference on a study, whereas I think it was easy to make the assumption that for EBRT versus IMRT that there was going to be a difference. When we get to smaller and smaller areas, I'm having a harder time making that assumption. I understand the argument that's all a continuum, and that's what I'm struggling with is that really it is a continuum. There's just different ways of treating the same thing, but these are imprecise measures, and are we ever going to see any data that it's better? I don't know.

Craig Blackmore: I mean it's sort of the burden of proof, which Kevin was saying. I mean, it may be that SBRT is cheaper and less expensive than existing modalities, but I mean, shouldn't you have to show that? So, I think our job is to look and see and if something is shown to be safer, more effective, or more cost effective then we support it. In this case, I'm just not seeing it. There's no data. So, you could always say, well there's a theoretical possibility we might want to do this. You can rationalize a lot of care and not necessarily have it be the right choice.

David McCulloch: So, we just leave it all other conditions subject to agency approval?

Craig Blackmore: Well, one choice is subject to agency approval. The other choice is not covered. I think that's kind of where we are.

Man: What's the cycle for revisiting these topics, by the way? Is it 18 months?

Man: When there's new evidence available.

Craig Blackmore: So, we have the option to re-review it at any time. We are required to consider re-review at 18 months and that's the extent of what we're required.

Man: But it's worth pointing out that we haven't actually re-reviewed anything yet.

Craig Blackmore: It's in process.

Michelle Simon: We did one. Upright MRI.

Craig Blackmore: We considered re-review for upright MRI and made the decision not to. We were asked to, and we made the decision not to, because there wasn't any new evidence, and we are in process on re-review on a couple of other technologies.

Man: But I don't think it's unreasonable to assume that if there's a registry with 10,000 people in it that there's going to be new data at some point, and that to re-visit this, we may – what we've already established is our threshold for data is pretty low for this, but how low are you willing to go?

Craig Blackmore: Okay, you know, I think – do we want to discuss this more or do we want to start the decision-making process? I've heard a lot of discussion. I think there's some differences of opinion. Is there more factual information or more that we want to bring to the table, or are we pretty much where we're going to be and we need to just vote?

David McCulloch: I think the question, Craig, would be – my sense is we're in pretty good agreement with the top paragraph. It's all the bottom part. So, do we need to vote on them separately? It's still unresolved. Do we subject to agency approval with all these caveats or do we say not cover?

Craig Blackmore: Okay, that's a fair – so, I mean, I think straw poll. Are we happy with the top three lines? Coverage with conditions for cancers of spine, paraspinal, and nonsmall lung cell stage 1 inoperable, both of which require multidisciplinary team analysis including surgical input. Can I just get hands and confirm? Okay. So, now we're down to the bottom, and I think our choices are no cover or cover subject to agency approval to spare adjacent critical structures to prevent toxicities within the expected lifespan.

Man: I see three different statements there.

Craig Blackmore: Alright, what's the third?

Man: Those are the three. One is all other indications subject to agency approval, that's one, two is not covered, and three is adding in sparing adjacent critical structure.

Craig Blackmore: Okay.

David McCulloch: I had seen that as giving some guidance as to that kind of thing, but maybe that's been too patronizing. They're clearly smart enough to figure out what the [inaudible] should be.

Man: But the problem with – critical is going to look different to people whether they own a Gamma Knife or not.

David McCulloch: I agree. I'd be fine with just either not cover or subject to agency approval and leaving the subtleties out of it.

Craig Blackmore: It's where we put the onus. You know, we can – if we say not cover, then the only way people are going to get it and have it paid for is if they're doing it in the context of a registry or some sort of study. If we say subject to agency approval, then the agencies will try to make decisions based on the same evidence that we have and that's – it is what it is.

Man: So, you're lumping not covered with…

Craig Blackmore: So, to spare adjacent critical structures would be included as guidance under the subject agency preapproval. So, we would give that information to them saying we want you to preapprove it in order to spare adjacent critical structures.

Man: And being in a registry, or?

Craig Blackmore: No. You can take being in a registry off. Being in a registry is…

Man: So, not covered stands alone.

Craig Blackmore: So, if you're not covered, you're not covered. However, even if we say not cover, at any time if it's an IRB approved study then these guys can pay for it. So, there's always that out, but that would be the only out we leave them if we say no cover. So, another way to make it a little more open if you will is to say subject to agency preapproval either with or without the additional guidance to the agencies that says to spare adjacent critical structures to prevent toxicity.

Man: I'm sorry, Craig. Could you say that one more time?

Craig Blackmore: Yes.

Man: That if we say not covered, that if you're in an IRB approved trial it will be covered?

Craig Blackmore: The…

Group: Could be covered.

Woman: But you can still deny it. For example, they could go out, get an IRB approve to just do every single patient they do they'll collect data and they may never publish it, and it's "IRB approved". You wouldn't be forced to cover it.

Man: We wouldn't be forced to, but we would typically cover it. That's what we've done in the past. If it's part of a decent study, we're going to cover it.

Woman: Decent.

Man: Well, we want to collect good data.

Group: Right.

Man: I just wanted to clarify the implications, thank you.

Craig Blackmore: There's still the research out even if we vote for not coverage, but there aren't other appeal mechanisms if we say not cover.

Woman: But when people look at this, I know that we did cover it with the trial or registry, but it seems worth it to me to put that in every time to emphasize the point, to encourage more data collection.

David McCullock: The only thing is that places quite a burden on, you know, creating the infrastructure for that. That's what's inhibited us in the past. I think the singular exception in this circumstance is that there actually is a registry structure. That's the only thing that makes a viable proposition in my mind.

Woman: I think she was saying for no coverage decisions, right?

Woman: Right.

Woman: Yeah.

Martin Fuss: Can I make one more comment, and that's, it's a little complicating, but you know, the concept of SBRT does not necessarily achieve more normal tissue coverage than IMRT does, but it does have a different biologic impact on the tumor, and thus you have a different expectation for local tumor control, because the sparing you can achieve with IMRT, but you may not, as you trickle it in, not get the same biological potent radiation accumulation that you get with an SBRT treatment in a few treatments.

Craig Blackmore: Boy, it would be great to see data on that.

Martin Fuss: So, it is the tumor effect that differentiates SBRT from conventional treatment, not so much the normal tissues. So, if a multidisciplinary team found that SBRT likely yielded a better impact on tumor control, that's how we select it.

Kevin Walsh: Based on no data.

Craig Blackmore: See, the job of the committee is to look at the evidence, and we have concluded already, I think, that there is no data on local tumor control.

Woman: That's a good finding though.

Craig Blackmore: But that would be a great study.

Woman: The registry sounds like it would be a great place to start.

Martin Fuss: The clinical intent is fundamentally different. One is an ablative intent, and IMRT is not an ablative intent. It's like surgical or radiofrequency ablation. Those are…

Craig Blackmore: Okay. Further comments from the committee?

David McCulloch: Straw poll [inaudible].

Craig Blackmore: Okay. If we elect for coverage with conditions, and I'm on the second half of the box, are we happy with the condition being subject to agency approval and to spare adjacent critical structures to prevent toxicities within the expected lifespan?

Woman: No.

Craig Blackmore: What conditions are we happy with?

Group: None.

Craig Blackmore: No, no, no, no. So, we have two choices. We're either going to vote not cover. We've already sort of decided we're not going to cover unconditionally. So, we're either going to vote not cover or we're going to cover with conditions. So, my question is not which of those two options. My question is, if we choose cover with conditions, are we happy with these being the conditions? Does that make sense?

Woman: Maybe see how many would vote for not cover first?

Craig Blackmore: Sure. How many would vote – straw poll, how many would vote for not cover?

Woman: Entirely, whatsoever?

Chris Standaert: So, not at all.

Woman: Well, they can say it's under IRB.

Woman: Are we talking about all?

Craig Blackmore: No, we're talking about just the bottom half.

Chris Standaert: Only the bottom half.

Woman: All other indications not covered, because there's inadequate data.

Craig Blackmore: Okay. So, what I would like the team, I don't know whose driving over there. Margaret, are you driving? I would like you to delete the blued out portion and whatever else is down there. So, let's digest this for a moment. Karnofsky score's not there. So, get rid of the SRS stuff. We're down to SBRT. We already decided on SRS, so thank you.

Kerilyn Nobuhara: Can I ask one clarifying question about SRS?

Craig Blackmore: Yes.

Kerilyn Nobuhara: Are you referring only to malignancies and neoplasms for SRS, because there are also other conditions like AVMs and trigeminal neuralgia? We need some specificity in the SRS decision.

Craig Blackmore: Okay, so the committee has been asked to clarify. We are going to have to revote on that, because…

Woman: You worded it primary brain neoplasm or metastatic disease.

Craig Blackmore: So, committee I think were we thinking just tumors?

Chris Standaert: Just intracranial neoplasm.

Craig Blackmore: So, direction to staff. When you take our decision and you turn that decision into a draft findings and decision, we would like it to be specified that these are tumors.

Man: But we didn't even talk about those other conditions. I mean, I, you know.

Woman: That's why we're not going to [inaudible].

David McCullock: Were we asked to?

Man: Well, that's the question, were we were asked? I mean, I didn't see any data, but did they actually pull data on trigeminal neuralgia? I don't even know if they even pulled data on that. I don't know if they pulled data on AVMs.

Martin Fuss: No. You wouldn't treat trigeminal neuralgia…

Craig Blackmore: Okay, sorry, sorry. Dr. Fuss, I'm going to cut you off. I have a specific question. Were nontumors in the scope of the literature review?

Martha Gerrity: No, they weren't.

Craig Blackmore: Okay. So, our decision only applies to tumors, benign and malignant. We have made no decision at all about the other things, because that was not part of our discussion.

Woman: Let's specify for both SRS and SBRT.

Craig Blackmore: And the same is true for SBRT. Okay. So now, let's scroll away everything but the SBRT. No, not malignancies – tumors. Yeah, thank you. Okay, so SBRT – so, these – so, we're going to have a binding – or getting eventually to a binding vote on SBRT, and it's either going to be cover unconditionally, never cover, or it's going to be cover with conditions, and this is the set of conditions that we are currently at. That is that we would cover cancers and spine/paraspinal structures. We would cover nonsmall cell lung cancer stage 1 inoperable, but we would only cover those two scenarios when there is a multidisciplinary team analysis including surgical input and all other indications would not be a covered benefit.

Man: Can I just ask a clarifying? I need some – I guess I'm just demented and can't remember, but how did we knock inoperable off of SRS?

Chris Standaert: That's why the whole team thing is there. It's a team decision to decide this is the best treatment.

Man: You're getting hypoglycemic and we need lunch.

Man: You're right.

Joann Elmore: Including surgical input.

Craig Blackmore: We knocked it off because no tumor is inoperable, but it might not be the best thing to do, and we were relying on this surgical input to consider that as an option.

Man: But there is a little bit more clarity in the evidence surrounding nonsmall cell lung cancer that is really only stage 1 that we're talking about that's actually demonstrated.

Man: Right.

Woman: That's a good point.

Craig Blackmore: Okay. So, we're going to proceed with the yellow cards. Alright, so back to the decision tool, and we've been through this, and we're now at the point of the first voting.

Man: Sorry, I just want to – on the basis of the straw poll we did, the agency discussion is off the board.

Craig Blackmore: Yes.

Man: Okay.

Craig Blackmore: So, is there sufficient evidence under some or all situations that SBRT is unproven, equivalent, less, or more effective, and again the comparator is external beam nonstereotactic radiation therapy. So, the first vote is on effectiveness.

Man: And this includes nonsmall cell lung cancer?

Craig Blackmore: That's a good point. So, if it's some or all situations, so if you thought there was a situation where it was more effective, you would vote more.

Josh Morse: One, two, three, four, five unproven; six more.

Craig Blackmore: Now, we get to safety, and again if you thought there was a situation, any situation which it would be more safe, then you would vote more.

Josh Morse: I see six unproven, five more.

Craig Blackmore: And then, cost effectiveness.

Josh Morse: Eleven unproven.

Craig Blackmore: Okay, any further discussion? Okay, now we have a binding vote. Based on the evidence about the technology, safety, efficacy, and cost effectiveness, it is, and your choices are not covered, covered unconditionally, and covered under certain conditions, which we have delineated on the board.

Josh Morse: Eleven cover with conditions.

Craig Blackmore: And again, we have to compare our decision to Medicare national coverage decisions, and there are none, so we are in compliance. We will now adjourn for lunch. It is about 10 of 1. Let's try for 1:30. Let's try for 1:20. Eat fast. Actually, let's all get back here at 10 after 1. We can eat a little more as we go. We're a little behind.

I'm going to ask the committee members to find their seats so we can keep moving here. Alright, we're going to call the meeting back to order.

I believe seven committee members. Alright I'm still short a couple committee members and short. We've got Josh. Okay, the meeting is now back in session. Our afternoon will be devoted to the topic of vitamin D testing and screening and we will start off with the scheduled and open public comments. For those of you who wish to address the committee, we have had a… We have two previously scheduled people who have asked to comment so we will start with those and then we'll give an opportunity for others who may be present in the room and we'll also have an opportunity at the conclusion of that for anybody who is on the phone that wishes to address the committee. For all of the presenters I would ask that you introduce yourself, you would state if you represent any organization, and also if you would please tell us if you have any conflicts of interest and we're allocating five minutes per presenter and Margaret or Christine will give an indication when you have a minute left and 30 seconds left. Thank you.

Eugene May: Thank you. I'm Eugene May. I'm a neurologist at the MS Center at Swedish Medical Center at the Neuroscience Institute. I'm here with Dr. Mitiku representing the Northwest Alliance of MS Centers, which is an alliance of MS specialists in the Puget Sound region. We get together to support each other's clinical efforts, research efforts, and also to advocate for our MS patients and we're here today to talk about what we know about the role of vitamin D in multiple sclerosis. As you know from the data that we've submitted so far in answer to the key questions, the role of vitamin D in MS is a growing topic. It's something that we're learning more and more about. As you know, multiple sclerosis is an inflammatory condition of the central nervous system. It disproportionately affects young people. It's a disabling condition and for reasons which are unclear, it's highly, highly prevalent in Washington State. Because it's a condition that affects young people, we find that as neurologists and physical medicine specialists we are the primary care providers for a lot of people with multiple sclerosis and as a result, when people with multiple sclerosis come to see us in our practices, we are almost always the only providers that they see and because we are concerned that increasing data is showing that vitamin D levels are critical in controlling relapse rates and disability in people with MS, that it's important that we be provided the ability to monitor our patients vitamin D levels and we're hoping by your reviewing the data that we've submitted so far and the answers to the key questions, that you see that this is an important area of understanding and that the additional information that we're going to provide to you this morning to supplement the data that we've already provided to you, that you'll

accept that it's important enough and real enough that we be provided with the ability to continue to check vitamin D levels in these patients. So I want to turn over the rest of the time to Dr. Mitiku to provide you with the additional data to supplement what we have already submitted.

Craig Blackmore: Dr. May, just if you could clarify for me, do you have any financial conflicts of interest?

Eugene May: I have no conflicts, no.

Craig Blackmore: Thank you. And I will ask the same question, please.

Nesanet Mitiku: No conflicts. So I'm Nesanet Mitiku, I'm the current multiple sclerosis fellow at the University of Washington. I'm also Ph.D. trained geneticist and actively involved in immunology research as pertaining to multiple sclerosis. Can we have the next slide please? Have control up here. I'm pressing the forward button here, but not getting a new slide. There's a mouse. Great. So we'd like to start by providing a comment on some of the randomized controlled trials that were provided in the evidence report and there are two in particular that were problematic. So one is the Soylu Hainan paper from 2012 and we'd like to comment that they demonstrated a dosing regimen that could certainly get vitamin D levels up to a reasonable level, however the one of the primary outcomes for the study was to demonstrate a change in T2 MRI lesion burden. And the level of change to which the study was powered was a volume of 1,000 mm^3 and that was an unrealistic volume. So if you go back into the literature and look for what an average lesion diameter in MS patients would be that's seven mm so that's a radius of 3.5 mm. If you were to calculate what an average lesion volume would be from that, that would be about 180 mm^3 so in patients that are currently being treated with interferon beta, they are saying that they expect to get on average five new lesions during this period of time that the study had taken place and that would be treatment failure actually and unethical to continue the patients on that medication. And if you look at their actual data, the change in patients that have not been treated with vitamin D was about 280 mm^3 so they could not have detected this level of change. So in addition to that, other outcomes that were measured in that study were also underpowered. So our recommendation is this study be discounted for the purposes of this analysis. And then we have Mosayebi et al. from 2011 and they chose to look at the effect of vitamin D supplementation on disability and designed the study to take seven months. And seven months is not a realistic period of time in which to detect a change in

disability. So for those reasons, both of these studies are not informative and they cannot be used as a basis to say that there is no effect of vitamin D on MRI results, disability, or health outcomes. And they cannot further be used as a basis for demonstrating conflicting results. They just need to be discounted. So we'd like to talk a little bit about prior studies that have also shown some relationships between vitamin D levels and MS risk. So from Munger et al. from 2006 this was a prospective nested case control study of active military personnel. There were about 257 MS patients and twice the number of controls. And these active military recruits had blood samples taken every two years. And there were on average two or more vitamin D levels prior to the onset of MS symptoms for each of these patients and looking in a correlational sense, those that had the highest were within the highest quintile of vitamin D levels having a level greater than 99 nanimoles per liter had a 62% lower risk of MS relative to those in the lowest quintile. This is in agreement with prior epidemiological data that indicate the risk of MS is related to the latitude at which a person has grown up. So the further away you are from the equator the higher your risk and UV levels have the same pattern as do vitamin D levels which the majority of people in the world are related to UV exposure. There is additionally a season of birth correlation. So in northern countries, the risk of MS is greater for people who are born in May. That would mean organogenesis and formal terminal differentiation is occurring in those months where vitamin D levels are often the lowest. In the southern countries the relationship is flipped. This doesn't argue necessarily for vitamin D in particular, but it argues for an environmental factor such as vitamin D. So now if you look at vitamin D and MS course, there have been two studies, the first by Maury 2011 prospective cohort study that demonstrated that there is a 15% reduction in terms of the acquisition of new T2 lesions for every ten nanograms per milliliter increase in vitamin D level. In pediatric patients, a similar finding but with respect to relapse rate was found. So a 34% risk reduction of relapse for every ten nanograms per milliliter increase in vitamin D level. So now if we turn to the genetics, which perhaps are the most clear cut. Alright, so CYP27B1 is a gene that encodes for the 1-alpha-hydroxylase enzyme. This enzyme is responsible for producing active vitamin D. If you have lost one allele, one copy of this gene, you have an increased risk of having MS. Similarly, the MHC class 2 allele HLADRB11501 carries a vitamin D responsive element and this vitamin D responsive element is active and functional. I'm going to fast forward through the immunology given the time. So MS patients also have other high risk features that put them at risk for osteoporosis and fractures. So to summarize, while the collective data have limitations, the studies to

date indicate that vitamin D levels can influence risk, course, and immunologic profiles in MS patients. There are multiple genes that further support a role for vitamin D in the pathogenesis of MS and MS patients are at risk for osteoporosis, falls, and vitamin D deficiency, all of which are indications for vitamin D supplementation. And until more data are available, based on epidemiological data a reasonable serum level vitamin D level as greater than 100 nanograms per, that should be 100 nanimole per liter. In clinical practices doses above 2,000 IU are needed to achieve these kinds of levels. It's almost always desirable to use the lowest necessary dose to achieve a particular goal. Vitamin D testing in these patients facilitates dose titration. Thank you. I'm going to open up to questions.

Craig Blackmore: Thank you. Are there, that's all we have for scheduled, right. Is there anybody else present in the room who had wanted to address the committee? And there was nobody signed up, I assume okay. Can we check the phone please? So if there's anyone out who, if there's anyone on the phone who wishes to address the committee, please let us know. We're going to put you back on mute soon so this is your chance. Okay, well that closes the public comment portion. We'll move on. Move on with the agency utilization outcomes.

Steve Hammond: Thank you. I'm Dr. Steve Hammond from the Department of Corrections. So a little background. In recent years particularly there has been a lot of interest in the possible role of vitamin D in health and disease. We've long known that vitamin D plays a central role in bone metabolism. However, given the ubiquitous distribution of vitamin D receptors throughout the body there is a great deal of interest in possible additional important physiologic roles of vitamin D. Also we have numerous epidemiologic studies that show correlations of vitamin D levels or history of vitamin D intake with various states of health and disease and that has sparked a great deal of interest. In the possible therapeutic value of manipulating usually augmenting vitamin D levels to achieve health benefits. However, many questions remain unanswered. First, basically there is still lack of consensus on what defines normal or inadequate, deficient, optimal, or excessive vitamin D levels. This is an important question because especially laboratory reference ranges which vary may be used to determine and make a diagnosis in the clinical setting of vitamin D deficiency. And yet some of those levels, some as high, lower limit of normal set at 30 nanograms per ml or, which is equivalent to 75 nanimoles per liter. If the lower limit of normal is set

there, then a very substantial proportion of the population is classified as being deficient in vitamin D on the order of 30 to 50%. Also in interpreting vitamin D levels, seasonal variations it's not clear how to accommodate those in interpreting the clinical laboratory results. So a question is aside from settings where benefit is proven such as in Rickets, osteoporosis, or the elderly at risk for a fall, is there a health benefit to taking vitamin D supplements. That's one question that's unanswered. Also is there health benefit to screening and/or monitoring of vitamin D levels to guide therapeutic supplementation even in those areas where there are known benefits. Again, vitamin D deficiency or inadequacy is known to be central to several disease processes including Rickets and osteomalacia. It's known to be a cause of secondary hyperparathyroidism and is a common sequela of intestinal malabsorption. Vitamin D supplementation may improve health outcomes in the setting of osteoporosis and in elderly persons at risk for falls. So when the topic was initially selected by the agency medical directors group, this was prior to review of agency utilization data or the evidence report. The initial level of concern for safety was set at medium, for efficacy set at high, and for cost a high degree of concern. Current coverage policy is as shown for state agencies. It's covered for Medicaid, for PEB it's covered although Regence which administers the PEB benefit considers vitamin D testing not medically necessary in the absence of clinical documentation of an underlying disease or condition specifically associated with vitamin D deficiency and you might want to hang on to that thought as something that might guide setting conditions if it comes to that. Vitamin D testing is covered in L&I and in the department of corrections it's restricted. All vitamin D testing requires pre-authorization. There is no national Medicare coverage decision and we were not able to find any local coverage decisions for Medicare. So these are agency utilization data from the four years from 2008 to 2011. First of all, in the PEB group we're looking at a population of about 200 to 200 10,000. And we see that extraordinary number of these patients had vitamin D levels tested and we also see really quite an impressive rising trend such that we're seeing upwards above 10% of the PEB population being tested for vitamin D levels. And we can see that that amounts to a significant sum of expenditure over the four year period. Here's the average paid per test and this is going to be a little different from numbers you see later about the cost of the test because this is what's paid out which is a little different from what's the allowed amount is. That has to do with copays and secondary payers. In the Medicaid population again, a higher population and still a substantial number of patients being tested, although a somewhat lower percent of the

population. Still and you can see somewhat lower expenditure to cover the cost of those tests. But if you add the cost for Medicaid and PEB over four years, it comes to approaching $8 million. Just a note on what tests we're talking about. Basically there are two clinical lab tests that are done to assess vitamin D status. The most commonly used is the 25 hydroxy vitamin D level and that's by consensus considered really the best and only appropriate measure of vitamin D sufficiency status. The 125 dihydroxy vitamin D level is most appropriately used to assess possible defects in vitamin D metabolism, but is not a good screen of vitamin D sufficiency or vitamin D status. So these numbers here simply show what percent of the vitamin D tests done under these different plans were the 125 dihydroxy vitamin D and you can see for the most part, I'm not sure what's going on at L&I why they have the higher percentage doing the 125 dihydroxy vitamin D, but this is what we would expect in ordinary clinical practice that far and away the preponderance of vitamin D tests are the 25 hydroxy vitamin D level. This shows a breakdown for PEB in terms of age and gender and what we see is that there is a predominance of testing in the middle aged group, although we see substantial testing in other age ranges. We also see a predominance of testing in female patients, reasons unclear. It may have to do with concern for bone density status or bone metabolism. It's possible that it's related to other factors. Similar breakdown for the Medicaid data we see a somewhat younger kind of a shift to the left in terms of age for the testing, but again distributed throughout the age ranges and again a predominance of testing in female patients. This actually just refers to the cost of the tests and you see that it's a little bit higher than the figures we saw as the figures that were outlaid by the plans. And again, this is the allowed amount and that would include copays and secondary payers. So this is excuse me, this shows the diagnoses or at least the top ten diagnoses that are associated with orders for vitamin D tests in PEB and it's really quite remarkable. First we're talking about 120,000 tests and these are the top ten diagnoses, but a total of 2,500 diagnoses were associated with the orders for these tests. We also see that for the most part these top ten are nonspecific diagnoses. You might say vitamin D deficiency sounds specific, but again given lack of consensus about what constitutes vitamin D deficiency you need to interpret this with caution and the remainder of these top ten diagnoses really are nonspecific diagnoses that really are not linked to conditions that are known to be closely related to vitamin D status or metabolism. So these are the data for PEB. For Medicaid we see a somewhat similar but slightly different results. Again the top one here is this vitamin D deficiency not otherwise specified, although again we need to use the same caution in interpreting

that. The remainder except for the end stage renal disease which where testing of vitamin D status I think is fairly universally agreed to be appropriate. The remaining diagnoses again are nonspecific. There are some drugs such as anticonvulsants that can have an effect on vitamin D status so that may be more justifiable, but again we're seeing 2,800 different diagnoses being listed for 84,000 tests. There's a great deal of variation in the stated indication for the vitamin D testing. So these are considerations that the agency made with regard to this question of how to manage utilization. We see that vitamin D testing is widespread, again over 10% of the PEB population tested in the last four years. And although the cost of a single vitamin D test is modest in the range of $40 to $50 if you multiply that by tens or hundreds of thousands, the costs add up. Again, the diagnoses we've seen associated with these tests ordered typically are not an indication what we'd call a clear indication and after reviewing our utilization data and the evidence report, we slightly revised our ranking of the primary criteria for the importance or concern about this topic. Safety was thought to be a low concern, but efficacy and cost remained high rated with a high level of concern. Again, going on the basis of the evidence report, we see that there is no evidence that routine screening or testing of vitamin D levels improves health outcomes. It is well agreed that testing is appropriate in certain clinical settings where vitamin D is known to play a role such as Rickets, osteomalacia, secondary hyperparathyroidism, malabsorption, and evaluation of hypo or hypercalcemia. For conditions in which vitamin D supplementation is known to be beneficial, such as osteoporosis and in elderly individuals at risk for falling, there is no evidence that testing aids clinical management. So in light of these considerations, the agency recommendation is to cover with conditions. I listed a possible set of conditions. This was a little bit narrower than the list of conditions that Regence used in their medical necessity definition. One could argue about just what conditions should be included, but we believe that it would be appropriate to restrict coverage to certain conditions which if the HTCC agrees will be tasked with trying to define. It's possible that the Regence policy could be used as a starting point for that, but in other conditions we would recommend that vitamin D testing be not covered. I believe that's the end. Questions?

Craig Blackmore: Questions for Dr. Hammond?

Man: Very nice summary of the data Steve. The only thing I would challenge you about is considering safety only of low concern. Vitamin D testing on over treating with mega doses as the current fashionable vitamin. Three

years ago it was vitamin E. It's been given all sorts of magical properties to do this and that and so I do have concern of over testing and then over treating. There is a significantly increased risk of hypercalcemia and is there potential.

Man: I'd like to ask a question. You told us there are 2,800 indications listed. Do you have a sense for this sample list of potential conditions that you've given us here, do you have a sense for what proportion of the currently performed testing would fit into this type of list?

Steve Hammond: Well, um, yes. I think I looked at it and it looked like less than 10% of the diagnoses listed could be reasonably understood to reflect a specific disorder of vitamin D status or metabolism, but if you want to go back, we can look at the top ten.

Man: I don't want to go back I was just a rough, yea.

Steve Hammond: Because that yea, it was definitely a small minority.

Man: Yes, that was a nice presentation, a very good summary. I had a question. One of our public comments was about the MS and its relationship. Did you see any of those testings for MS in your…?

Steve Hammond: Yea, I mean some, there was a certain percentage of the tests ordered that were associated with a diagnosis of MS. I don't remember the exact percentage. It was small. If you need it I think Margaret might be able to dig it up. It was small.

Man: More of a curiosity, I just…

Craig Blackmore: Thank you. So next on the agenda is going to be the vendor evidence report and while you are all setting up I want to introduce our clinical expert. Dr. Ott has joined us from the University of Washington, correct? Thank you. And so she will help provide clinical context and expertise on the test itself and some of the clinical conditions. So procedure is as we said we'll definitely have questions for you as the discussion goes on, but we don't require a specific presentation. So thank you for being here.

Susan Ott: Thank you.

Woman: Can I make a comment while we're waiting?

Craig Blackmore: Sure.

Woman: So I've seen the presentation and I largely agree with it. With a couple of exceptions. I think that the list you didn't see the list from Regence, but it includes a few diseases that I think are closely enough related that should be tested. Now sometimes if there's like for example hyperparathyroidism, there's a huge long condition that vitamin D is intimately a part of the pathophysiology of that disease and I don't think anybody ever even thought that they should do a study to see whether there is evidence that we should check it because it's just sort of so much part of the disease that just because there's no evidence doesn't mean that we shouldn't do it.

Craig Blackmore: We'll get in to the after we've heard all the presentations we'll get in to our deliberations and we'll solicit more input from..

Woman: Right, right. But I have to totally agree with David's comment. There was actually really an excellent little article called the vitamin de jure and it went through all of them, A, B, C they went in alphabetical order until we skipped D and went to E. And there's just been a fad. It's part of our culture. And then a really good randomized trial comes along, shows it really isn't as good as people thought and it dies down again. And vitamin E we should all remember that, because it's a good point.

Craig Blackmore: Thank you.

Teresa Rogstad: Thank you, thanks. I am Teresa Rogstad I also answer to Terri and this report was prepared by a team of people at Hayes Incorporated. Dr. Susan Levine is also with me here to my right. And we did get some information and feedback from Dr. Ott after the final report was prepared, so I'll be reflecting that information in my oral presentation today. This is how the presentation will be organized. I want to take a moment at first to just talk about some of the challenges associated with this topic then give, expand a little bit on the background that has been presented already, describe how the report was framed, and then present some conclusions and some gaps in the evidence which are big. Vitamin D testing was a difficult topic because the molecules associated with a lot of different health conditions and the relationships go in different directions with some disorders causing low vitamin D and low vitamin D being thought to cause other conditions. A lot of different tissues and diseases are implicated and it's always more difficult to evaluate a medical test than it is to evaluate a therapeutic intervention,

but in this case we are not even dealing with a straightforward diagnostic test. It's more of a prognostic test and at best makes a minor contribution to outcomes. Another concept that we tried to keep in mind in the report was the difference between screening and testing. And I'll go into that more later. We had two sets of populations based on the presence or absence of disease and we were interested both in the accuracy of the test or clinical validity as well as its ability to impact outcomes, so clinical utility. The very biggest problem was that we could find no direct evidence evaluating the effectiveness of screening and testing. It would have been nice to find randomized controlled trials or even good cohort studies where one group of patients underwent testing and then were given advice by their clinician about supplementation compared with another group that wasn't tested, but does follow their own personal supplementation regimens or were given advice without the benefit of test results, but there were no such studies as best we could tell. So we came up with kind of a next best solution in consultation with the HDA work group and that was to evaluate the evidence for the effectiveness of supplementation. We reasoned that that could demonstrate the potential or plausible clinical utility of testing or screening because if there's no effective treatment, then you can't expect the test to have good impact on outcomes. And we were especially interested in whether or not the effectiveness of supplementation varied by baseline serum level. If it can be shown that everyone does better with supplementation regardless of their vitamin D status at the beginning of treatment or if it can be shown that no one gets better then the information provided by the test or the screen will not be particularly helpful. The next couple of slides present the biology behind vitamin D and some of this has already been alluded to. The white boxes on the left are risk factors that put people at risk for low vitamin D status and these are some of the factors that were specified in the key question having to do with differential effectiveness. On the right hand side we have conditions that can result from low vitamin D and these are related to the role that vitamin D plays in regulating absorption of calcium into the bone. The gray boxes represent conditions that are not controversial and they were not specified in the [40:47] statement. The two bluish boxes are they were specified as outcomes of interest in this report, although they are of less controversy than some of the other disease outcomes we looked at. On this slide, we see the kinds of conditions, the kinds of medical conditions that can cause low vitamin D. That would be obviously malabsorptive disease, chronic kidney disease, and bariatric surgery because it can lead to malabsorption. On the right hand side we see the kinds of disorders that are known to result from low

vitamin D or are purported to result from low vitamin D. The gray boxes on that right side are not included in the report because those were considered intermediate outcomes, but the blue boxes were considered as outcomes in healthy populations or we also looked at populations that had a diagnosis of one of these blue conditions and then we looked at disease related outcomes. Vitamin D can produce toxicity by increasing the level of calcium in the blood or the urine and that in turn can produce kidney stones. In 2010, the Institute of Medicine issued a report that defined 50 nanimoles per liter of serum vitamin D as a sufficient level for good bone health. This was based on epidemiological data that looked at the association between serum levels and health outcomes. The Institute did not feel that the data supported a cutoff point for any health outcome other than bone health. Using that same threshold, the data from the most recent national health and nutrition examination survey showed that about a third of the American population is at risk of insufficiency, meaning that their serum levels are below that 50 nanimoles per liter, and the term at risk is used because not every individual requires that level of serum vitamin D to have good health, but that's the level that covers about 97.5% of the population. There was a lower incidence or prevalence rather of deficiency and it was more common in females than in males. As was mentioned earlier, the molecule that gets measured when a vitamin D test is done is 25 hydroxy vitamin D or 25 OHD. 125 dihydroxy vitamin D is the metabolite of 25 HOD and that is actually the form that's active in the body. Another name for that form, which is actually a hormone is calcitriol. There are a wide variety of types of assays for testing vitamin D, but there is no gold standard. There are quality assurance programs that help laboratories make sure that their results are close to a mean across all the participating labs. When vitamin D tests are done universally in all patients or on the basis of a risk factor like age or ethnicity, that would be considered screening. When it's done in the presence of a disorder that's known to cause vitamin D depletion or radiographic or laboratory evidence suggesting low vitamin D, then that would be considered testing because there's a sign that vitamin D is low. Monitoring may also be justified particularly if very high doses of vitamin D are given. Monitoring would serve the purpose of justifying that more potent treatment in the first place and determining when it can be discontinued. The Institute currently recommends that adults receive 600 IU per day and that is assuming no sunlight exposure, because most adults in the U.S. receive inadequate sunlight exposure at least for part of the year. I highlighted the recommendation for adults over the age of 70 years because a disproportionate amount of the evidence that was available to us came

from the Women's Health Initiative which enrolled post-menopausal women and in the treatment arm the individuals received only 400 IU per day so half of the currently recommended dose and that limits the generalizability of that evidence. Vitamin D supplementation outside of food can take several different forms. The type of vitamin D supplements that we typically buy in the grocery store are considered inactive vitamin D, not because they're ineffective, but because they have to be further metabolized in the body before they're physiologically active. Calcitriol is the natural active form of vitamin D and then there are synthetic analogues that are also considered active forms. Another term for those active forms of vitamin D is pharmaceutical. So the policy context has pretty much already been said because of the variety of health problems with which vitamin D has thought to be linked. There is the potential of overutilization of tests and then in addition to that, key professional and public health organizations in both the U.S. and Canada have acknowledged that there are no definitive cutoff values for specific outcomes and in fact it's thought that those cutoff values probably vary depending on what target outcome you're interested in and then most of those organizations do advise against routine testing. We found 17 generally good quality guidelines, eight of them had recommendations specific to testing or screening. The other nine guidelines just had recommendations about supplementation. Five of the guidelines explicitly recommended against routine screening, except in individuals who were at high risk, but unfortunately the guidelines didn't provide very good definitions of high risk. Three of the guidelines did recommend testing for individuals with known poor bone health and that included skeletal fragility in children and osteoporosis in adults. One of the guidelines recommended that for very high doses of vitamin D supplementation or for pharmaceutical supplementation, also known as active supplements, monitoring every three or four months was advised. We looked at four payers and the only payer to have a policy on testing and screening was Regence and you've already heard what their policy is. The PICO statement specified two general sets of populations. First was healthy populations. And by that we mean individuals who are not showing signs or symptoms or findings of the outcome of interest. So when we selected evidence for these populations we looked for studies that didn't select patients on the basis of the disease outcome that we were interested in. The other set of populations were people who already have these chronic diseases that vitamin D is thought to contribute to and then we looked at the disease related outcomes. The comparator with no testing and the outcomes I've already talked about. The key questions had to do first of all with the association between

serum levels and health outcomes. That's a clinical validity question. The second question had to do with the effectiveness of testing and screening, so clinical utility. There was the usual safety question, differential effectiveness, and cost implications. This graphic depicts the analytic framework that we had in mind when we designed the report. The most important question obviously is arrow number six, does testing in the population of interest improve outcomes. But as I mentioned before, we didn't find any direct evidence regarding that question. We also didn't find any studies designed to answer arrow number two, if you have a test result that shows low vitamin D, does that result in a change in patient behavior or clinical decision making that in turn changes treatment and ultimately outcomes, but no evidence there either. So we focused our analysis on arrow number five, does supplementation improve outcomes. The arrows number one and three represented by gray those are addressed in the background section of the report, and yes it has been shown that an increase in intake does improve serum levels. Our evidence sources were the traditional sources for systematic reviews and clinical studies and practice guidelines. For key question number one, we discussed with the work group whether it was necessary to do a full analysis of this question and they agreed with us that we could focus our efforts on key questions, number two through four and the thinking here was that even if you can prove an association between serum levels and disease, that doesn't answer the question of whether testing is necessary to achieve better outcomes. So we provided a non-analytical descriptive review of representative evidence having to do with those associations. For the questions number two through four, we selected systematic reviews if they were available and focused and analyzed primary RCTs in their absence. The next bunch of slides presents the findings from the evidence that we reviewed and I'd like to explain the color coding. We used green, red, and yellow to denote positive findings, negative findings, and unclear findings generally because of inconsistent study results. And I want to clarify that these, the color coding doesn't have anything to do with the quality of evidence, only the direction of the findings. So the largely systematic and narrative reviews that we looked at indicated that there are several conditions listed in that first column for which a beneficial association has been demonstrated between serum vitamin D and the risk of these diseases. So that means that higher levels of serum vitamin D lead to a reduced risk of osteoporosis, colorectal cancer, etc. Curiously, that same type of longitudinal data showed that higher levels of serum vitamin D are associated with greater cancer mortality in men. I don't know why that would be. For other types of cancer, the findings were inconclusive and then for the remaining disease

outcomes of interest, the evidence was insufficient. There is a biological rationale for assuming a link between vitamin D and all of those conditions listed in that fourth column, but any available evidence was cross-sectional in nature, which doesn't provide any information about the direction of causality, so low vitamin D could cause gestational diabetes or it could be the result of gestational diabetes for some reason based on the available evidence. In disease populations, we found that higher levels of serum vitamin D are associated with better outcomes in individuals who have certain types of cancer, fewer cardiovascular events in people with hypertension, and fewer complications in individuals who have diabetes. There was insufficient evidence regarding the disease association for these other disease outcomes. Key question number two had to do with the effectiveness of screening and testing and as a substitute for that missing evidence we looked at the effectiveness of supplementation trials. And here again we're using the green yellow and red color coding. There was evidence suggesting that supplementation improves bone mineral density and reduces falls and fractures in older adults and also improves mortality risk in older adults, but this evidence came predominantly from trials that included mostly post-menopausal women. The evidence was also of low quality. We found other evidence suggesting that supplementation does not reduce the risk of diabetes or mood disorders in healthy adults and then as far as the risk of other disorders in other age groups go, the evidence was conflicting. So the benefit of supplementation is uncertain in those groups and for those outcomes. And then there was insufficient evidence to draw a conclusion about the ability of vitamin D supplementation to prevent multiple sclerosis or non-skeletal outcomes in anyone other than older adults. Two B had to do with disease populations. We found moderate quality evidence suggesting that active vitamin D or pharmaceutical vitamin D improves osteoporosis in individuals who already have that diagnosis or a high suspicion of osteoporosis. We also found evidence suggesting that hypertension is reduced in individuals who have cardiovascular disease and that outcomes related to abnormal blood glucose are improved by vitamin D supplementation. There were a handful of trials that looked at supplementation with inactive vitamin D at ordinary doses and they generally suggested no benefit. Trials of supplementation in individuals who are already obese also suggested no benefit. The evidence was conflicting concerning the ability of supplementation to improve the outcome for patients with prostate cancer or MS. We heard public testimony that two of the studies that we looked at in patients with MS should have been excluded because they were underpowered or the follow-up interval was too short and if we throw those out, then we have

even less evidence. We're left with actually one trial that looked at clinical outcomes. It was positive, but a single, very small trial didn't seem like enough evidence to draw any conclusions from. And then there was no evidence having to do with cancer other than prostate cancer or individuals who already have a diagnosis of depression. Both vitamin D testing and supplementation are relatively safe. It just involves a blood test. Inactive forms of vitamin D do lead to a moderate increase in the risk of hypercalcemia and kidney stones. The best evidence there came from the Women's Health Initiative, which showed about a 17% increase in the incidence of kidney stones over a seven year period. Active or pharmaceutical vitamin D is associated with a greater increase in the risk of hypercalcemia, so there is a concern there and we didn't find any quantitative data about the safety of megadoses of inactive vitamin D, but anything that exceeds the Institute of Medicine's defined safe level, which is 4,000 IU a day, might be suspect. This is really the 64 million dollar question in this report. Does the effect of supplementation vary by baseline serum levels. We've found that there is some evidence suggesting that there's a differential effect according to baseline serum levels for the outcomes listed here on this slide, but it's very confusing evidence because the direction of the trend is different for different outcomes. So for falls in older adults, a lower baseline vitamin D status means that individuals are going to benefit more greatly from supplementation, but according to the available evidence for prevention of hypertension it's the individuals with a higher baseline vitamin D status who are more likely to benefit from supplementation. So that would be very difficult evidence to apply clinically.

David McCulloch: On, if you go back to that slide, on [1:00:05] for nonvertebral fractures that was from the Women's Health Initiative Study showing the benefit was actually in women whose baseline was greater than 43. So again, from your bigger report so both the second and the fourth line showed that increased baseline serum value had increased.

Teresa Rogstad: Right.

Man: Can I ask one more question about that slide. So by increased do you mean above 50 or do you mean increased compared like 30 versus 40 so thinking of somebody who's way in the high end of normal or do you mean somebody who's super normal, somebody who these people are still low, but they're not…

Teresa Rogstad: Just well, in most studies it was the upper quartile compared with the lowest quartile. So the cutoff points were different in different studies and analyses. So I'm talking here about the general trend. We can come back to that. An analysis of the Women's Health Initiative suggested that there's no difference, no differential effectiveness according to baseline serum levels for prevention of type 2 diabetes. The evidence was conflicting with regard to bone mineral density in children and the evidence was insufficient for other populations and other factors. That key question specified besides baseline serum levels it specified factors such as age, sunlight exposure, baseline risk of the disease in question, and there was just there were no patterns that were demonstrated by the analyses that were done. There was a lot of missing data about this question as well as shown at the bottom of this slide.

Man: Could I just ask you to [1:02:14] down a little on one RCT with an N of greater than 36,000.

Teresa Rogstad: That was the Women's Health Initiative.

Man: And they were randomized to either get vitamin D supplementation or not?

Teresa Rogstad: Right, vitamin D supplementation with calcium or a placebo.

Woman: And did you say earlier that they got 400 IU versus.

Teresa Rogstad: Yes, 400 and the current recommendation for that age group is 800. Oh correct, that's true, right.

Man: What was that?

Teresa Rogstad: Well the current recommendation is 600 for adults under the age of 70 and that would include some post-menopausal women 800 for adults over 70.

Man: So I'm still struggling with a randomized clinical trial that had 36,000 people in it for giving it a low quality of evidence. I mean what, it's not like 18,000 got one or the other and it was blind. I mean tell me more that there's a disconnect here.

Teresa Rogstad: Well it's not so much that, the trial was very well done. So let me, look back at my notes about why I said that. It was definitely a good trial. I

think part… part of the reason was that the women were under-dosed according to current standards, which may have masked a treatment effect. So that was a big part of it. And it was a single trial. It obviously was a very well done trial, but it was just one trial. So that has an impact on how much confidence you can have in the overall body of evidence. So I mean the results weren't corroborated by any other trials.

Man: That was the Women's Health Initiative? What was the name of it?

Teresa Rogstad: Women's Health Initiative.

Woman: I think the reason that you're saying that they gave too little is because of the results of that trial. When the trial was designed, the recommendations were much lower. And so then they gave 400 which at that time was considered a high dose. But it didn't work. So now everybody says oh, it didn't work because you didn't give enough. Because the Women's Health Initiative didn't work. You see that's a little bit of circular reasoning that should be clear. It was an excellent study, funded federally by the NIH.

Woman: Since we're on this topic on slide 26 there were nine RCTs and they were all considered low evidence as well? Is that the same issue?

Teresa Rogstad: Let me back up to that.

Woman: For the bone mineral density.

Teresa Rogstad: Forgive me, but I do have to look back to my notes. There's just so many groups of evidence here. And that's not to say that all nine RCTs were poor RCTs. It means that when you take into account the consistency of evidence and its direct application to your population and outcomes of interest and so forth, then the overall evidence might be low. In that case, in a lot of the studies, the estimates of relative risk did favor vitamin D, but they were statistically non-significant. There were variable vitamin D doses across studies so this goes back to the comment about the Women's Health Initiative based on what we know now, they may not have shown the optimal treatment effect and yea, I guess those were the two main factors.

Woman: I have a question for you. On your standardized method that you're using to rate the quality of evidence, you're defining these with terms of low, moderate, and high. What methodology are you using. Because just

because a study has a non-statistically significant finding that doesn't mean it's low quality.

Teresa Rogstad: No, no it doesn't say anything at all about the quality of the study itself.

Woman: So what methodology did you use in rating these?

Teresa Rogstad: We, the methodology that we used is very similar to the grade methodology. So we have an internally developed checklist that we use to assess the methodological quality of individual studies. The studies themselves can be very good. But the quality of the body of evidence can be low based on the findings of the studies, whether they're consistent, whether they were statistically significant. Those things are not the fault of the people who designed the studies, but it does mean that you can, it gives you less confidence in the evidence.

Woman: Isn't that kind of our job?

Teresa Rogstad: Pardon me?

Woman: Isn't that kind of our job though? I mean I think my understanding is the evidence is presented to us and the quality of the evidence is separate from the interpretation that we take from it. So it sounds like you're mixing the two of those things when you're grading the evidence.

Teresa Rogstad: Well I would have to give you quite a lot of detail about the, about the statistical significance and the width of the confidence intervals in all of the studies.

Man: That would be great.

Teresa Rogstad: And whether, how many of them.

Group: That would be helpful.

Teresa Rogstad: That's what you'd like to see?

Man: We'd like you to, yea.

Teresa Rogstad: Okay.

Woman: For example, did two people do the rating independently on the quality and then you would meet in consensus to decide your terms that were used in our report?

Teresa Rogstad: No, we did not have dual rating.

David McCulloch: It's just, it's hard for us to believe that nine randomized controlled trials gives you low evidence. I mean we're drooling at that, a topic on which there are nine randomized controlled trials.

Man: And 38,000 patients. I mean compared to what we just did. Good lord.

Woman: Could I just maybe make a couple of comments. The Institute of Medicine report that came out two years ago now, was 1,000 pages long and they used I think it was grade, they used the tough medicine committee, department of their evidence based medicine department was part of the report and the, they came up with the final conclusion that vitamin D treatment didn't help with any disease except bone disease. They didn't find any of the other claims to be true and with bone disease they found that it made a positive effect, but it wasn't really a very strong positive effect. And when you look at all the trials there are a lot of trials, but they have different outcomes. And a lot of the trials were negative. The Cochrane also did a review of this and they found that if you put them all together in a meta-analysis there was a, it came out slightly to the positive side, but again it wasn't really a very strong positive. And then people have tried to look at subdividing it instead of looking at everybody. The one that's the most consistent is if you look at really elderly people, frail elderly people, then the message comes out more clearly that the vitamin D was helpful. And that came from the Women's Health Initiative and some of the large studies in Europe. And then some people thought that if you took it along with calcium it made a difference. But there's been I think eight or nine meta-analyses of the trials and they don't agree with each other, so what I think what you're seeing is a lot of disagreement because the results are so variable.

Teresa Rogstad: Thank you, it is the variability of results that is mainly behind that low quality rating.

Man: Is there a table somewhere in the report that has this, the information?

Teresa Rogstad: Well, if you look at appendix, it would be five… appendix three, that's where the musculoskeletal data came from and that was largely from

systematic reviews because we had a lot of good ones and so if you can find that it's on page 114. And then in the fourth column there's some more detail about the findings.

Susan Ott: One of those was a, let's see it was a meta-analysis that was done to inform the United States preventive task service force committee, and that meta-analysis was done by Chung and actually I was supposed to comment on it at the Annals of Internal Medicine for their journal club. And the overall report of that meta-analysis was that if you gave it with calcium there was an overall beneficial reduction in fractures in the women who took vitamin D compared to placebo.

Man: So we're getting a little out of order. We need the vendor to help us get through the evidence and doctor I thank you, we need you to help us with the clinical context. So at this point we're trying to drill down on the evidence.

Teresa Rogstad: Yes, we did. The report that Dr. Ott just mentioned the second one listed in appendix three.

Man: So this is the Chung et al. HRQ report is that.

Teresa Rogstad: Well actually the one you were talking about I think is Chung 2011 that begins on I think that begins at the bottom of…

Man: Page 118.

Teresa Rogstad: Right, 118.

Man: So it's the U.S. preventive services task force focused update review of the report. So it sounds like Chung reported an overall risk ratio of 1.03, which was not even close to being significant and there was moderate heterogeneity in the five RCTs. And they looked at subgroups including institutionalized, community dwelling, and found no effect.

Teresa Rogstad: But then they did demonstrate a benefit for just looking at studies where vitamin D was combined with calcium and so that's the basis of a positive conclusion if you look.

Man: Right, so but [1:14:20] I mean it says in the Chung thing here, 11 RCTs were of good quality. So the quality of the evidence for a lot of these studies is good. The outcome happens to be kind of modest or

inconclusive or not all that impressive. You don't judge the how good the studies are by what the outcomes are.

Teresa Rogstad: Well, but here we were drawing a conclusion on the basis of a meta-analysis, not the, it's not that 11 RCTs showed a benefit. It's that when you pooled the evidence across those 11 RCTs, which differed in their results, then you got a beneficial association, but that analysis is…

Man: But that's confidence.

Man: Strength of recommendation.

Man: Yea, that's confidence in the ability to answer the question as opposed to, that's a different thing from quality.

Teresa Rogstad: Well, that according to the grade process you want to look at the quality of the body of evidence and what that means is that your, the confidence you can have in the conclusions suggested by the evidence. And here we had if you had looked at the individual trials you'd find conflicting evidence and so you would say that overall that's low quality evidence even if every single one of those trials were very well done. In this case, we have a meta-analysis that pooled data from those somewhat contradictory trials, came up with a positive conclusion, but this type of analysis is called meta regression is subject to ecological fallacy because just because you can see an association between an average value in studies and the outcome doesn't mean that that relationship exists in all the individuals who participated. So you're just a level removed from.

Craig Blackmore: Dr. Gerrity would you like to comment for, I need you at the microphone, however. We're relying on you as an epidemiology meta-analysis person.

Martha Gerrity: I think one of two things might be helpful, either the forest plot from the meta-analysis so people can do the eyeball test to see if there's inconsistency across studies and how wide the confidence intervals are, or if you have the i^2, which is a measure of heterogeneity.

Teresa Rogstad: Okay.

Man: Tornado diagram.

Teresa Rogstad: I don't know how to put the forest plot up on the screen. I'll call it up on my computer here real quick.

Craig Blackmore: I fear that I've opened Pandora's box by drilling down on these slides before we gave you the opportunity to finish the presentation and at some point we need to finish the presentation and at some point we need to get back to all of this.

Teresa Rogstad: I think so.

Craig Blackmore: So that would be, that would be great.

Teresa Rogstad: Yea. We can look at that later if you like. Alright, we were already up to there, I think. Alright, so there wasn't any clear pattern about a differential effect according to factors other than baseline serum levels. In populations who already have disease, there was evidence suggesting that baseline serum level does not, is not related to the effectiveness of supplementation in adults who are at high glycemic risk and then there just wasn't any evidence about other indications and factors. The cost of a vitamin D test ranges from something around $40 to $250 depending on whether retail prices are being paid or there's a steep discount. The cost of the supplements themselves, at least the ones that patients can buy without a prescription are relatively inexpensive, even at the mega doses for a one year supply. We did not find any cost effectiveness studies looking at the cost effectiveness of vitamin D testing. We did find three studies looking at the cost effectiveness of supplementation for prevention of fracture in older populations. These were done from the payer perspective in Canada and Europe and they assumed that the payer would pay for the cost of the supplements so they're not entirely applicable to the policy situation here. We might say that the results apply to a societal perspective in the U.S. perhaps. It's important to note that in these studies they assumed that all patients would receive the supplements, so supplementation was not based on test results and the cost of testing was not included in the model. They did conclude that supplementation was cost saving. One study showed hip protectors to be a cost effective alternative. So in conclusion, we really cannot make very any definitive conclusions about screening and testing per se. The potential effectiveness of screening and testing has been demonstrated by an association between serum levels and outcomes for certain populations and certain outcomes and a positive effect of supplementation on some outcomes and both the testing and the treatment is reasonably safe. So to try to give you an overall handle on the evidence, we looked at the evidence across all of the five key questions and tried to group that by populations paired up with

outcomes and that all appears in table four on page 94 of your report and you might want to keep your finger on that. It's the best, it was our effort to come up with an overall summary. That table is divided into three sections. The first part has to do with indications where you might consider vitamin D testing or screening or there's some hint of value then the next section are indications where the evidence seems to suggest no clinical utility to vitamin D screening and testing largely because for those indications there is evidence showing that the effectiveness of supplementation doesn't depend on baseline serum levels. So there it's not the testing doesn't provide information that can guide treatment. And then the last part of table two is for indications where the evidence was too sparse to make even a tentative conclusion. So in my slides, I called out the two areas where it might seem reasonable to consider testing and screening based on the evidence. The first one is in adults who have a known diagnosis of osteoporosis or a high suspicion of osteoporosis if they are going to be treated with active vitamin D or mega doses of inactive vitamin D. And the concern here is to prevent toxicity, because active vitamin D is associated with much greater risk of hypercalcemia compared with inactive vitamin D, about a threefold increase according to one meta-analysis and then megadoses of inactive vitamin D, for instance 50,000 IU per week seems to be a common dosage that translates to more than 7,000 IU per day and the safe upper limit defined by the Institute of Medicine is only 4,000 units per day. So there would seem to be a need to take a baseline measurement to demonstrate that the individual is vitamin D deficient in order to support this more potent treatment and then to monitor so that the treatment can be discontinued once the desired serum levels are reached. And I need to point out a few caveats here. As Dr. Ott pointed out to me, the treatment of osteoporosis with active vitamin D is not standard and we didn't see that in practice guidelines either. However, there is a body of evidence, a body of randomized controlled trials looking at the use of active vitamin D to treat osteoporosis and there is good evidence that it's effective, particularly when it's combined with other pharmaceutical treatment. So it seemed reasonable that that might be a clinical choice and then we did deduce from review articles and from practice guidelines that megadoses of inactive vitamin D, doses that exceed the safe level defined by the Institute of Medicine that those are often used for people who are known to have low vitamin D. I should also point out that the FDA has not approved active or megadose vitamin D for osteoporosis, but we're just pointing out that if that were the chosen treatment then you would have a safety issue in the absence of testing and monitoring. The other area is far, far less certain and the only reason we're bringing it up

is there was some evidence that the effectiveness of vitamin D would vary by baseline serum levels. This evidence came from the Women's Health Initiative, so it only applies to post-menopausal women and the differential effect was seen for prevention of some types of cancer, for prevention of cardiovascular disease, and for all cause mortality. But the trends went in opposite directions, as I pointed out earlier, so before this kind of evidence can be considered reliable and translatable into clinical practice, a great deal more research would be needed. And for the other populations and outcomes, the evidence either suggested that supplementation that the effect of supplementation did not depend on baseline serum levels or it was insufficient to allow a conclusion. The biggest gap in the evidence of course is that there's no direct evidence designed to measure the effect of screening and testing, definitive cutoff values are lacking. There is lots of missing evidence about differential effectiveness according to serum levels. In the evidence we have in older adult populations, some of them didn't receive the currently recommended doses and some of the study populations represented kind of a narrow range of baseline values. So the generalizability of that evidence is somewhat in question. And then there was just little evidence at all in populations, at least in healthy populations other than older adults. So what would you like to go back to.

Craig Blackmore: So I'm just going to editorialize for a moment and this is actually for both of the groups that presented to us today. I appreciate all the hard work and there's a ton of publications that you all had to go through and analyze, but what the committee needs is the evidence. So we need to see the effect size and the confidence interval and we need to know how many people are involved in the trials. We don't need little arrows that say six trials went up and two went down. We need the data. The most valuable piece of information on the report that you've given us is appendix three, that's the information that we need. It would be most useful if your presentation could summarize that for us, but not interpret it but bring it to us so that we can interpret the evidence and make a judgment. So if you bring your reports to the committee in the future, thank you for all your hard work. I'm not, I appreciate all that, but please, please bring us the data directly. There may be a lot of it, that's great. Usually there's not enough. But we need the information, so that's my sort of editorial if you will. Questions for the team?

Gary (?): Craig I have a question, do you mind?

Craig Blackmore: Sure.

Gary (?): It's Gary. So I think one of the confusing things here is we're so used to looking at randomized trials and saying that's a high level of evidence. The grade methodology, you've used grade methodology or something similar, which combines not only the risk of bias in these studies, but it also allows you to downgrade what you're calling level of evidence if there are, if there are inconsistencies between the trials or if there are other flaws and so this is not kind of what we're used to looking at. And that's what's confusing people here. And that's why we want to see the actual results, because the downgrade to a low level of classification of evidence isn't clear why that happens.

Craig Blackmore: We always want to see the results. Always.

Woman: But it's a good point. And I would request going forward that we have our future vendors always use the same standardized methodology and that we as a team be educated about what methodology they're using. Because this has come up before. It would be very helpful to us.

Craig Blackmore: So returning to the.

Man: So I have a question. I find all this, it's a bit confusing. And fundamentally what we have to figure out is the utility not of, as you pointed out not of giving people vitamin D, but of testing vitamin D.

Teresa Rogstad: Right.

Man: And this idea of so I'm a doctor right. So if I get a test, the test should be useful to me if it will change what I do with my patient. And what I am trying to gather from this is if I draw not that I do, but if I were to draw a vitamin D level on somebody are there circumstances that really would change my treatment. Is this a completely invalid test for which we don't even have normative data and nobody should be bothering, or really is there a very good reason for doctors to be drawing this. And you list a number of diseases that are extremely common. You're talking about associations with all cause mortality, with hypertension, with cardiovascular disease, with number of neoplasms. I mean these are lots of reasons why someone might want to know what a vitamin D level is.

Teresa Rogstad: The problem.

Christopher Standaert:

And like you said, so I don't think we're ever going to expect that we're going to have data to prove that every single one of these things correlates. I suppose if there's data to say that it doesn't matter what the vitamin D level is under any circumstances, all things come out the same then the test becomes sort of meaningless. But this issue of helping me understand this issue of if we get a vitamin D level and it is low, it is 20, it is 30, it is 40. You said that giving them more vitamin D raises their level. If there are very valid clinical circumstances where that is what we want to do, and we want to know what that is, then this is a very valid test to be doing in those people. And that's what we're trying to figure out.

David McCulloch: And those trials haven't been done Chris. Those trials haven't been done. I mean you need a randomized controlled trial where you either test or not test, give supplements or not give supplements.

Christopher Standaert:

So but yea, we don't have there are gazillions of tests we do for which we don't really know the effect of all the stuff we give people based upon those tests. And I get it with vitamin D I mean I've seen people take it for pain, people take it for all sorts of stuff. It makes no sense whatsoever to me. But that's fundamentally what I'm trying to pull out of all this stuff you gave me. And I understand the surrogate you're using, but it gets confusing when the surrogate's on a large population and they're not testing vitamin D levels and then you're trying to extrapolate back. That's not a valid extrapolation. Because you don't really know which you know. So that's what I'm trying to understand from this and where these boundaries really exist, what we know and what we don't know.

Teresa Rogstad: Right, well that's why we tried to focus on the question of does the effect of supplementation vary according to vitamin D status beforehand, because if it does, then that can guide your treatment recommendations. But the other thing that really complicates this whole question is that it's recommended that everybody take supplements and for the ordinary doses. Payers don't pay for it and it's safe and they're…

Christopher Standaert:

It's recommended that everybody take what?

Teresa Rogstad: Well the Institute of Medicine recommends that all adults take 600 IU of vitamin D per day. Without testing. So it's a safe treatment at the

standard doses. It's not something that payers have to pay for, so is there any reason that my physician wouldn't tell me to take supplements.

Christopher Standaert:
I guess that would tell me I should take them, frankly. But that whole concept, but yea.

Teresa Rogstad: Right, well there's enough right, there's a rationale for taking them. What we don't have are specific cutoff values for all those different outcomes. We have one for bone health.

Woman: So I'm a primary care physician, this is what I do, and I was so excited for this topic because patients come in all the time asking what do I do about my vitamin D. I want to get it tested. All this stuff. I was really interested to see the Institute of Medicine come out with their report and they actually doubled their recommendation and it was a big deal actually, I thought. And then reading this report, I just found myself struggling, the same questions you have. Like how do I apply this information in my practice. Or how does anybody do that. And so I just decided to Google back pain and vitamin D, because that seems to be what most people are talking about. Which is not really addressed in this report. And I found lots of studies, actually six studies that were done recently that were about interventions with vitamin D in back pain. Though I'm not going to go through all the studies and I didn't have time to read them all. But they're out there. But they're more recent than the aggregated data that you pulled together. So if the musculoskeletal conditions that are in this report are mostly concerning bone mineral density and osteoporosis, not so much any other kind of musculoskeletal condition like pain so much. So I'm just curious, like relying on previously aggregated data doesn't really provide us with the most recent data. 2007 study is getting data from 2006 and earlier and that stuff is six years old by now and there has been a lot of evidence done in the last even couple of years. So I guess I'm wondering if perhaps we're missing some of the most recent data in this current analysis.

Teresa Rogstad: Well, we didn't address chronic pain because it didn't seem to be one of the bigger indications in the claims data.

Woman: It sure is, it's a big indication in primary care medicine though.

David McCulloch: But that, yea, exactly. That doesn't indicate that it's got any association. Patients with chronic pain are desperate for something. That's why they

want to get epidural steroid injections. They're completely ineffective, but patients feel better within six weeks because that's the natural history of acute back pain blah blah and the number of things done for chronic pain that have no rational basis is a very long list. I can add vitamin D to that.

Woman: My hope was that the studies at least would be evaluated so we could have a chance to learn more about it. Like one of the studies was vitamin D in failed back surgery syndrome. Like wow, if there was something that helped that, that would be awesome. So it would be just nice to have a chance to look at this data objectively rather than me spending my time trying to pull it off of PubMed.

Man: So remind us what the cutoff time for the search was?

Teresa Rogstad: July 31, for randomized controlled trials it was April 30th, for systematic reviews.

Woman: Of this year.

Teresa Rogstad: Yes. Now there was a Cochrane review published in 2010 on vitamin D to improve chronic pain. And I referenced it in the report, but we didn't analyze that and they concluded that the evidence was insufficient. But that was published in 2010 so I don't know what's been published since then.

Christopher Standaert: I mean we have certain things that were omitted from this. Like on the list of limitations they omitted chronic pain, neurologic disease, infectious disease, autoimmune and allergy disease other than MS. And so when we get to if we're going to put conditions on something theoretically you start saying well these conditions we can't even we didn't pull the literature on these. So what do we do with that. We're not there yet. We may go there, I don't know. But it does create a problem. Because we're talking about only bone health sort of stuff we're looking at.

Susan Ott: So the Institute of Medicine did look at all those things and the only thing they found where there was any evidence that vitamin D was helpful was in musculoskeletal disease and so that's why they concentrated on that one. But they looked at all the other ones. And now that is a couple years old, but I haven't seen anything very good come since then.

Teresa Rogstad: Well I think actually that the Institute of Medicine was looking at data that pertained to healthy populations, right. So they I don't think patients who were recovering from back surgery, I mean we consider that to be a disease population. A group that already have the outcome you're trying to prevent with vitamin D.

Susan Ott: But reducing the risk of those diseases, right, not improving disease outcomes.

Craig Blackmore: I want to just bring this all back together a little bit, because we're wandering and I'll take blame for that. I wonder if Margaret or Christine, could I get you to put a copy of the key questions on the screen for us? I'd like us to try to understand that a little better as there seems to be issues around that.

Teresa Rogstad: Well I can, they're in my slides if you'd like me to do that.

Man: Sure, that would be great.

Teresa Rogstad: Unfortunately, they're not all on one slide.

Man: I want the key questions. Alright, so we've got slide 18. Thank you.

Craig Blackmore: Okay, so again, as always we have three choices. And we're specifically addressing testing. We're not addressing supplementation, I believe. So our choices will be then to say that we'll cover vitamin D testing without condition, we can say we'll never cover vitamin D testing, or we can say we'll cover vitamin D testing with conditions. And I'm going to sort of speculate that probably there might be some condition under which it would be appropriate to do this. I'm looking for nods so that I can direct us a little bit. That we're not pointing towards a never cover decision. Right? So I think what we would be looking at is either we would cover unconditionally or we would cover under some set of conditions and those conditions might be based on the particular demographic, they might be based on particular disease history that put a patient at risk, they might be based on some clinical presentation, pain or whatever. So I want to just sort of focus if possible, focus us in on trying to understand the differential effectiveness or try to understand the factors that we think might affect the effectiveness of screening. So with that sort of maybe narrowing things a little bit, I want to get us back to the discussion. Maybe this would be a good time for a volunteer to

summarize our position or summarize a position about where we are. Do I have to volunteer somebody or are they just going to jump in?

David McCulloch: I think this is a relative no brainer at this point. I think some version of what Dr. Hammond mentioned that we should not be covering use of vitamin D screen or monitoring outside of the conditions for which it's clearly a known part of the disease process. I mean all the passionate stuff with multiple sclerosis is a classic example of I mean it prospective cohort studies and epidemiological associations are a great way to generate possible hypotheses. But they don't ever show cause and effect, so they should do your randomized controlled trial supplementing and not supplementing, testing and not testing. But at this point my proposal would be shouldn't be covered except for the specific known conditions for which it makes a difference.

Craig Blackmore: And I don't want to drill down any more on that right now, but just to get other people a sort of broader perspective. Kevin what do you think on this topic? Where are you in your thinking?

Kevin Walsh: I'm unable to generate any reasons to cover it beyond specific conditions. It's not even, I mean it's not clear what baseline levels mean in terms of disease. It's not clear what supplementation means in terms of disease for the most part except for institutionalized older women. So I would agree with David.

Craig Blackmore: Marie Annette

Marie-Annette Brown:

We don't know that testing leads to taking the supplement. We don't know that if you did a test whether if you gave that would mean that you would give a recommendation for someone to take it and how much they would take. So that's what we don't know. So to cover what we're doing I think we do have some reasonable evidence with older women.

David McCulloch: Well no evidence that testing and following vitamin D levels does anything. We've got evidence that giving those women supplements helps.

Marie-Annette Brown:

Yes. So I would be interested in covering several of the conditions which have some evidence.

Craig Blackmore: Is there anybody who wants to, who sees things a little differently that wants to chip in at this point?

Man: Well I guess I don't see, I see good evidence you should not do this as a routine screening test on a healthy population. I don't know that we covered or that I personally know all the potential medical reasons why you may do this as a very valid test. There may well be unusual medical conditions for which you would do this and it would be a very valid thing to do that have nothing to do with falls or other things and that's just, so getting a language so that we give enough leeway for the very unusual sort of medical things and don't just say you can't do this. Because again, I totally agree it should not be a screening tool, it shouldn't be done on everybody and it's very unclear that in a healthy population testing this and doing something about it does anything. It's probably more harmful than helpful.

David McCulloch: It's a potential harm, yea.

Man: Yea, it's probably more harmful than helpful. But it's just, my question is just getting the language so that neurologic, you know we didn't look at neurologic disorders, didn't look at other things that might be associated with bone mineral problems, metabolic problems, or endocrinologic problems and how we cover all of them in our language is my only thing I'm pondering at the moment.

Man: Well, the thing I'm still confused on is slide 32 and how these effects, how we get these inverse effects with fractures and hypertension and I the way.

Man: Some go up and some go down.

Man: The way yea.

Man: Some are higher levels and some are lower levels.

Man: The way I read it is in a trend you're looking at your baseline levels going up, so the higher your baseline level right the higher the effect.

Woman: I think one thing I'd like to see on that slide is when those studies were done, because it seems like since the change in recommendation for daily RDI has gone up, then maybe the studies after that recommendation showed positive trends. I mean we don't have, it's not scattered across

time. We don't know when these studies were done. We can't make any assessment out of it, to me.

Man: Right we don't, we don't know the studies, the effect.

Man: This is the same study, right. This is interpretation of the Women's Health Initiative data.

Man: You could look at this…

Woman: I don't know, is it? And that's before the baseline change too so.

Man: You could look at this again, but you could also say about this is there's a threshold of vitamin D level you need to achieve to have benefit and if you start too low and you take 400 you never make it. So you don't see an effect until you start high enough to get up to that threshold. That would be another way to interpret this. Or that it's all totally screwy and we're getting random associations. I'm not sure which.

Man: That's kind of what it implies.

Woman: Absolutely it should be done.

Man: So these conflicting arrows if you will, that's what drove your statements about low level of evidence despite, is that my.

Teresa Rogstad: Well even by themselves, it didn't seem like high level evidence because it in the one case even though it was conducted in a really well done trial, it wasn't corroborated by other trials or by and we don't have evidence pertaining to currently recommended doses for the falls and the fractures. Those findings were the basis of meta-analysis, which is just a little bit more indirect form of evidence.

Man: So in the…

Woman: I didn't think they measured the baseline vitamins D in the Women's Health Initiative.

Teresa Rogstad: Well they didn't overall, but that, well they did in a sub-population.

Woman: Yea, but they did not in 36,000 women.

Teresa Rogstad: No, no they didn't. Okay, good point, right.

Man: Did the authors of the Women's Health study discuss these things. So the fact that all cause mortality was decreased more profoundly in patients who had a lower serum level. They had a bigger effect from taking the vitamin D. I mean that would be a relevant population piece of information for the population, yes? That people who are lower will have a lower, a better effect on their all cause mortality if they supplement up. I mean is that what that says? Or did the author sort of say this is all very muddy based on what we did. Were they clear in their…

Teresa Rogstad: They, for the mortality one the problem is the three bottom rows on that slide, those are the ones that came from the Women's Health Initiative and the audience or I mean the authors didn't even address that finding in their discussion. So I don't know what they make of it. And the fact that you have these different directions just makes you wonder about how valid the findings are too. It doesn't quite make sense.

Woman: I actually am I allowed to say something? The Women's Health Initiative was a randomized trial. 36,000 women. They either got placebo or calcium and vitamin D. The only, they did not have significant improvements in anything that they measured. The main outcome that they specified was fracture and the other one was cancer. And with those two main outcomes there was not a significant difference. And then all the other things that they looked at: mortality, hypertension, all that actually in the overall trial it didn't matter. It was only in certain subgroups and things that they could tease out benefits.

Man: So these are all based on subgroup analyses.

Woman: Yea, they didn't even measure a baseline vitamin D. What they did is after it was over they did some nested case controlled studies. And they would look at the ones who died and then they would get some stored sample, you know, you all know nested case controlled okay I won't go into it. Those were nested case control studies and that's a little different.

Man: So the context is the Women's Health Initiative with 36,000 people with the individual studies that drove these particular conclusions were based on subgroup analyses, nested case control.

Teresa Rogstad: That's a failing on my part. That's a misleading number. If you would like to look at those at the actual data I can point you to where they are.

Craig Blackmore: I think I, it's about 130, 129 in there in the appendix. Okay, Joann.

Joann Elmore: Besides hoping that there's chocolate over there, I am feeling like the group is moving towards approve with conditions.

Craig Blackmore: I think we are.

Joann Elmore: And if that's the case, I'm assuming that the agency will have to operationalize on the ICD-9 codes that we put on the lab slips.

Craig Blackmore: Is that…

Joann Elmore: Is that how you operationalize? Okay, then there's a little difference between the wording in what the agency recommended, which actually is quite specific with diseases versus the wording that Regence used. And I would appreciate our clinical advisor to help us. Because I think we as a group are moving towards approve with conditions and I want to make certain we are inclusive enough and the, do you have these slides Susan?

Susan Ott: Yea, I've seen them. I don't have them in front of me.

Joann Elmore: If you could get them in front of you, I'd appreciate input from you.

Susan Ott: Can we put them on the screen, is…

Joann Elmore: It's the agents well, I mean I can basically tell you. The agency recommends very specific inclusions. You know Rickets, osteomalacia, secondary hypoparathyroidism, intestinal malabsorption, and hypo or hypercalcemia. Otherwise nothing else. You know what about monitoring patients who have seizures on treatment. What about sarcoid. And so that's what they recommended. I'm worried that it might be too specific and I figured you could advise us on the wording to help move us. And I looked at the Regence and theirs is much more generic and it's on slide 18. Maybe 15. Slide 15, payer policies of the Hayes.

Susan Ott: So which one is that?

Joann Elmore: Slide 15.

Man: Slide 15 of the Hayes.

Joann Elmore: Of Steven's talk. And so he basically says testing in individuals with one of two things. He says a disease or condition known to cause vitamin D depletion or radiologic or lab findings that are positive for markers for insufficiency. And so that's a little bit more all inclusive. And so could you advise us on the best fit for conditions that is specific enough but inclusive enough?

Susan Ott: Right, and I actually did that for somebody else. It was for one of the Medicare people. But I think that the what I would recommend is somewhere in between. That of course the ones that were listed by Dr. Hammond I agree with, but I thought it should be broader than that and in terms of the, you know a disease or condition you can actually make a list of the, excuse me the diseases or conditions that are known. For example anti-seizure medication. Any kind of malabsorption, bypass surgery is a kind of malabsorption. Then you're going to have the findings that relate, didn't they have one diseases that are closely related where vitamin D is part of the pathophysiology of it?

Craig Blackmore: There's sort of an operational question here, and that is who makes the list and I'm sure that you're qualified to make the list, but I'm also sure that we're not. And so we can, we can word things in such a way that we leave the definition of that list to the agency directors and I'm sure they would love your help. But I think.

Susan Ott: Yea that looks more like what I saw.

Craig Blackmore: But I think I'm getting uncomfortable with…

Susan Ott: They had a more specific list, but all of the things on the list definitely have been shown to be involved with vitamin D metabolism and I would have added you know we said low and high serum calcium but I would also add low and high serum phosphate, for example. Because although pretty rare, that's definitely some you know if somebody comes in to my clinic and their phosphate's way out of whack, I want to know but this is not screening. This is diagnosing.

Woman: This is testing.

Woman: But how can they tell the difference? They just get a charge.

Man: Yea we're not talking about, we're not making a, this isn't based on, I'm using the term screening I'm saying…

Susan Ott: But still, if it's screening they're going to have one of those you know that list you showed us. You know it's going to be what fatigue or, but if it's really the diagnosis then that…

Man: No, people do it for yea.

Susan Ott: No but I mean when you get the test, you have to say what, at least when we do it. You get, you say what the ICD-9 code is and it would have to be…

Craig Blackmore: I've got too many people and we're recording this and we're supposed to be able to, we're supposed to say who's speaking and so we can get the transcript, but I need to have only one at a time.

Woman: Well in primary care, and we have people come with symptoms, a common one is fatigue and we check thyroid, we check vitamin D. So there are some…

David McCulloch: Well you shouldn't. There's no evidence for doing so.

Woman: There's no evidence that fatigue is related to thyroid?

Susan Ott: No, to vitamin D.

David McCulloch: No, we're talking about vitamin D. There isn't, I mean that's the growing balloon of worried well people saying I'm stressed or the economy's bad, I'm feeling fatigued, can I have my vitamin D level tested? That's what we want to avoid, because that's stupid medicine.

Woman: Well what I'm asking is that are we going to look at this for groups of, for groups of symptoms? Not just diseases, but as you're trying to make a, if you're looking at a…

David McCulloch: No.

Woman: If you're looking at different.

David McCulloch: No.

Craig Blackmore: Okay, so that's an alternate proposal. One proposal that we have is sort of loosely on the Regence, maybe expanded a little bit and that's based on conditions known to cause vitamin D depletion, markers, etc. Another way to look at it would be to define some sort of symptom list to say these are the sorts of symptoms that we would look at. And Mike's been very patient.

Michael Souter: It may not be very sufficient of a filter to actually meet everybody's needs. But I think that clearly what we all want to do is stop the routine practice of screening. And if you look at the PB top ten diagnoses, I mean there is a test number for that of what the very least one of the things we should do is that say that what is not covered as opposed to saying what is covered.

Man: Screening.

Michael Souter: And just say screening is not covered in any shape or form. I think that's an immediate caveat, a blanket statement that we can all feel confident in applying.

Man: I like that.

Craig Blackmore: As a starting point, but that isn't terribly restrictive of itself because you can always.

Michael Souter: But it still accounts for over a million dollars of the expenses over that four year period. It's at least it's a start and then, then there's a lot more diagnostic categories that possibly you might want to fit vitamin D testing in to. But that's a little bit more difficult to nail down than whether we say that there are certain things that you don't investigate for, I don't know. But there does seem, there does need to be a pathophysiological mechanism at the heart of our testing method rationale it would seem to me. And what we want to do is avoid the kind of the spurious what ifs and maybes.

Craig Blackmore: Okay.

Woman: Is there a paper that's on the physiologic effects of low vitamin D and symptoms that occur at what level, like the low 30, the low 20.

Group: No.

Woman: Somebody must understand and have written about the physiology of vitamin D deficiency

Man: I mean we don't need to go there. We can say symptoms of vitamin D deficiency and I mean there are no symptoms of vitamin. I don't know. I mean we can say diseases or conditions known to cause vitamin D depletion. We can phrase it a different way. We can say…

Susan Ott: We can say abnormalities instead of…

Man: High risk for vitamin D deficiency.

Susan Ott: Don't forget that some people are too high.

Man: If we go back, if we go back to our…

Susan Ott: Not just depletion you want, excuse me not just depletion but abnormal. High too.

Woman: That's a good point.

Man: That's a good point.

Man: So if we go back to our evidence right, so the evidence we got looks at none of these things. We didn't look at hyperparathyroidism, we didn't look at any of them. Right, they weren't. So us picking out particular diseases is really problematic because we looked at none of them. We can say what Mike said, that this is inappropriate, this is not should not be covered as part of routine screening. And I think it's reasonable based on sort of biologic data that we say something, Regence I think is reasonable. It's relatively big. It says if there's some known disease or problem associated with vitamin D issues or you have some other test giving you reason to suspect such is the case then you can get it. Otherwise you know, but we didn't really get in to these individual conditions. So us sort of stacking them and saying this and that and this and that I think is really trouble, we have no data. And we excluded some specific things that one might do this for legitimately. And so I think we can say instead of Mike's I like Mike's idea, you put a sentence in saying this is not covered as part of routine screening and coverage is based on something. Some known condition or some you know rational reason to some known condition associated with vitamin D disorder.

Craig Blackmore: So can I have a proposed wording up here just to give us an anchor?

Woman: Populations with known disease that may be linked but does not cause vitamin D deficiency, some variation of that?

Woman: I like the Regence.

Man: So if we say, let's start with Mike's thing saying vitamin D can we start with not cover? Or do we start with what is covered? Vitamin D testing is not covered as part of routine screening, as part of routine screening. That takes care of the top diagnoses as Mike pointed out. And then you know sort of I'd start with Regence. Disease or condition known to cause vitamin D depletion.

Woman: Or vitamin D abnormality.

Man: Oh abnormality, yea, okay. Better.

Man: Can I just amend one thing. Let's say that you need to be careful of people trying to get 'round the screening thing as well.

Man: I'd say of itself that won't do anything.

Man: No, no, that's why we're.

Man: But that doesn't mean it's not appropriate.

Man: You could say that you're not covered as part of routine screening or in the absence of a defined disease process. I don't know, something like that.

Man: So keep it in the negative. Yea.

Man: So you've actually got to have testing but on the basis of something you could substantiate. I am testing this because I am investigating this pathology. And it gets a little bit harder than just to start coming up with things like okay well I think you're fatigued so I'm going to put that down as a label. I mean that's something that'd be very easy to follow up on.

Woman: But that also leaves open for if research comes out about fatigue, that'll still apply too then. So I think that's great.

Man: And if the research comes out about fatigue we can revisit it.

Woman: Well no I mean I think it would cover it, it would be covered. I'm saying we won't have to revisit it.

Craig Blackmore: Okay, so we've got a, I mean we can adjust the wording a little, but we've got a starting point. I just want to make sure, I've heard from a few people, but I mean are we all on board with this sort of approach? No screening, yes based on some wording around high risk, which is what we're doing? Is that approach okay?

Man: Well I don't like number two. I mean if you've, abnormal bone mineral density you don't need to do vitamin D screening, you need to treat the person for osteoporosis. It's too loose.

Christopher Standaert: No well that means if you have, if you have an unexpected view x-ray if you have somebody who you have no reason to think, has no other risk factors for osteoporosis and you happen to x-ray them and they have very low bone density they get an insufficiency fracture.

Man: Then you treat them, Chris.

Christopher Standaert: Well no, you figure out why they have it, right? You don't just treat them, you figure out why they have it. So a 25-year-old you'd go figure out why they have it, right? And all you have is an x-ray. Then I would think yea, you'd, it's part of the diagnosis. Right you'd go.

Susan Ott: That's not screening, that's diagnosing.

Group: Right.

Woman: We also have a use to track if someone is giving a high dose, you want to make sure they're not getting too much either.

Susan Ott: You shouldn't give it in the first place.

Woman: But they're doing it.

Susan Ott: Why should you approve a test for doing something…

Craig Blackmore: Thank you. I appreciate your enthusiasm. Alright.

Man: In number one, so if something is known to cause vitamin D abnormality, what about putting in with that the calcium phosphate abnormalities. Because they all sort of integrate together. And that way we don't have to get in to enumerating the individual conditions, hypophosphatemia, calcium…

Man: We're all trying to avoid enumerating individual conditions.

Man: Yes, but you could say including and list some.

Man: Yea, I don't think it's that big of a list, Craig. I mean you've got three or maybe two and a half since [02:03:49] I mean that's not a big list to come up with. I mean the list that Steve came up with supplemented by those others, those are the conditions which…

Craig Blackmore: That's not…

Man: It wouldn't be unreasonable to put that in there.

Man: It's not, my only problem is that is not remotely what our [02:04:05] was on. It was not on the appropriate conditions under which you do this. It was on population screening and treatment with but with vitamin D.

Man: I mean that's beyond the expertise, this is an evidence based group. That's what our strength is, that's what we're trained to do, that's what we're charged to do. And we can say it has, there has to be a reason and it has to be in this category, but then we need a panel of experts or some mechanism for the agency directors to go with Dr. Ott or whoever and figure it out. It's just not, we're not clinically qualified to be the ones who do that. So that being said, how do we basically, we're in effect charging another group with generating that list. And so what rules do we want them to follow in generating the list? And first is not screening, that's easy. It probably doesn't make a difference because people always change the indications.

Man: Well that's why I think you need to be a little bit more specific. I think in terms of the, as part of routine screening but you've got to say something about the absence of a disease category. If you can't put down an ICD-9 code on there then you shouldn't get to do it.

Man: But I think what we're talking about is what constellation of ICD-9 codes should we be including. And we're not going to generate the list of codes, but we're going to say that those codes should be things known to cause vitamin D abnormality and then another thought was should it be vitamin D, calcium, and/or phosphate abnormality. I mean do we need to include those other two aspects or not? Or do we want to be even more general and say testing is covered in individuals with a disease or condition known to be I don't know, related to vitamin D abnormality. I'm not proposing that, but I'm asking the question. Joann.

Joann Elmore: For point number one, I would recommend just having the word vitamin D. Not calcium phosphate. And I would also change the word cause to associated with. Or at least I would want to ask input from others.

Man: The problem there Joann is there's the associations shown with multiple sclerosis, the associations with low vitamin D levels in people with cancer.

Man: That's really general.

Woman: Obesity.

Man: It doesn't suggest that you treat it.

Woman: That's a tricky point.

Man: I like, I like cause and I personally don't know enough about the biology to know why calcium phosphate would be in there. Seems like vitamin D makes sense.

Woman: Yea I just think vitamin D.

Craig Blackmore: Okay.

Man: Can I make a comment?

Craig Blackmore: Please.

Man: From the agency point of view what would help I think trying to come up with a general statement of when it's appropriate and let the agencies then apply that as you know, let them work out the methodology. There is some language in the Regence policy that I didn't see shown here, but I

think could be useful. It says, it suggests that it may be necessary in patients with a clinically documented underlying disease or condition which is specifically associated with vitamin D deficiency or decreased bone density. I don't 100% agree with that latter one, but anyway. I think a statement like that would be helpful. And then we could operationalize it at the agency level. And that language is, does, is in the Regence policy.

Woman: Rather than deficiency, I think we want to say abnormality.

Man: Yea.

Woman: To take into consideration the hyper.

Man: Yea we sort of just restating one and two there I think, aren't we?

Group: Right. I think so.

Woman: I'm happy with one too.

Craig Blackmore: One and two.

Man: Yea it's saying the same thing.

Susan Ott: Yea, I'm…

Man: And one is known to cause a vitamin D, not to be caused by. Known to cause. Known to cause a.

Man: If we change it to associated, it opens up a very wide door for all sorts of things.

Man: It's fatigue, it's…

Man: If we say cause.

Susan Ott: Wouldn't you want it to be number one cause or caused by, wouldn't you? Like if you have a GI disease, that's causing vitamin D abnormality, on the other hand if you have vitamin, if you have Rickets you certainly want to know, then it would be caused by it. So either way.

Woman: That would be covered in number two though.

Man: Eventually.

Craig Blackmore: So causality in either direction I think is what we're hearing in several ways here. Known to be caused. Known to cause or be caused by.

Man: Yea this, I mean this is where we don't have the data on this, that's our, I mean this is where the agency is going to have to go look at, because people are going to throw MS and fatigue and pain are going to say oh, vitamin D causes pain. Therefore I can, therefore…

Man: If they can prove that to be the case.

Man: No but that's what I mean that's up to, they're going to have to get their own experts and put together a list.

Craig Blackmore: Okay so let's, if I, if we could erase the bottom bold piece.

Susan Ott: You guys could say that cause means it has to be shown together with an RCT.

Man: No.

Susan Ott: You could.

Craig Blackmore: Thank you, but no. Alright. Operationally, if I could ask the agency team. Members of the committee, are there additions or subtractions? Sort of a different way of looking at this? That we haven't dug down on?

Man: Just to, if we're keeping number two, it should, markers for vitamin D insufficiency, we should put the vitamin D in. It's too vague to say markers for insufficiency.

Craig Blackmore: Okay.

Man: Insufficiency.

Man: Did you catch that, Margaret?

Craig Blackmore: Before the word insufficiency, the final word in the thing if you could put vitamin D. Should we change insufficiency to abnormality or are we happy with?

Woman: Abnormality.

Group: Yea.

Craig Blackmore: Other thoughts?

Man: I like it.

Woman: Great job.

Man: Do we need a chocolate break for Joann or are we going to go straight on?

Craig Blackmore: Do we need to what?

Man: Have a chocolate break for Joann.

Craig Blackmore: I think that's the reward. All right. So we're going to move on to our decision making thing. So we've been through the tool, we're all familiar with it. I'm going to skip ahead to the first voting question. This is our non-binding vote and the question you will be asked to vote on is is there sufficient evidence that under some or all situations, vitamin D testing is of unproven equivalent less or more effectiveness than not testing.

Woman: That's a weird question.

Woman: Because there are some diseases that could be helped.

Craig Blackmore: And that's, if you think there's any circumstance in which vitamin D testing is more effective than not testing, then you would vote more.

Man: Can we do that on more.

Craig Blackmore: Okay. The next question is is it safe compared to the alternative of not testing.

Man: Under some conditions.

Craig Blackmore: Under.

Man: Yea, some and unsafe in others.

Craig Blackmore: And then the next is, is testing more cost effective than the alternative of not testing. Okay, further discussion at this point. I don't want to shut us down. Okay, we'll move to the binding vote now. And this is for coverage and based on the evidence about the technology, safety, efficacy, and cost effectiveness and your choices are that we will not cover it under any circumstances, that we will cover vitamin D testing without condition or that we will cover it under certain defined conditions and those conditions are that it is not covered as part of routine screening, but testing is covered in individuals with a disease or condition known to cause or be caused by vitamin D abnormality or radiologic or laboratory findings that are positive for markers of vitamin D abnormality.

Man: Cover with conditions.

Craig Blackmore: We are charged with.

Man: Determining if our decisions are in line with Medicare national coverage decisions and I think we have local, we didn't have… There's no national, right? I just want to confirm there are no national Medicare coverage. And so we are we don't have to worry about not being compliant with that.

Craig Blackmore: I thank you all for your help and…

Man: Could I make one little comment?

Craig Blackmore: Yes.

Man: I'm only slowly realizing the importance of how the key questions are phrased.

Group: Yea.

Man: I've never taken the time to respond when there's that open period. But I'm realizing that maybe we all should.

Craig Blackmore: I think it would be great.

Man: Because it might alleviate some of the pain we feel.

Craig Blackmore: It would be great if we all took advantage of those emails that we get from Christine that say the key question draft key questions and you know I totally agree with what you're saying and I think we are uniquely able to look at those questions and think through how we're going to make a decision because we're always, it seems like in the same spot of struggling to define the separation line and we want to make sure that the questions asked for all of the information that we're going to need to make that decision. Joann.

Joann Elmore: First, this is very important. I want to tell you, you're doing a great job with this committee. You work as hard but this voting today probably is going to save five million. So you're doing a phenomenal job.

Craig Blackmore: You're too kind.

Joann Elmore: Number two, I was thinking also about these key questions and the emails we get that are among hundreds that we get every day. And we may not pay enough attention to them and I'm wondering if we could devote 15, 20 minutes of our next meeting in advance just to always go over key questions. Because sometimes the back and forth communication among members is really helpful. And then finally, I would make a plea again that we try and standardize our evidence based reviews and the rating of the evidence and that we as a group sort of are all in agreement with how it's done and also so that we know how it's done. That would be helpful to us because it is complicated.

Man: I think those are great suggestions there and we'll follow them.

Man: We do have key questions out right now for draft for a meeting in May. We have some time. We can put those up and look at those if you'd like to.

Woman: Yea, once we have chocolate.

Craig Blackmore: So I guess I will adjourn the decision making piece of the meeting, but we're still technically in session. Since we have a forum and we can look at those key questions for a few minutes and while we're setting those up I have got an overwhelming message that we need to hit the side bar. So not the side bar, bar, but the food on the counter side bar thing. So why don't we do that. And if you have to go that's fine, but if we can all most of us can stick around that would be great too. Okay we're going to bring the, bring the meeting back to order. If we can bring the meeting

back to order we can all go home sooner. Okay, we have a quorum again so the meeting is back in session and we've completed our business and now we're providing input to the team on key question development. Josh can I get you to.

Josh (?): Sure so this topic was selected last year. We've put this forward before a meeting beginning to work on this for May. Hayes has been assigned this topic so we've been working with Terri and Sue on some scoping background and these are the draft key questions. These are, these went on the internet yesterday, so we have a two week comment period on this is what we normally do. We can you brought this up so I thought we'd throw this up there since it is a draft period and you can see what our scope is. So the question is for individuals who may be eligible for cochlear implants, the key focus here is bilateral implantation versus unilateral. And our focus initially is on children and adolescents. That was the question that the agencies brought up with hearing loss. So we can read through this and or I can just point you to the fact that it's out there and you can send in your feedback.

Man: So I've tried to critique the key questions a few times and I think it's hard because until you've sort of sat through an afternoon or morning of detailed discussion of these topics, it's hard to kind of grasp them all at once. But what I've tried to do is to try to think through okay, usually I know if I'm going to make a non-coverage and I know if I'm going to make a coverage, but if I have to make a coverage with conditions argument will all the information be identified from the search. And I don't know, that's helped me to try to help this process, but I won't say it's always been that, the answer.

Man: Just to clarify, we can comment on the questions but we cannot comment on the scope? Is that correct?

Man: No, you can comment on well the scope as far as bi versus unilateral is defined. That's what was selected initially.

Man: Adults and children or?

Man: Adults and children, so as far as the evidence search goes through comments that have already been provided, it's evident that you wouldn't want to limit the evidence to just children and adolescents. We would want to enlarge our search to find any evidence for bilateral versus unilateral. That is not reflected here, but that could be or will be at the

end of this in the final draft. So that would be a population change to make sure the lit search finds everything that you think is valuable to the question.

Man: So just to maybe provide a little more information to the committee, both Seth and I have already looked at the key questions on this topic and provided a little bit of input. And the piece of input that I provided maybe as an example is this is a key question that is focused on children and adolescents and so the literature search is going to be children and adolescents, but one comment I had was that if we're looking at the effectiveness of cochlear implants in adolescents and non-adolescents, it might be reasonable for us to look at how well it does in adults and try to extrapolate that information. But this search as written actually wouldn't tell us about adults. And that's this scenario that we've encountered in other situations where because the search was narrowed on a specific clinical area or population, we ignored information that might be relevant to that group from other populations.

Man: So the individual words matter quite a bit. You saw SBRTSRS this morning and when Dr. Gerrity presented in her slides she actually used the term malignancies, but the actual scope was that word was changed to tumors mid course. Maybe republished the question. So we scrutinize every word and we're trying to make sure that we get the words right, because they make a big difference in the search.

Man: So the question isn't to cover cochlear implants, cover unilateral or bilateral. Is that the question?

Man: The question is in what circumstances would should bilateral, does the evidence support using two versus using one.

Woman: So it looks like unilateral plus a boosting hearing aid?

Woman: Those are the comparatives.

Man: Yea, so there's two different comparatives.

Man: So one of the things that would, I think on first looking at this the question that springs immediately to my mind is okay, what's the impact then of somebody still being effectively deaf in one ear. That may be somewhat simplistic and I'm not an ENT surgeon, but I think that would be an important thing to actually have covered in our evidence survey as

part of the contents just to see if there's no evidence for adolescents in this population so let's look at adults. Is there evidence to be looked at for the effects of unilateral deafness upon children as compared to children with intact hearing on both sides. Does that seem reasonable?

Man: Yea. I am an ENT surgeon and that's a very, that's a very insightful comment. Because that's exactly right. I mean that's where the whole evidence based comes from for doing bilaterals in the first place, but it does get lost if you just look at the question directly. So looking at, I think that's a great point, that looking at the literature on the handicap of unilateral deafness in children would be very helpful for the discussion as it's going to pan out.

Man: But one question is one is the handicap from unilateral and the second question is does bilateral reverse that handicap. And we might get the latter, but not the former.

Man: Part of the problem there is the duration of effect. So you know a lot of the times when you're looking at what are the outcomes of unilateral deafness, it's you identify a child at birth as being deaf in an ear or when they're quite young but then you want to look at educational outcomes, so how do they turn out. Sometimes it's hard and some of that long term data is not available for cochlear implants. So you end up forcing yourself to extrapolate. So we can debate whether that data is useful or not, but that's ultimately what the question here is. Is are you going to…

Man: And that's really the reason to look at adults. Is because I mean, this…

Man: I was going to say the same thing, yea.

Man: I mean this is impacting language acquisition.

Man: What you want to know is adults who had their hearing fixed when they were young versus adults who didn't and sort of are they functioning differently at 40 or whatever would be a very useful thing to know if it's out there.

Man: But also adults.

Man: I just said adults, I'm agreeing with you.

Man: I'd still like to know about kids though in terms of you might get there as an adult, but it could be later. That would be a difficult thing to pick up, whereas if you're looking at children in terms of how they're attaining their milestones of development and etc. that's important to me as well. So I think just you know knowing what the natural history of unilateral deafness would be, would make a lot of difference to me in deciding what somebody should actually just have one cochlear implant or two.

Man: Isn't patient satisfaction a reasonable outcome? Are people happier with two than one?

Man: Well then we'd start funding the placebo effect.

Man: No it's hearing I mean I would imagine your life is different if you hear out of one ear than both.

Man: Is it?

Man: That's what I'm asking. So that will be the question. But is that are people you know a broader, I mean that's why you're you know they probably hear things but sort of how they interact, how they function.

Woman: Their quality of life.

Man: It translates into all sorts of stuff. Maybe. It depends how they measure it I guess.

Woman: Right.

Man: So Josh is more below the, do we need to scroll down.

Josh: Yes, but this is the whole document of key questions, so this is the population intervention…

Man: Second outcome is… Ah, there you go.

Man: The one thing I think that we'll see and it comes up a little in the unilateral versus bilateral is the data on why we have two ears. You know, sort of what situations does hearing with one ear or does hearing with both ears benefit us over and a lot of the data on this question on the unilateral versus bilateral is about the different conditions under when and the different ways in which hearing out of both ears is

improves your function. Because sometimes it's difficult to document a quality of life difference on some of the blunt instruments that have been used, but you can demonstrate clearly that there are functional differences in certain circumstances where people with bilateral are going to do better than unilateral. I'm not sure exactly how you operationalize that into the key questions, but maybe something about functional outcomes as opposed to you know, I mean having something about functional outcomes be part of the outcomes.

Man: I think we've incorporated functional outcomes. So the scope of bilateral versus unilateral won't be modified at this point. That was not what was selected. But if you have word changes on.

Man: So for specifically hearing and noise is one of the big ones. Hearing background noise. So that should be on there.

Man: As an outcome.

Man: As an outcome, hearing and noise. You know one of the controversies that you have a person and you put them in a soundproof booth and you test their hearing and it doesn't really matter if you have one ear or two ears, but then you put that same child in a classroom, when there's background noise around them and they function very, very differently. So hearing background noise is an important outcome.

Man: So when you say that the scope of unilateral versus bilateral wouldn't be changed, does that mean that you wouldn't be able to adapt this to look at simply the effect of unilateral hearing loss versus normal children?

Man: Right, that is not what the policy question is…

Man: No but in terms of I understand the question, in terms of actually giving contextual information to inform that decision.

Man: Yea.

Man: We're you're looking for the natural history of the disease process of unilateral hearing loss.

Man: Yea, well just that you know how much difference is there between having one ear working and having two ears working. That's what I want to know.

Man: Yea, okay.

Man: What I'm hearing is in order to answer the question we need more background contextual information such as…

Man: There's the scope of the question we're answering and there's the scope of the literature review if you will address that.

Man: Yea, that's what I was wanting to do.

Woman: And there is a lot and this is a resource intensive question. I mean that there is that when we look at the resources used for this by the State of Washington. It makes a big difference. This is my question, does it make a big difference financially?

Man: Fiscal impact.

Woman: Physical impact.

Man: Fiscal, fiscal impact.

Man: I don't know the cost, I don't know the exact fiscal impact. I know the current policy within our Medicaid program is unilateral is covered under some circumstances for people under 21. Bilateral is currently not covered. That's the situation we have right now.

Man: Yea, they're very expensive.

Man: So wouldn't, I mean if you…

Man: Cost, safety, and efficacy are all in question.

Group: Yea, right.

Man: I mean if you started thinking cost though, I guess you'd get in these bigger pictures of sort of you know if you're saying is it worth the money to give somebody another implant, not just to make them happy or to make them function better you get into employment. I mean that's where you have to factor employment, insurance status, all that stuff that they never make it off of Medicaid, they're a lot more expensive. If they make it off of Medicaid and get a job then they're a lot less

expensive. I mean how you, but this gets into looking at what happens to them when they're an adult.

Man: We'll see this when we look at cost effectiveness data which a lot of which comes from Great Britain you know where they have nationalized healthcare. Because a lot of the cost outcomes outcome have to do with educational costs of dealing with children who are more expensive to educate. But we'll, if we do cost effectiveness if we look at these cost effectiveness studies which we will, a lot of that data has come out.

Woman: Has come out?

Man: Will come out. I mean there's a lot of data on that. And we'll see NICE has determined, NICE has determinations on what their recommendations are for children. We'll see all that stuff so. So it's expensive but they might argue it's about saying I mean we'll see all that stuff.

Man: I was just going to ask as well I mean if we're looking at cost as a thing given that we're including the unilateral cochlear implantation plus acoustic hearing aid, knowing what the lifetime cost of a hearing aid. I mean I assume that would be there, but I just want to make sure that it is there. Because again, they're expensive to replace. They get lost, you know broken, etc.

Woman: Do cochlear implants need to get replaced ever? Or is it once it's in it's done?

Man: No, there's a failure rate. You know they can last a lifetime, but generally you know the thinking is that if you implant a child who's one year's old when you implant them that their likely going to need two revisions through their lifetime so. You know if you estimate a lifetime of the device of 25 years. It can be a lot less than that or it can be more, but the technology really has only been around for 30 something. We don't know.

Man: Are there other key question issues, I mean are there other questions besides cochlear implant that are currently.

Man: No.

Woman: And we are going to have adults.

Woman: We'll have data from adults.

Man: Data from adults.

Man: We're not, the decision won't affect adults, but we'll have data from adults that will allow us to make the decision.

Man: The decision may affect adults. I mean it depends on your decision. I think the scope includes we're going to change the population to include adults. So the situation is when bilateral should be. It may not be applicable in all agencies. So would that.

Woman: With that population is everyone. Older adults, adults, young adults, children.

Woman: Right now, Washington Medicaid does not have a hearing benefit for adults. So we do not cover hearing aids, BAHAs, or cochlear implants for anyone older than age 21.

Man: One question I had, you may have, I was not here when you started, but what we're doing is we're comparing single versus bilateral. That's it. Is there any other technology that really is you know in a clinical spectrum for options to people we should be looking at. In other words, is there a second tier of therapy that is relevant? No?

Woman: Well actually there's another comparator. It's unilateral only, unilateral with hearing aids, and bilateral.

Man: There's no other technology. I mean these are for people that are deaf and cochlear implants are really the only intervention that offers any change in their outcome.

Man: Are there any safety indications? So I know with vision it's sterioptic vision.

Man: Again, we'll get there. We don't need to answer the question today. We just need to make sure we have the information to answer the question.

Man: So I have some notes, I'll incorporate these notes. If you have other suggestions, we have a two week period.

Craig Blackmore: Thank you all.

Man: Thank you.

Craig Blackmore: We're adjourned.

Man: Josh, did they include adults or not? Because I think it's important to realize that the benefit in Medicaid for these hearing, not just cochlear implants, but all this stuff was cut when the dental benefit was cut. It was a budget issue. And so I do think it's important for the committee to realize that that's how it happened, that's what happens so the question I have is do you really want to look at adults.

Craig Blackmore: So I already adjourned the meeting. I already adjourned the meeting. We are not official. We shouldn't talk about this. But everybody has the opportunity to provide further input on the key questions.