Washington State Health Care Authority

Copies of this audio recording are available by request to HTA.

Health Technology Clinical Committee Public Meeting

November 16, 2018

Josh Morse: So, some background on the HTA program. The Health Technology Assessment program is administered under the Washington State Health Care Authority. This was created in 2006 by legislation that designed this program to use evidence reports and this panel of clinicians to make coverage decisions for selected medical procedures and tests based on the evidence of their safety, efficacy, or effectiveness, and cost-effectiveness or value. The agencies that participate in this program, the State agencies, include the Health Care Authority, which manages the Uniform Medical Plan for State employees and retirees, and the State Medicaid Plan, also known as Apple Health, the Department of Labor and Industries, and the Department of Corrections.

So, the goal of the program and the committee and this process is to ensure that medical treatments, devices, and services paid for with State healthcare dollars are safe and proven to work.

We go through a process that is mapped out here of nomination and selection of topics. The Health Care Authority director, Sue Birch, has the authority to select topic for review. Once technologies are reviewed, key questions are developed to address the policy questions asked by the agencies. A technology assessment center, or a TAC, helps us develop the draft key questions and then develops an evidence report. The report is then published and brought to the committee for review here. The Health Technology Clinical Committee makes a coverage determination and ultimately the agencies are charged with implementing these decisions.

So, after the meeting today, in January, there are two topics scheduled, sacroiliac joint fusion and peripheral nerve ablation for limb pain. In May, the scheduled topic is proton beam therapy, and that is also a re-review. We do not have other topics scheduled for next fall, for next year.

So, there are many ways to participate in the Health Technology Assessment program and this program. Our webpage is shown here on

this slide. Anyone can sign up through the Health Care Authority webpages for program notifications by email. Anyone may provide comment on proposed topics, key questions, draft and final reports, and draft decisions, and at the public meetings, and anyone may nominate technologies for review or update, or re-review. Thank you, very much.

Gregory Brown: OK. Thank you, Josh. Next topic is our previous meetings and business. The minutes are in your folder. Any additions or clarifications or edits?

Male: Motion to approve.

Gregory Brown: Second?

Laurie Mischley: This is Laurie. I second.

Gregory Brown: OK. All in favor, say aye.

Group: Aye.

Gregory Brown: Any opposed? That was approved unanimously. OK. And, since we . . . July we reviewed our decisions from our main meeting from last year. We have a retreat in September. So, we have no new decisions to review. So, we will start with our tumor treating fields. Who is presenting today for the agency?

While we're waiting for a minute, do we want to talk about that other topic that we're putting out?

Josh Morse: Sure, talk about the end of the meeting business now?

Gregory Brown: Yeah.

Josh Morse: OK.

Gregory Brown: We'll just fill that in.

Josh Morse: Great

Gregory Brown: Make use of our time.

Josh Morse: So, in the back of your binders, you should have . . .

Gregory Brown: For technology review or re-review.

Josh Morse: Yes, two petitions. These are . . . so to remind you about process, anyone may nominate topics for re-review. And we have received two petitions, we have a form on our website. We have State administrative rules that guide this process. And we have two submissions for a petition for re-review of the stereotactic radiation surgery and stereotactic body radiation therapy, specific to, I believe, for both of these, for prostate cancer. This is . . . these are the second and third petitions that we have received on this topic in the past I think 18 months. The first one we brought to you and it was determined that it was not ready for a re-review. The second two, because we have two in a relatively short timeframe and because there is a significant volume of literature to consider, we have assigned the topic to determine what new literature is there to one of our technology assessment centers. So, we sent these petitions to the Center for Evidence Based Policy. They are conducting a signal search is the term for it. It's basically an update literature search with more rigor than we can provide with staff support in the agency. We anticipate having that report back from the center in December to help us determine what the quantity, quality, and meaning of any new publications, since the original decision has become available, and then we can bring that back to you, but our . . . we are obliged by the administrative rules to provide you these copies for your consultation on whether this topic should be selected for a re-review. Does that make sense? Do you have any questions about this?

Gregory Brown: So, basically, there's no action from us right now. We're simply letting you know we received the petitions and, as Josh said, just for transparency purposes, we have one of the evidence contractors reviewing the literature. And then, they'll report back, and we can look at that report then make a recommendation, which, ultimately, the director of Health Care Authority will make the final decision as to whether it's a re-review topic.

Josh Morse: Yeah. The director, um, has the authority to select for re-review. The process does allow somebody to petition you directly for . . . if the director were to say no, she doesn't think it's ready for re-review, you could . . . a person could then petition you directly. And you would then have the ability to select it. So, rather than go through that, we want you to know, we want you to consult with the director basically and let us know what you think.

Male: When we get the product of the re-review in December, will be discussing it in January, or will it go to the director and . . .

Josh Morse: Yeah. We'll ask you in January, after we get that report what your thoughts are on whether the new information could change the previous policy.

Male: Can you share it with us online before the meeting so we can . . .

Josh Morse: We'll distribute it when we get it.

Male: OK.

Josh Morse: And we'll publish it on the, on the website, as well.

Male: Thank you.

Josh Morse: So anybody can have it.

Gregory Brown: OK. And, uh, whenever we're ready. Actually, I'm sorry. I've also been remiss. We usually go around the table and introduce ourselves. I did at the beginning. I do want to introduce Dr. Jason Rockhill who is the radiation therapist at the University of Washington. Welcome. Thanks for taking the time and participating and being our expert for this topic.

Shana Johnson: Good morning. I apologize for holding things up.

Gregory Brown: You didn't. We did something we needed to get done.

Shana Johnson: OK. Fantastic. OK. So, I am Shana Johnson. And I am one of the physicians of the Health Care Authority. My background training is as a physical medicine and rehab doctor, but I have certainly cared for many glioblastoma patients on acute inpatient rehab service. So, these patients are a bit near and dear to my heart. Alright, so jumping into things. This topic was last reviewed in 2016. At that time, it was determined to be not covered. We elected to re-review this topic for multiple reasons. There has been some new papers published. There has been Society guidelines, particularly the NCCN that's been updated. And in addition, we had stakeholder input requesting us look into this.

In regards to agency concerns, our concerns for safety are low. Our concerns for the level of efficacy and the level of cost are high.

Our current State agency policies, each agency has implemented the 2016 decision, as decided by the Health Technology Clinical Committee.

In regards to other payers coverage policies, it's fairly uniform across private payers in regards to new diagnosis is covered. There is kind of a split in regards to coverage of recurrent glioblastoma with roughly the payers covering that and half not.

Interestingly, the guidelines are also somewhat split. The NCCN guideline recommend tumor-treating fields as an adjunctive treatment for patients with good functional status with a Category 1 recommendation. They also recommended for recurrent with a lower level of evidence recommendation. NICE, however, does not recommend the use of tumor treating fields and in the report, it was cited as not an efficient use of resources.

So, the next part of this presentation, I just wanted to pull out some of the key evidence that brought us to our agency medical director's recommendation. So, I think it's fair to say that one of the strongest studies in the report was the 2000 study from the Journal of the American Medical Association looking at tumor treating fields in glioblastoma. On my review of a very well done study, I didn't see any significant flaws in their methodology that made me question the validity of their conclusions. When we look at the Kaplan-Meier curves for the patients included in the final analysis, accumulative probability of survival is on the Y-axis. And the timing loss is on the X-axis. The primary outcome of medium progression survival was 6.7 months in a treatment group and four months in the control group with a significant hazard ratio. The secondary outcome was median overall survival, which was 20.9 months in the treatment group and 16 months in the control group, also with a significant hazard ratio.

To get a broader view of the effects, we also looked at the annual survival rates, and the probably estimation of survival based on the Kaplan-Meier curve. Progression free probability at six months was 56 in the treatment group versus 37 in the control group, which was statistically significant and I would say clinically significant, as well. The probability of annualized survival at years two, three, and five were also significant. You see here two at 43 versus 31, year three 26 versus 16.

However, when we look at the annualized survival rates, one of the things that occurs in my mind is the quality of life when you're living with a progressing glioblastoma. They did try to study that quality of life questionnaires; however, the dropout rate for the completion of the questionnaires was anywhere between 50% and 2/3 of the population. So, I think it's fair to say there's too much missing data to really draw any valid conclusions on the quality of life and there is high bias that the people who did better completed the questionnaire.

So, for newly glioblastoma, there is increased progression free survival as a primary outcome. Some might argue a small magnitude of effect when you're looking at the median. Looking at progression free survival at six months of 56 versus 37, I think that's a little bit more impressive. In

regards to quality of life with treatment, which I think was the topic of the 2018 paper that was studied, the percent of dropout on completion of the questionnaire was extremely high. I really don't think that data is valid enough to draw conclusions. Tumor treating fields did have minimal harm. With this technology particularly, cost-effectiveness has been a big point of interest. There was a, what our vendor thought was a fairly well done cost-effectiveness study done in 2016 where the incremental cost-effectiveness ratio was $800,000 per life year gained. They estimated the cost reduction from the price of $27,000 would have to be reduced to $2700 for an ICER of $97,000.

So, we also looked closely at recurrent glioblastoma. For this diagnosis, I thought the quality of evidence towards this was particularly poor in my view. The findings of the study was that there was no significant survival time set between groups. And they used that as a basis to claim noninferiority. However, the study was designed and statistically analyzed for superiority. Based on the median overall survival in this group, which was very low, and the use of various chemotherapeutic agents in the control group, you could also claim that it is unclear. The lack of difference between groups simply reflected that neither treatment was very effective. In addition, this study with the quality of life of data that was reported, of all the patients in the study, only 27% actually completed the questionnaire. So, again, I thought the dropout rate was too high to assess quality of life.

It was also interesting in this study that only 79 of the 120 patients completed one course of the tumor treating fields. That level of dropout rate from the treatment group seemed to be correct in the second study, as their completion rate . . . compliance rate was much higher.

So, these are probably the two key studies that most strongly swayed our opinion. There were some studies . . . there was a study, in particular, that compared the treatment group to a historical control, which had some pretty fantastic results that I think it's telling when you improved the quality of the trial, how much those results are reduced and how biased that study was and why it's . . . I don't know that it's valid to compare against the historical control, because you bias so strongly toward the intervention. And I thought these studies really demonstrate that point well. I know that's been a back and forth between stakeholders with us in the past when they've done a study like that, that shows an effect and we don't feel that that's adequate quality.

Our agency recommendations are cover with conditions. Our conditions draw strongly from the 2017 study, and I'd be very interested in our

oncology expert's opinion on whether . . . how appropriate these parameters are, as far as how specifically to generalize from the paper to a medical policy. So, what our group recommended was tumor treating fields be covered with conditions for those with a new diagnosis of supratentorial glioblastoma and a histologically confirmed diagnosis followed debulking or a biopsy, radiation therapy, and initial course of standard chemo, that it be given with maintenance chemotherapy. And due to the poor prognosis and aggressive nature of this disease, that it be done in the setting of shared decision making so the patients have a clear understanding of what decision they're making. For exclusion and discontinuation criteria, we recommend that it be discontinued when the MRI and clinical findings support progression. When there is poor functional status below a KPS score of 70, infratentorial location of the lesion, and if there is evidence of progression at the end of radiation and chemo for a poor prognosis patient. Then, for recurrent glioblastoma and other malignancies, we recommend a noncoverage decision.

So, with that, I'll open it up to any questions.

Gregory Brown: So, the two randomized control trials, did they have a sham, or were they . . .

Shana Johnson: They did not have a sham. They were open labeled; however, the outcome assessment was a blinded radiologic assessment of the MRI.

John Bramhall: Dr. Johnson, can I ask how . . . so if the, if your suggestion, if your recommendation was to stop the treatment on evidence of disease progression, if that were the case, how does that effect the cost of the treatment? What I'm really asking is, is this treatment an upfront cost, which then disregards the duration or is it priced per month, per week?

Shana Johnson: My understanding is it's priced monthly. I'm open to anyone who knows better.

John Bramhall: So, your cost, if you will, to be involved in the costing analysis then, you'd be advocating a period of time, which looks like it would be about six months on average, you know, loosely six months of treatment, and then perhaps curtailing the treatment when MRI showed progression. And that would have an associated cost per month. Is that correct?

Shana Johnson: Mm-hmm.

John Bramhall: And do we have a feeling for what that per month is?

Shana Johnson: Well, so the company has its cost, but then on rate setting within Medicaid and L&I and contracting may be a whole other piece of it. So, I don't know that we necessarily pay the sticker price.

John Bramhall: OK. Thank you.

Mika Sinanan: Hi, Mika Sinanan. In the 2017 study, I'm really asking about your proposal to discontinue when MR and clinical findings support progression. Is that what they did? Is that the cur-, the standard of management that was actually studied in the 2017 study? Or did they keep treating people even if they showed progression?

Shana Johnson: Well, they also studied overall survival. So, wait. Let me go back so I'm answering the same question. So, if they showed progression between, like, their surgery and their first course of chemo, then they were removed from the study. However, once they were in the study, if they were progressing, they were studying overall survival. So, they were kept in.

Mika Sinanan: Kept in the study and treated? I mean, they continued to receive the same treatment?

Shana Johnson: I think so. There was crossover at some point where the control group, there was a significant percent of patients that crossed over to the tumor treating fields group, 'cuz they were progressing. However, they analyzed them as though they were in the control group to prevent bias in the study. Yeah. I think that's a good question. I'd be curious as to the oncologist on his opinion on the criteria, as well.

Jason Rockhill: So, this is Jason Rockhill. And one of the challenges in the treatment of GBM's is monitoring response to treatment. It is well known that after patients get radiation and chemotherapy that there is about a 40 to 50% pseudo progression rate where the imaging will look like progression, but it actually is a treatment effect. So, a lot of individuals are concerned about looking at progression free survival, because of the confounding factor about whether it's true progression or just pseudo progression due to imaging changes. It also will make a difference, in terms of how long therapy is continued, because oftentimes we're always stuck with that question of, is it true progression versus pseudo progression?

Shana Johnson: And does it often take, like, a month for the MRI to stabilize between surgery and radiation and steroids?

Jason Rockhill: It can take even longer than that. Patrick Glenn [sounds like] has a paper showing pseudo progression taking up to eight months showing a response.

Shana Johnson: Whoa, that's, wow. That's very telling.

Jason Rockhill: Yeah.

John Bramhall: So, what's this, what is the rationale for discontinuing of there is disease progression?

Jason Rockhill: So, that's the challenge in saying whether it's effective or not. The trend seems to be that the longer people are using this, the more of a response they saw, but you could also say that's also just better disease. So, you have a confounding factor there.

John Bramhall: Sorry, not to take, but, so I mean, it's sort of unconventional in general therapeutics to just stop the therapy when it seems like things are not progressing the way that you had hoped. I mean, is that a fair statement? I, I'm not quite sure that I understand why you wouldn't just carry on the treatment and . . .

Shana Johnson: I think . . . and Dr. Rockhill, I'll really need your help on this, but, from the cancer cases I look at, it appears that many of the therapeutic agents are stopped or switched upon progression happening. So, that is the standard in cancer care. I think.

Jason Rockhill: Yes. So, oftentimes, we will switch treatment. And that's one of the challenges in brain tumors is that you have this confounding pseudo progression as a treatment effect. Do you go from what's best available therapy to second, third, or fourth line agents, all of which have limited proof of efficacy but are used very, very routinely. So, we do end up with this challenge often of do we really think it's working? Do we want to continue and see if we can ride this out? Or do you switch and go to a second or third line agent that you know if going to be less effective. I hope that addresses . . .

Shana Johnson: And I think there is a big challenge, as far as in our . . . the current state of our healthcare system. Some of the value propositions of how things are being priced, the $27,000 a month price on . . . its price is far disproportionate to the perceived value it brings to the patient. I know we're seeing this more and more, but I think in this technology's particular case, it's kind of the elephant in the room.

Mika Sinanan: I had the question about exactly that issue. Is underlying all of this the fact that this is a terrible disease with very few options for treatment, which is one reason that anything is grabbed onto if it shows any benefit and highlighted, and why you can charge a lot, because there are very options. Is that . . . that's the under- . . . kind of an expansion of the elephant in the room.

Shana Johnson: It is with the avid note that, I think, and someone correct me if I'm wrong, but I think when it comes to looking at costs per QALY and stuff, this one is at a whole other level compared to . . . because there's kind of a standard acceptance that you pay a lot in a severe disease and a bad prognosis. You pay more, right, for everything you said, but I think this one, the pricing is even a level beyond that.

Gregory Brown: You had said cost per QALY, but my understanding . . .

Shana Johnson: You're right.

Gregory Brown: . . . analysis was life/year not quality adjusted . . .

Shana Johnson: Correct.

Gregory Brown: . . . life year. So, if you had a 10% improvement in your quality of life, your cost per QALY would actually be 8.2 million dollars.

Mika Sinanan: Fun times.

Gregory Brown: Franklin?

Gary Franklin: I can't even imagine [inaudible].

Josh Morse: Microphone please? Thank you.

Gary Franklin: The Stupp Study, they only started using tumor treating fields after radiation and after the initial chemotherapy. I think the average was, they didn't start treatment until four months or something after the diagnosis. And if there was any progression at that four-month period, they were excluded. So, the point about confusion progression from treatment or whatever, if they were progressing at that point, at the initiation of the study, they were excluded.

Chris Hearne: Sorry, but with the proviso that we just heard about pseudo progression, they're including up to 50% of pseudo progression if, if it's an absolute determination. I mean, if they say, if there's any enlargement or any

increase in size, half of those, up to half of those could be pseudo progression. Right? So, they're excluding potentially 50% who might actually be getting a good benefit from the treatment, the prior treatment, theoretically. Is that right?

Shana Johnson: That's how I interpret that. I think that creates a problem, because that's primarily how they assess progression was radiologically.

Chris Hearne: Can you talk a little bit about the quality of life in the . . . during the course of treatment? I'm especially commenting or thinking about the number of people who didn't fill out the survey questionnaires who dropped off.

Jason Rockhill: So, I think quality of life is something we're really challenged with in brain tumors, because oftentimes, you're getting it from caregivers, because individuals may have speech difficulties. If it's a form, filling out forms are all gonna be a challenge to completing that and getting that data. Plus, there's just the fatigue component. People just don't have the energy to fill out a lot of forms. So, I think it's really challenging to get quality . . . good quality of life data in brain tumor patients.

Shana Johnson: Dr. Rockhill, would you say, at all, I mean, my experience on the rehab unit was the patients that I saw with glioblastoma, I would not say had high quality of life. I saw a lot of suffering. It's one of the saddest diagnoses on my unit. And I see everything. So, that's another piece to this. Like, we're prolonging life, but what type of life are we prolonging when a quarter of your, anyway.

Jason Rockhill: So, and a lot of these individuals where there's not a screening test, the way it was found is that they had a significant neurological deficit. So, they could be completely functional. Then, a month later, they're hemiparetic, can't talk. So, I think anybody would say your quality of life has changed dramatically.

Gregory Brown: I think we need to progress. Thank you, so much. We are ready for scheduled comments. We have one person that's.

Josh Morse: Yes. We have one person signed up for comments in advance, and that is Justin Kelly.

Gregory Brown: So, it's our custom that as you introduce yourself, also identify if you have any conflicts related to the topic.

Justin Kelly: Great. Good morning, everybody. My name is Justin Kelly. I'm the regional vice president of health policy for Novocure. So, I work for the

manufacturer of Optune. I'm here today to ask the Washington State Health Care Authority to grant coverage of tumor treating fields therapy for appropriate patients diagnosed with glioblastoma multiforme, an aggressive brain cancer with few proven treatment options. Optune is the device name. It's a portable medical device that delivers alternating electric fields or tumor treating fields to the brain. The device consists of an electric field generator, which is battery powered, and it's connected to four in-plated transducer arrays. These arrays are placed with specific positioning on the patient's scalp and deliver tumor treating fields therapy from the electric field generator to the brain. The tumor treating fields disrupt the formation of the mitotic spindle in a dividing cancer cell, which leads to programmed cell death or apoptosis. Optune is FDA approved for both recurrent and newly diagnosed glioblastoma brain tumors and was approved with a premarket approval pathway. The most stringent device approval pathway available by the FDA. As Dr. Johnson mentioned, Optune is included in the National Comprehensive Cancer Network guidelines with a consensus 2B recommendation for recurrent glioblastoma as a monotherapy and a category 1 uniform consensus recommendation for newly diagnosed glioblastoma in combination with temozolomide chemotherapy. Optune is covered by almost every commercial insurance company in the United States, including every major commercial payer in Washington State. The therapy is also covered by positive coverage policies by multiple State Medicaid programs, including California and Oregon. In terms of the Health Technology Assessment, our primary concern was the potential bias concerns that were raised by the authors. I'd like to speak briefly on this topic, as we disagree with that assessment. The EF14 trial study design was similar to radiation therapy trials, which were also open label, and no sham treatment was given to the control arms. A sham-controlled study was discussed with the FDA and clinical investigators. The FDA did not require placebo as a condition for the trial to be accepted for consideration of approval. The investigators decided that it was 'practically infeasible given the heat and easy to measure current associated with Optune, as well as ethically unacceptable to expose patients to a sham device. Moreover, as Hoethinger [sounds like] et al noted, requiring a placebo or sham device would also mean a paradigm shift in conducting clinical trials with survival endpoints in oncology. Although placebo effect can influence subjective endpoints, such as quality of life measures, objective endpoints such as a blinded central radiologic review, and overall survival are independent of placebo effects in cancer treatment. The magnitude of the effect size in these objective endpoints far exceeds anything that could be attributed to placebo effect. Additionally, we do have some concerns with the one cost-effectiveness publication that is available. Particularly, the monthly cost amount used in the study is thousands higher than our list price and

doesn't consider any of the discounts, contracted rates that we have with insurance companies. Lastly, regarding health economics, there is an upcoming study about to be published by a health economist at University of Washington, which will provide additional information on this topic, but unfortunately given publication times and the date of this meeting, we . . . that isn't available at this time. In closing, we appreciate the opportunity to be here today to ask for favorable coverage position for tumor treating fields with Optune. Optune is a proven technology that extends both overall survival and progression free survival in patients with newly-diagnosed glioblastoma and recurrent glioblastoma. Optune provide comparable benefits to physician choice chemotherapy without the toxic side effects. Glioblastoma is a rare disease, which we estimate impacts just over 60 patients covered under the Washington State Health Care Authority each year. Given the significant extension and overall survival in patients with newly diagnosed glioblastoma, we respectfully request that you grant coverage for appropriate patients.

Laurie Mischley: Can I ask you a quick question?

Justin Kelly: Sure.

Laurie Mischley: You say that it's not nearly as much as what the 27,000 number, but can you give us a ballpark?

Justin Kelly: So, the device is classified as durable medical equipment requiring frequent and substantial servicing. So, the way CMS categorized this. We fall in the same benefit category as, like, a apnea monitor, a home ventilator. So, all the costs and supplies, the home visits and the service that we provide are all bundled under one cost per month. So, it's all a bundled payment. Our list price is $21,00 per month, and we contract with insurance companies and negotiate off of that.

Gregory Brown: So, the number is?

Justin Kelly: $21,000 per month is our list price.

Gregory Brown: OK. So, that doesn't include any professional fees to provide . . .

Justin Kelly: So, with durable . . .

Gregory Brown: . . . that [crosstalk].

Justin Kelly: . . . medical equipment, it's typically, you know, when you're looking at the physician office visits would be per standard of care. Patients are typically

seen every month to assess the skin irritation underneath the transducer arrays. Then, bimonthly, per standard of care, they typically get an MRI whether they are getting chemotherapy, Optune, or any other intervention to assess response to treatment.

Mika Sinanan: You quoted us 60 patients a year. Is that right?

Justin Kelly: Yes.

Mika Sinanan: And how many of those are recurrent and how many are new? Do you know?

Justin Kelly: We based it off of the incidence rate. I think it was 3.14 per 100,000 patients, but that's both new and recurrent.

Mika Sinanan: That would be newly diagnosed.

Justin Kelly: I mean, the life expectancy for these patients is about 12 to 15 months, and obviously, you're going to have patients that do better than that and patients that do less.

Gregory Brown: Thank you.

Justin Kelly: Thank you.

Gregory Brown: I see nobody else on the list here to speak. Are we on the, OK. This is Gregory Brown, chair of the Health Technology Clinical Committee. We are checking the line to see if anybody is on, would like to make a public comment. And we are unmuted? OK. I am not hearing anybody. So, OK. I think we are then ready to proceed to our evidence report.

Rachel Weber: Good morning. I'm Rachel Weber. I am the program manager for the RTI-UNC Evidence-Based Practice Center in North Carolina. With me today is Rachel Clark, our research analyst on the project. I also want to acknowledge Karen Crotty, co-investigator on the project, and Leila Kahwati, our scientific reviewer. Just a brief background on my training, I'm an epidemiologist by training and have been working with the EPC for about four years now. I'll skip over the overview.

So, as you've heard today, glioblastoma is a rare cancer. It is considered a high-grade glioma, astrocytic in origin and most commonly presents in the supratentorial region of the brain. From 2006 to 2010, the age-adjusted incidence rate of glioblastoma in the United States was 3.19 per 100,000 persons. The median age at diagnosis is 64 years of age. Rates are higher

among males than females. This is a highly-aggressive disease with a very poor prognosis. Less than 5% of all patients will survive five years after diagnosis, and the median survival is 14 to 15 months. If patients go untreated for the disease, median survival is only about three months.

For newly diagnosed glioblastoma, the standard of care is surgical resection followed by six weeks of radiotherapy with concomitant chemotherapy, temozolomide. There is a minimum of six month's chemotherapy after that. For recurrent glioblastoma, there is no current standard of care. Surgery, additional surgery is fairly rare, as is additional radiation. So, the majority of the patients will undergo chemotherapy, and it is usually in combination with bevacizumab, an angiogenesis inhibitor.

So, this technology comes from the field of physics. It's a novel therapy for the treatment of cancer. It's a noninvasive treatment. Tumor treating fields are alternating electric fields that enter the cancer cell and disrupt the mitotic spindle microtubule assembly, which eventually will disrupt cell division of the cancer cells, resulting in cancer cell death. Tumor treating fields are externally delivered, and they are a very low intensity and intermediate frequency, and the exact frequency is determined by the size of the particular cancer cells. So, the frequency for glioblastoma is 200 kHz. I believe that's also the same frequency for the treatment of ovarian cancer, and it varies by other cancer cells. Normal cells are not affected by this treatment. So, the treatment deliver the alternating electric fields. It affects the cancer cells, ultimately resulting in cancer cell death, and it essentially leaves normal cells alone.

This treatment, all of these things were shown in animal models and human cancer cell wise, and they were shown to arrest cell proliferation, destroy cancer cells, and impair growth of the tumor.

So, Optune previously referred to as the Novo TTF100A system or Novocure. It's been referred to as multiple things in the literature over time, is the system that delivers these tumor treating fields. The Optune is portable and operated by the patient. The tumor treating fields are delivered through transducer arrays. They are insulted ceramic discs that are positioned on, for glioblastoma, a shaved scalp, based on the tumor location and the size of the tumor. There is a software, NovoTAL that uses recent MRI images to determine the optimal placement of the transducer arrays. With this software, it can use the most recent MRI images. So, if there are changes over time, this software can help pinpoint where the transducer arrays should be placed. There is no half-life for this treatment. So, it requires continuous application. It's not like a systemic therapy, like, chemotherapy. It is recommended that the patient wears the Optune

device for at least 18 hours a day. Novocure recommends that a minimum duration of four weeks of treatment, and it's portable. When a patient is prescribed Optune, paperwork is sent to Novocure, and a Novocure specialist can come and set up the device for the patient. The patient does not have to return to the physician for repeated . . . for changes to the placement of the transducer arrays. They are taught how to place the transducer arrays. It is recommended that they remove those arrays at least twice a week so that they can clean the scalp and re-shave so that there's optimal placement of the transducer arrays.

Tumor treating fields were approved for the treatment of recurrent glioblastoma based on evidence from the EF11 trial. This is FDA approval in April of 2011. It was indicated to be used as monotherapy. The approval came based on similar efficacy between the tumor treating fields and other treatments, improved quality of life and reduced adverse events. The FDA then approved the use of tumor treating fields for newly diagnosed glioblastoma in October of 2015 based on the interim results of the EF14 trial that showed an increased efficacy of the treatment and the requirement is that tumor treating fields be used concomitant with temozolomide. Based on the prior 2015 report, the State of Washington's Health Technology Clinical Committee voted to not cover Optune and the topic was selected for re-review based on newly available published evidence, and it was rated low concerns for safety and high concerns related to efficacy and costs.

Up here, we have our analytic framework for this review. Essentially, we asked three key research questions. What is the clinical effectiveness of tumor treating fields? What are the harms associated with tumor treating fields? What are the costs and cost-effectiveness of tumor treating fields? For the efficacy and the safety questions, we also asked if the efficacy and the safety were different among subgroups, usually defined by patient characteristics, such as age and functional status at baseline, but we looked at a number of different subgroups. Unfortunately, the studies that we've included in this report were not powered for subgroup analyses. So, all of those analyses were post-hoc. And really, any of the results that came out of the subgroup analyses should be considered as hypothesis generating. The full details of all the subgroup analyses are in the report. I'm not going to focus on those today. I do have a couple of slides prepared if you're interested, but all the details are in the report.

So, based on . . . we based our inclusion for this review on a number of factors. Studies have to includes adults or children with a confirmed diagnosis of incident or recurrent glioblastoma or other cancer. So, we did not limit by age of the patient. We evaluated studies in which at least one

of the groups received tumor treatment fields with or without an additional therapy. We did not exclude based on comparator, especially for recurrent glioblastoma. There are a number of different second line, second, third, fourth line chemotherapy agents. So, we did not exclude on comparator. The outcomes that we studied for efficacy, we looked at overall survival, progression free survival, quality of life and functional status as defined by validated measurements. For the safety question, we looked at serious adverse events, other adverse events, and we paid particular attention to dermatologic adverse events. For the cost question, we looked at costs and cost-effectiveness.

We included studies with a comparator group for the efficacy question. So, controlled clinical trials or cohort studies with a historical or concurrent comparator group. For the safety question, we also included studies without a comparator group. So, those essentially were just case series in the report. Then, for the cost question, we included cost-effectiveness analyses. All these studies were conducted in countries that were rated as very high on the United Nations Human Development Index. A note about study designs, we included primary studies. We did not include other systematic reviews or health technology assessments, but we did hand search all of those that we identified in our search to ensure that we had all of the primary research studies relevant to these questions.

At the level of the study, we rated risk of bias, sometimes thought of as a study quality, and we only did this for studies with comparator groups. So, this is for all studies included in the efficacy question and studies included for the safety question that did have comparator groups, and for the cost-effectiveness analysis, we graded quality using the quality of health economic studies instrument. For risk of bias, the terminology that we'll use is low risk of bias, some concerns for bias, and high risk of bias. For the quality of the cost-effectiveness studies, it's good, fair, and poor.

So, where we rate the quality and risk of bias at the study level, we graded the strength of the evidence as a whole for the different research questions. When we grade the strength of evidence, we have to stratify by a couple of factors. One is study design. So, we grade the strength of evidence among randomized trials and separately we grade the strength of evidence among observational studies. We do not include any studies without a comparator group in our grading of the strength of evidence. The strength of evidence ratings range from very low to high. In this body of literature, all of our strength of evidence ratings were low or very low. The domains assessed in the strength of evidence grade are risk of bias, consistency of . . . in terms of the direction and magnitude of effect of the treatment, the directness of the research question, precision of the effect

estimates, and publication bias. Bodies of trail evidence start at a high strength of evidence and then are downgraded based on factors related to those domains. Observational studies start at a low strength of evidence. Again, those can be downgraded for the same issues related to the domains of interest. Observational studies can also be upgraded for things like a large effect estimate, a dose response, or proper control confounding.

So, in addition to stratifying our strength of evidence ratings by study design, we also stratified by the indication for treatment. So, newly diagnosed glioblastoma and recurrent glioblastoma. And we also stratified by the particular comparison being made, and I'll go over that when I get into the results.

So, we searched the Medline and Cochran databases from inception to mid-June of this year. We identified 423 title and abstracts to screen. We dully screened the title and abstracts for inclusion and then any that were moved forward, we dully reviewed the full text. After that process, we included 11 studies that were described in 15 articles. The two randomized clinical trials had multiple articles related to their trial.

For newly diagnosed glioblastoma, we included two studies each for the efficacy and safety questions and one for the cost-effectiveness question. For recurrent GBM, we included four studies that answered the efficacy question, five that answered the safety question, and none that answered the cost question. For other cancers, we only included three studies that answered the safety question.

So, I'll talk briefly about the differences between this report and the prior report. In terms of newly diagnosed glioblastoma, in this report, we have included the final published results from the EF-14 trial. The prior report included the interim results. They are very similar on the interim and the final results. We have a new cost-effectiveness analysis for newly diagnosed glioblastoma that were not included in the prior report. For recurrent glioblastoma, we have no new trial data since the last report, and we have one new observational study that ends up being an extension of the EF-14 trial, and I'll describe that in a little bit. There were a couple studies in the prior report, small observational studies that we actually excluded based on our criteria. One was really a subgroup analysis of the trial data that didn't have any eligible data, according to our criteria. The other was a chart review of a therapy that we determined was actually not a study looking at specifically tumor treating fields. It just happened to be part of the therapies that they studied. For other cancers, as an indication for tumor treating fields, we included one additional new case series.

So, the strength of evidence comparisons that we made, again, stratified the study design and by indication for treatment for newly diagnosed, we looked at tumor treating fields plus temozolomide compared to temozolomide alone. For recurrent glioblastoma, most of the evidence looks at tumor treating fields compared to second line therapy. There is one study that looked at tumor treating fields plus second line therapy and compared it to second line therapy alone. For other cancers, we only included case series. So, there are no comparator groups, and we did not grade strength of evidence.

So, first I will point out, we have a bit of a color coding through this report and through the presentation here, just to help you orient yourselves. Purple is related to newly diagnosed glioblastoma. Orange is for recurrent glioblastoma. Blue is for the other cancers. So, that's where the colors are coming from today.

So, I want to talk about the newly diagnosed glioblastoma studies. We included one trial, one observational study, and one cost-effectiveness analysis. The trial that we included is the EF-14 trial. It was conducted in 83 centers across the United States, Europe, and some additional countries rated as high human . . . very high human development. We rated it as some concerns for risk of bias for the overall progression free survival outcomes, as well as the safety outcomes, and a high risk of bias for the quality of life outcomes. Again, the intervention compared tumor treating fields plus temozolomide to temozolomide alone. The median age of the patients, they were in their mid-50s. They were high-functioning, according to their Karnofsky Performance Status score. In the meantime, between diagnosis and randomization was a little less than four months. The observational study that we included is a pilot study, meant as a pilot for the EF-14 trial done by some of the save investigators. This is a cohort of ten patients with newly diagnosed glioblastoma. They were compared based on the outcome of interest to either a concurrent comparator group or a historical comparator group. So, the intervention group who received tumor treating fields, there were only ten patients, and the comparator groups were . . . one of them, the historical comparator group, was not really described very well. So, I . . . we don't know the sample size. It was not reported, but the concurrent control group only had 32 patients. The median age of the historical control group was similar. There were 54 . . . the median age was 54 years old. Again, the, uh, these were pretty good functioning patients with higher Karnofsky Performance Status scores. And patients in the intervention group, the ten patients receiving tumor treating fields, were at least four weeks post-radiation therapy when they were assigned to receive tumor treating fields. For this study, they only presented the safety data among the intervention group, the ten patients

receiving tumor treating fields. So, we did not rate risk of bias for that, because there is no comparator group.

We also completed one cost-effectiveness study that was done from the French healthcare payer perspective. They used a Markov chain model analytical approach with hypothetical cohort of 1000 people who were receiving the same treatment as the patients in the EF-14 trial were receiving. They used a lifetime [inaudible], discounted it 4%, and the costs were in 2014 Euros, which we calculated to U.S. dollars. The direct healthcare costs that they included excluded the cost of surgery and concomitant radiotherapy and temozolomide treatment. The effectiveness data, the imports for their models, are from the interim analysis of the EF-14 trial. QALY's were not used for this analysis, because the authors reported that there was a lack of published data on health state utilities associated with glioblastoma.

So, I'm gonna move through the results. First, I'll talk about the survival outcomes. So, for overall survival, we rated the trial evidence as low strength of evidence for benefit with tumor treating fields. The median overall survival was 20.9 months in the group receiving tumor treating fields compared to 16 months among the patients using temozolomide. And that is a statistically-significant hazard ratio, about a five-month survival benefit. And that was over a median 40 months of followup. The observational study, that small pilot study of ten patients receiving tumor treating fields we rated as very low strength of evidence for benefit with tumor treating fields. The direction of affect was consistent with the trials. So, we saw an increased survival with tumor treating fields. The magnitude effect was dramatically different. The median overall survival among those ten patients receiving tumor treating fields was greater than 39 months and the overall survival for those receiving temozolomide in the historical control group was 14.7 months, and that is similar to what we saw in the trial. As noted previous today, this is kind of a dramatic difference in terms of the overall survival. I just want to remind you all that it was among ten patients. The study did not really report descriptors of these patients. So, it's hard to sort of even speculate why they may have seen a much higher overall survival benefit.

Similar to overall survival, we see very similar results for progression free survival. We have low strength of evidence for benefit with tumor treating fields in trial data and very low strength of evidence from evidence from the observational pilot study. Again, the progression free survival among patients receiving tumor treating fields was 6.7 months compared to four among patients in the temozolomide group. Again, that was over a median of 40 months of followup. At six months, 56% of the tumor treating fields

group versus 37% of the temozolomide group were progression free. Again, in the pilot study, we saw similar direction of effect, but a different magnitude of effect. Those ten patients receiving tumor treating fields had a much higher median progression free survival at almost 39 months compared to the 7.8 months in the temozolomide group.

For quality of life, only the trial provided data related to quality of life and functional status outcomes. We rated the strength of evidence based on the trial data as low for a benefit with tumor treating fields. For such a highly aggressive disease with a very high mortality rate, we don't really think of improving quality of life. Really, in this patient population, we kind of framed it as slowing down the progression of a decline in quality of life or maintaining maybe a stable state, in terms of the current quality of life. So, in the trial, the time to stay decline and functional status was significantly longer with the tumor treating fields group. And that was measured by both the Karnofsky Performance Status and the mini mental state examination. Significantly more patients in the tumor treating fields group experienced stable or even sometimes improved global health status, pain, weakness of legs, and physical, cognitive, and emotional functioning, according to the measurement that they used, which was a validated measurement.

For the safety question, again . . .

Gregory Brown: I'm sorry. Can you . . . I'm a little confused. Everywhere in healthcare, we look at QALY's.

Rachel Weber: Mm-hmm.

Gregory Brown: And so, you're saying in cancer, that's not really the measure? It's just life years, irrespective of your quality of life?

Rachel Weber: So, this is just the quality of life that was measured in the trial. Self-reported . . .

Gregory Brown: OK.

Rachel Weber: . . . by the patients.

Gregory Brown: OK.

Rachel Weber: This doesn't factor into the cost-effectiveness analysis.

Gregory Brown: I understand, but I thought I heard you say that in terminal . . . or patients with poor function, we don't really QALY as a measure. Are you just saying . . . are you saying this trial didn't, or are you saying we, as a society, don't?

Rachel Weber: I think for this trial and this body of literature, explaining the quality of life outcomes . . . really, we're looking at a comparison between the groups receiving tumor treating fields or not. So, it's a comparative benefit. So, when we rate the strength of evidence as low or very low as a benefit with tumor treating fields, we're not necessarily saying that tumor treating fields is improving quality of life. It's really more of a less of a decline.

Gregory Brown: Right. So, I guess I view that as a source of bias. In other words, frame the question that you look good at, and not what we normally look at. So, I hear what you're saying. I'm, again, normally when we're looking at any healthcare topic, we look at QALY's, not just life years. Is that correct?

Rachel Weber: I believe so.

Gregory Brown: OK. Thank you.

Jason Rockhill: I would say more and more, we're trying to incorporate quality of life and the EORTC is a validated measure that's being used in numerous kind of brain centric trials.

Seth Schwartz: I'm not sure what that means. I mean, I think if we're doing cost-effectiveness analysis, you're clearly looking at QALY's, but if you're just doing outcomes assessment, we oftentimes do look at quality of life alone. So, I would say that, but my question here is, is there a differential response rate in the, in the tumor treating fields group versus the other group on the quality of life questionnaire? So, we heard that only something like 27% of the patients completed these questionnaires at all. So, is there a . . .

Rachel Weber: Right.

Seth Schwartz: . . . differential response rate in the two groups?

Rachel Weber: So, there were statistically significant differences between the groups, but as you know, we rated these outcomes as high risk of bias, because of the very high attrition rate, in terms of completing these results.

Seth Schwartz: Yeah, but was the attrition rate different in the two groups?

Rachel Weber: I don't think that was reported.

Seth Schwartz: OK. Thank you.

Rachel Weber: So, I'll talk about adverse events. Again, only the trial provided safety data for both the tumor treating fields group and the comparator group. We rate the trial data as low strength of evidence for minimal harm with tumor treating fields. There were mild to moderate dermatologic adverse events reported by more than half of the patients receiving tumor treating fields. The addition of tumor treating fields to temozolomide treatment did not significantly increase the rates of systemic adverse events that are often related to the chemotherapy treatment. So, there were really no serious adverse events or really other adverse events reported that were associated with the tumor treating fields. Really, the adverse events that were reported and related to the tumor treating fields were dermatologic in nature, which really was kind of to be expected. In the pilot study, again, the only reported safety data on the ten patients receiving tumor treating fields, and it was the same story, mild to moderate adverse events not really related to the tumor treating fields and mild to moderate dermatologic events.

Mika Sinanan: So, we heard earlier that a sham study was felt to be not feasible, because the patient could actually tell whether the thing was turned on or not. Is that the dermatologic or do they feel heat, or, I mean, that's not considered a side effect. Is that right?

Rachel Weber: Well, so, they do feel the heat. I think there is a heat. So, they feel that. So, the . . . most of the mild to moderate dermatologic events reported were things like itchiness or mild skin ulcerations associated with the placement of the transducer arrays, and you are correct. The sham study was sort of deemed to be impractical, unfeasible, and unethical. So, these dermatologic events really were attributed to the tumor treating fields therapy.

Gregory Brown: Could you explain the rationale of why they thought it's unethical to do a sham? I'm . . .

Rachel Weber: I believe in an oncology setting, and maybe Dr. Rockhill might be able to speak more to this. I think in an oncology setting, especially with a disease that's so aggressive and with a high mortality rate in glioblastoma, that it was just deemed unethical.

Jason Rockhill: I don't know that this was ever looked at, but I think there was a biasness toward having people have to carry a battery pack around that would be seen as an undue problem to have to shave your head, wear something as a sham device, and carry a battery pack around when you might be dealing

with other neurological deficits. So, I think that's maybe why it was deemed unethical to have more of an intervention than just wearing the device. It's changing outward appearance, changing your lifestyle to manage the battery pack. So, that's how I would interpret it.

Gregory Brown: OK. Thank you.

Sheila Rege: Did the studies, in any way, go to noncompliance in terms of the 18 hours?

Rachel Weber: Yes, and I will talk a little bit about that when I talk about the limitations of the studies. Compliance and adherence were certainly a factor, as was attrition.

So, we have one cost-effectiveness analysis that answered the cost question for patients with newly diagnosed glioblastoma. It was done from the French health payer perspective. The discounted payer perspective incremental cost-effectiveness ratio in 2014 U.S. dollars, again the study is Euros. We calculated to U.S.D., was over $800,000, per life year gained. And as I explained before, they did not use QALY's, because they didn't have enough information from the literature to include that in their analysis. The authors of the study reported that it is a monthly cost for the Optune system and support were reduced essentially by about 90%. The discounted incremental cost-effectiveness ratio would be under $100,000, per life year gained, and that's a typical threshold used in looking at whether something is cost-effective. For comparison, I'm gonna kinda bring us out of glioblastoma and compared to biannual mammography screening. The cost per QALY gained from a societal perspective of biennial mammography among women 50 to 74 years old of average risk for breast cancer ranged from $112,000, to about $214,000, and that's 2010 U.S. dollars. So, we're looking at a much higher ICER for the glioblastoma for the tumor treating fields.

Seth Schwartz: I think, Greg, this is where your comment is applicable, which is that you're not really comparing the same thing, because . . .

Rachel Weber: Right.

Seth Schwartz: . . . QALY's is totally different than simply life years, and you're telling us that there's no estimate for hat the actual slowing of quality of life decrease is in these patients.

Rachel Weber: No.

Seth Schwartz: Do we have any idea of that magnitude? Is it . . .

Rachel Weber: No. We don't.

Seth Schwartz: . . . so we're, so we're . . . it's a total shot in the dark of anything more than . . . so this could be anywhere from $800,000, to $800,000,000, if there's limited benefit. Thank you.

Mika Sinanan: And the dollar values here are costs or what was paid for, because we heard that it's discounted from list price, but we don't know what discount is.

Rachel Weber: The authors . . .

Mika Sinanan: So, it's variable.

Rachel Weber: . . . described it as the direct healthcare cost. So, this is in France where, you know, they're . . .

Mika Sinanan: It's centralized.

Rachel Weber: . . . it's quite different. And I think that factors into some of the limitations of this cost-effectiveness analysis, that it may not be as applicable to the United States setting, but they were reported as direct health costs.

Mika Sinanan: OK. Thank you.

Rachel Weber: I'm gonna shift gears now to recurrent glioblastoma. And this is the first of two comparisons. This is the tumor treating fields group compared to the second line therapy group. We include one trial, two observational studies, and one case series. So, the trial with the EF-11 trial conducted in 28 institutions across the U.S., Europe, and a few other countries. It compared tumor treating fields to the physician's choice of best chemotherapy. The total patient population in the sample size was 237. The median age was 54 years. These were relatively high-functioning patients with a median KPS score of 80. These patients were a median of 11 to 12 months, since their initial glioblastoma diagnosis, and the number of recurrences in this patient population varied, and actually almost half of these patients were at their second recurrence of glioblastoma, and a slightly lower percentage were at their third or higher recurrence of glioblastoma. And I think that the maximum was five recurrences. So, this is a pretty ill population; 80% of the patients in this trial had received prior temozolomide therapy, and about 19% received prior treatment with bevacizumab. One of the observational studies is the PRiDe data set. It's a patient registry. And it's a little over . . . it's about 457 patients in this data set who received tumor treating fields. And the authors of this study

actually compared their results to the two arms of the EF-11 trial. So, I won't . . . they compared that, but I won't, you know, repeat all of the EF-11 trial data when I talk about the PRiDe results. Again, the median age was mid-50's, high-functioning patients. In this study among the patients receiving tumor treating fields, the median number of recurrences was two. So, I think about half of the patients were at their first recurrence. So, this patient population is a little bit different from the EF-11 trial. So, with the EF-11, most of the patients were on their second or higher recurrence. In this study, it's a good mix, but about half of them were on their first recurrence.

Mika Sinanan: Can I ask Jason, what does 'recurrence' mean? After treatment, initial treatment, does all evidence of the disease go away? Or are there persistent abnormalities on an MR scan that are called scar or something else? Or does it completely disappear?

Jason Rockhill: It does not completely disappear. Most often it's a mixture of treatment effect and tumor.

Mika Sinanan: So, what is a recurrence then?

Jason Rockhill: That's something we're struggling with. Recurrence is when somebody has clinical progression along with imaging progression. Then, you make that decision to switch treatments. It means that there are some patients that are switching treatment before they probably need to. I mean, we can't always identify those.

Mika Sinanan: So, it becomes a pretty subjective decision between the patient and their . . .

Jason Rockhill: You can use [inaudible] criteria. You can use the McDonald criteria. Everybody has tried to define this. You can use advanced imaging with trying to get additional studies with MR perfusion, spectroscopy, PET scans, all of those have been tried. There is a very nice paper from Susan Chang from UCSF where they looked at 85 patients with recurrent tumors that got two operations. So, their initial operation and then, at the time of recurrence. And at the time of recurrence, they tried to clearly identify looking at pathology, that it was clearly tumor, clearly treatment effect, or somewhere in between. Then, they allowed any kind of additional therapy afterwards. It made no difference in survival at the time of recurrence whether they defined it as tumor, treatment effect, or a mix.

Mika Sinanan: You're not helping. [laughs]

Jason Rockhill: I know.

Laurie Mischley: I have a question, too, about this KPS score. Can you just orient me to a 60, 70, 80?

Jason Rockhill: So, the treatment that I have heard, KPS is somebody that you can set down in the middle of any city, and they could find their way home. So, that's kind of roughly a KPS of 60. Somebody who is an 80 or 90 or 100 should be able to complete all their activities, basically go back to work, but have some limited effect. By the time you get to a KPS of 40 or 50, you're spending a significant amount of time probably bedbound.

Rachel Weber: Alright. So, just to reorient you, again, to the evidence, the EF-11 trial had a large population of patients on their second or higher recurrence in the PRiDe data set, the 457 patients that were receiving tumor treating fields. Again, there was a mix of number of recurrences, but there was a higher percentage of patients at their first or second recurrence. In this population, 78% had received prior temozolomide therapy, which was similar to the EF-11 trial, but 55% of them had received prior treatment with bevacizumab. So, that's another difference between the PRiDe patients and the EF-11 trial.

Similar to the group of patients with newly diagnosed glioblastoma, there was another pilot observational trial by the same authors that was meant as a pilot for the EF-11 trial. Again, the intervention group, there were ten patients who received tumor treating fields, and they were on their first recurrence of glioblastoma. They were compared to a number of historical comparator groups that were receiving a variety of different second line therapies. The median age of these patients was 50 to 54 across all of these different groups. Again, the KPS score, the median was about 80 to 90 across the studies, and patients receiving tumor treating fields, that group of ten patients were at least four weeks from any brain surgery and at least eight weeks from radiotherapy.

The other observational study was a case series of over 500 patients that were part of a post-marketing surveillance program. These were all the people [background noise] tumor treating fields. There were very little details provided about these patients. So, I can't really report much on them.

So, for overall survival, we rated the strength of evidence as very low based on trial data for no benefit with tumor treating fields. The median overall survival was very similar in the two groups, 6.6 months compared to 6 months, and this was [background noise]. Among the two observational

studies, we rated the strength of evidence as very low for a benefit with tumor treating fields. The studies were consistent in direction. So, a survival benefit with tumor treating fields, but not magnitude of effect. The patients in the PRiDe registry reported significantly longer overall survival than those in the EF-11 trial. We did not . . . the authors did not report an actual number. They just described it as significantly longer. The median . . . actually, they did report it at 16 months. Sorry. The median overall survival in those ten patients was actually more than double that of the overall survival in the observational pilot study across the several historical comparator groups. I'll just take a second here, you'll note that I rate . . . that we rated the strength of evidence as very low for no benefit with tumor treating fields based on trial and for benefit with tumor treating fields based on the observational studies. This actually sounds like a discordant finding, but with strength of evidence of very low, which is the lowest we can rate our strength of evidence, essentially means that we have no confidence that the effect estimates reported in that, in those bodies of evidence are, in fact, close to the true estimate of effect. So, there is not really a discordant assessment here between the two types of study designs. We just don't have any confidence at all in the findings that they are different from each other. So, the benefit and no benefit is really just speaking to a magnitude of effect between the trial data and the observational data.

For progression free survival, again, we have similar results, rating the strength of evidence for no benefit with tumor treating fields and very little strength of evidence for a benefit with tumor treating fields from the RCT and the observational studies respectively. In the trial data, the median progression free survival was two months in both of the intervention and comparator groups. That was not a statistically significant finding. It has a ratio of 0.81; 21% of the patients receiving tumor treating fields and 15% of the patients receiving second line therapy were progression free at six months. In the observational data from that one pilot study of ten patients who were receiving tumor treating fields compared to the multiple historical comparative groups, the historical comparator groups reported similar results in the observational pilot study, but a much higher proportion of the tumor treating field patients, so 50% of them, so five of the ten, were progression free at six months. This is consistent, again, with the RCT in terms of the direction of effect, but not the magnitude. Others reported that the median time to progression was more than double for the ten tumor treating field patients compared to the second line therapy patients but confidence intervals were very wide in that intersection group, since there were only ten.

For quality of life, we rated the strength of evidence as very low for benefit with tumor treating fields based on the EF-11 trial. There were no observational studies that provided quality of life data. After three months, the patients in the EF-11 trial who were receiving tumor treating fields showed larger improvements on several of the quality of life subscales. They showed less of a decline on the role functioning subscale and improvement, as opposed to a decline, that was seen with chemotherapy on the cognitive functioning subscale. There were no meaningful differences between the two groups in terms of the global health status and social functioning subscale, and patients receiving the second line chemotherapy agents experienced less of a decline on the physical functioning subscale. So, a little bit of a mix of results, but overall, a little bit of a less of a decline with the tumor treating fields.

In terms of the adverse events, so the safety question, we rated the strength of evidence as very low for minimal harm with tumor treating fields from both the trial and the observational studies. Similar to what we saw in the newly diagnosed patients, none of the severe adverse events were attributed to the tumor treating fields. There was mild to moderate dermatologic adverse events reported that were attributed to the tumor treating fields, but in general, none of the severe adverse events were attributed to the tumor treating fields.

I'm going to move to the second treatment comparison among the recurrent glioblastoma patients. We have one observational study that reports data for this treatment comparison. This is actually a little bit of a different study in the sense that these were originally patients with newly diagnosed glioblastoma who enrolled in the EF-14 trial and who experience a recurrence of glioblastoma. At that point, they were invited to enter into an observational sort of phase of the study that compared the tumor treating fields plus additional second line treatments to a group who were just receiving the second line therapy. So, again, these were originally EF-14 trial patients that then experienced a recurrence and the continued treatments and were followed forward in time.

A little bit more about them. Only 31% of the patients randomized to the tumor treating fields group in the EF-14 trial and about 26% of those who had been originally randomized to temozolomide experienced a recurrence and enrolled in the observational followup studies. So, we have a very high attrition rate. There was really no explanation for the patients that experienced a recurrence and did not continue into the observational phase. So, I can't speak to those. The median age, they were a little bit older. They were 57 to 58 compared to, I think, 54 in the original trial. Again, they were high functioning with a median KPS score of 90.

So, from this one observational study, we only had evidence related to the overall survival outcome and adverse events. So, we rated the strength of evidence as very low for no benefit with tumor treating fields from this study, and very low strength of evidence for minimal harm with tumor treating fields. In terms of median overall survival, it was similar in the two groups, 11.8 months in those patients receiving tumor treating fields plus their second line therapy, and 9.2 months among the patients just receiving second line therapy. That was a . . . it was not a statistically significant finding when they compared the hazards over time in the Kaplan-Meier analysis. It's the same story in terms of adverse events, no severe adverse events or serious adverse events, just mild to moderate dermatologic adverse events related to the tumor treating fields treatment.

So, for other cancers, we only included three case series that looked at these tumor treating fields for other cancers. One was a small case series of male pediatric patients who had glioma, and there were only five in that study. A second was adult . . . included adult patients with non-small cell lung carcinoma, and a third was a mixed population. There were six patients, and they had different cancer diagnoses. So, the ranged from breast cancer to mesothelioma. There were multiple diagnoses across the six patients. Because there are no comparator groups, we only evaluated the adverse events for the safety question for these three studies, these case series. And again, no serious adverse events related to tumor treating fields. It was mild to moderate dermatologic adverse events.

Mika Sinanan: Before you continue, is there any animal data or biologic explanation why there might be a difference between a primary treatment response lack of recurrent treatment response. I mean, it would seem to me that this technology would be less prone to not being effective the second time around than many other things based on the explanation that's been provided.

Rachel Weber: I have not seen animal studies that looked at an incident case of cancer versus recurrent case of cancer. I guess, theoretically, the effect of the tumor treating fields would not distinguish between . . . I guess . . . I don't know if there is a biological difference in cancer cell division between primary and recurrent. I'm not a cancer biologist. It's not my understanding that there is. There are probably other factors related to that, I think.

Mika Sinanan: Any thoughts?

Jason Rockhill: I can't think of anything that I'm aware of, except for, you know, we develop resistance to chemotherapies that are mitotic spindle inhibitors. I don't know.

Mika Sinanan: Thank you.

Rachel Weber: OK. So, we included six clinical practice guidelines that included in their guideline recommendations any reference to the use of tumor treating fields for either newly diagnosed glioblastoma or recurrent glioblastoma. Only three, so half of these clinical practice guidelines made a recommendation for patients with newly diagnosed glioblastoma, and the NCCN recommended the use of tumor treating fields for newly diagnosed GBM, whereas NICE and EANO recommended against the use of tumor treating fields. For recurrent GBM, all of the clinical practice guidelines included a recommendation, and it was a mix of yes and no.

Gregory Brown: [not using mic-inaudible]

Rachel Weber: I will briefly discuss that when I talk about the limitations.

Sheila Rege: Alright. I got a question. The NCCN, is it category 1 or 2B for recurrent? Correct?

Jason Rockhill: For recurrent, it's 2B.

Sheila Rege: And for new, it's category . . .

Jason Rockhill: Category 1.

Sheila Rege: [inaudible] low level of evidence.

Jason Rockhill: Just for disclosure, I do sit on the NCCN panel, as the radiation oncologist.

Gregory Brown: How dare you? [laughs]

Rachel Weber: So, just to summarize all of our findings. I know the next couple slides have a lot of information on them. So, again, the purple is to remind that we're talking about newly diagnosed glioblastoma. So, essentially, we have low or very low strength of evidence for a benefit with tumor treating fields in terms of overall progression free survival, quality of life outcomes, and a low strength of evidence for minimal harm with tumor treating fields, and a low strength of evidence that tumor treating fields are not cost effective, and that's based on one study. So, just a couple things to point out on this slide, you'll notice that we really only have one study for each of these

strength of evidence grades. So, again, trial evidence starts at high and gets downgraded. Observational studies start low and can be upgraded or downgraded. So, that's part of the reason why we are landing on low to very low strength of evidence. There is also some concern or high concern for risk of bias, especially for the quality of life outcomes. We see a little bit of a different story in terms of the benefit or no benefit with the recurrent glioblastoma patients, in terms of the comparison of tumor treating fields compared to second line therapy. Again, with very low strength of evidence, we do not have confidence in those findings. Again, it's really one or a couple of observational studies that we are grading the strength of evidence on. For the . . . we had one study that looked at the tumor treating fields plus second line therapy compared to second line therapy alone. That was that followup of the EF-14 trial. And again, we see very low strength of evidence for no benefit with tumor treating fields and for minimal harm. We did not grade strength of evidence for the other cancers. We only have the three case series. So, no comparator groups. We couldn't really rate risk of bias, and we could not include them as strength of evidence grading.

So, I think there are a lot of limitations of the evidence base here. One is that we have a limited number of comparative effectiveness trials. We only have two RCT's, one for newly diagnosed GBM and one for recurrent GBM. We also think that there is a range of some concerns for risk of bias related to some of the outcomes and a high risk of bias for the quality of life outcomes. We've discussed a little bit the lack of blinding for the patient reported outcomes. So, again, the patients who were receiving tumor treating fields versus the patients who were not, there were no sham groups, due to practical and ethical reasons. We don't think that the lack of blinding really effects the overall progression free survival outcomes, because those outcome assessors were blind to the treatment allocation, but I think that the lack of blinding related to patient reported outcomes, specifically the quality of life and functional status and some of the safety outcomes, because the patients are aware of their treatment, there is still room for risk of . . . there is a potential for a risk of bias related to any of the patient reported outcomes. We had a variety of attrition, adherence, and crossover issues in these studies in the EF-14 trial among newly diagnosed patients; 8% of the tumor treating fields group and 6% of the temozolomide group were lost to followup; 11% of the temozolomide group crossed over to receive tumor treating fields after the interim results that were positive were published. So, in the EF-14 trial, remember, those who experienced a recurrence then went on, some of them anyway, went on to continue their treatment, and they were followed up in that observational study. So, that group who was receiving tumor treating fields as kind of a mixed group of patients who are originally randomized

to receive tumor treating fields and patients who crossed over to that group. The others didn't report sort of the distribution of patients across those groups in terms of the crossover and where they finally ended up landing. In the EF-11 trial, among the recurrent GBM patients, 78% of the tumor treating fields group received at least one month of treatment. So, that leaves over 20% who did not receive at least one month of tumor treating fields treatment, and that was compared to a nice 6% of patients receiving their second line therapies receiving at least one month of those treatments.

Gregory Brown: I'm sorry. Can we go back to the lack of blinding, and not so much directed at you and Jason and maybe you, Sheila, I . . . the lack of blinding I have concerns about, and you guys know the literature a lot better than I do. So, my understanding is, there is at least a study in lung cancer looking at active chemotherapy versus palliative hospice care, and the patients that got the palliative and hospice care had longer survival. Is that . . . am I misinterpreting or?

Jason Rockhill: I think the British trial that you're talking about that looked at people with Stage 4 lung cancer with brain mets, looking at survival with best supportive care versus intervention. I think it was whole brain radiation, and in very poor quality patients, in other words, they were poor performance status, there may not have been any benefit to treatment. So, yes, you can find that.

Gregory Brown: So, I guess my point is, is that in a subgroup of patients that clearly know they're getting different treatments, you can find the survival benefit of even supportive care, which isn't a non-treatment. So, but anyway. So, there are certain, I mean, whether you call it placebo or not, there are certainly a treatment effect that can be out there. Is that a misinterpretation?

Jason Rockhill: There's a treatment effect of having patients participate in clinical trials, because they tend to have better followup, kind of better supportive care.

Gregory Brown: OK.

Jason Rockhill: So, I would add that when the interim results came out, one of the things that patients were very aware of is that the trial showing the benefit of temozolomide chemotherapy was two months median increase in survival, and when the interim results of NovaTTF came out, it looked even better. So, a lot of them were thinking, well, I'm on this chemo. Maybe this is even better. So, I think that's one of the big pushes why people wanted to crossover.

Gregory Brown: OK. Thank you.

Rachel Weber: Another source of potential risk of bias was selection bias in the observational studies. In the pilot studies where there were the two different groups of ten patients receiving tumor treating fields, there is very little reported about those patients. So, we just don't know how they were selected into the studies and allocated to receive tumor treating fields. The followup of the EF-14 trial, in which patients experienced a recurrence and were invited to the followup observational phase, only 50% of the tumor treating fields group and 60% of the temozolomide group enrolled. And they're just wasn't an explanation or a description of the number of patients who recurred and did not continue into the observational followup. So, we just don't know enough about those patients.

Studies were under powered to determine the clinical effectiveness and safety of tumor treating fields for subgroups of interest. Again, they weren't powered. They were all post hoc analyses. So, really, any other results are really meant to be hypothesis generating. We did have a very heterogenous group of patients in some of these studies within some of the bodies of evidence, specifically the patients who were experienced recurring GBM. In the trial, there was a wide variety of number of recurrences, and in some of the observational studies, there was a range of patients who were experiencing their first recurrence, and then a mix, but certainly trending towards first recurrence. So, it's difficult, really, to compare these studies within the body of evidence for recurrent glioblastoma, because there is such heterogeneity in the patients, and just not enough information about their prior treatment and everything that they had experienced up until the point of their entry into the studies.

Another limitation is applicability to current standard of care in the United States. So, bevacizumab was approved towards the end of the EF-11 trial for use among recurrent glioblastoma patients. So, the timing of that kind of resulted in a lower use of bevacizumab in that trial compared to some of the observational studies where the use was much higher. So, the groups that were receiving second line therapy in those studies, the physician's choice of best chemotherapy during those studies may very well be different from current clinical practice, especially with the addition of bevacizumab to the market. In terms of the cost-effectiveness analysis, we have a lack of U.S. cost studies. So, with the cost-effectiveness analysis from the French payer perspective, the input into their model, in terms of the efficacy, those probably don't differ between France and the United States, but the costs and the different healthcare systems between the

two countries, that certainly would factor in, into an applicability issue with these studies.

Gregory Brown: The inclusion criteria for EF-14 trial is the new?

Rachel Weber: Yeah.

Gregory Brown: OK. What were the inclusion criteria again?

Rachel Weber: So, they had to histologically confirm diagnosis of new glioblastoma.

Gregory Brown: OK.

Rachel Weber: And they were . . . they received cervical resection followed by the standard of care, the radiotherapy and temozolomide, and I believe they also had to have undergone maintenance temozolomide.

Gregory Brown: I thought the agency . . .

Rachel Weber: I can read that to you now. It's patients eligible for the study were 18 years or older, had a Karnofsky Performance Status of 70 or higher, and had newly diagnosed histologically confirmed supratentorial glioblastoma. All patients had undergone maximal safety bulking surgery when feasible, or biopsy, and had complete standard radiotherapy with concomitant temozolomide at the time of enrollment.

Gregory Brown: So, there was no issue on progression or non-progression? I thought that came up in the agency report?

Rachel Weber: So, yeah, 2017.

Gary Sullivan: They couldn't be progressing at the time they were considered at the end of the radiation and the initial temozolomide. So, they got four months of treatment. At that point is when the trial started, and they could not be progressing at that point. They were excluded if they were progressing at that point.

Gregory Brown: So, you're basically only studying responders?

Gavin Sullivan: They took milder patients into that study.

Gregory Brown: Thank you.

Rachel Weber: So, some of the limitations of this healthcare assessment, we included English language articles only, although we did not identify any articles in additional languages. And we excluded studies that were conducted in countries not designated as very high human development. Again, we did not exclude any studies based on the country of origin. We limited our search to three databases, PubMed, Cochrane, and clinicaltrials.gov, but with the extensive hand searching of systematic reviews and health tech assessments that we identified in our search. We're very confident that we have identified all the primary studies related to this topic. Some aspects of the analysis were tricky with this limited body of evidence, particularly using the GRADE approach to rate the strength of evidence. It's difficult with a small evidence base, especially since we have to stratify by study design, treatment comparison, and indication. We actually modified our GRADE approach to downgrade the domain related to consistency when there was only one study being evaluated for that body of evidence, and that was essentially most of our strength of evidence grades were downgraded in terms of consistency because of the single study body of evidence. There were some limitations of the AGREE tool for evaluating clinical practice guidelines. So, the quality of those clinical practice guidelines are really based on the methods for reaching a recommendation. They do not evaluate the evidence on which those clinical practice guidelines came to fruition. So, I think we had to take that with a grain of salt. So, it's really limited to the methods of the clinical practice guidelines and not the underlying evidence on which their recommendations are based.

So, just a couple of kind of loose ends with the review here. As I described earlier, there is no policy identified for the, uh, coverage of tumor treating fields for any cancer under Medicare. All of the major payers do cover tumor treating fields treatment for newly diagnosed glioblastoma with conditions. Usually, it's age, functional status. For recurrent glioblastoma, it's a mix. Some major payers will cover it. Some won't. Again, those who do, there are conditions placed on them. There are no policies identified that cover tumor treating fields for the treatment of other cancers. Again, this technology, this particular treatment is only FDA approved for the treatment of glioblastoma.

John Bramhall: Do you happen to know whether the commercial payers cover for the survival of the patient for the duration of their life, or up to a point of change in condition?

Rachel Weber: I believe it's . . . some of them it's up to a change in condition. I couldn't tell you which ones specifically right now, but I think it's a mix.

So, this is sort of the overall summery of our findings. Again, we have very low or low strength of evidence, which really means we have very limited to limited confidence that any of the estimates that we reported, lie close to the true effect of tumor treating fields for these outcomes. Substantial evidence is needed before we can conclude that either the findings are stable, or that the estimate of effect is close to the true effect. So, for newly diagnosed glioblastoma, we concluded that tumor treating fields increase overall in progression free survival, quality of life, and that there is minimal harm associated with tumor treating fields, but that the treatment is not cost effective. For recurrent glioblastoma, there may or may not be survival benefits with tumor treating fields. There is a . . . we concluded that there is an increase in quality of life and minimal harm, and we could not rate the evidence in terms of other cancers, because we only have the three case series without a comparison group.

I have some additional slides, if anybody happens to ask questions about those particular things, but I guess I open it to additional questions.

Gregory Brown: Anybody? Yeah, we've kind of asked as we've gone, but any additional questions?

Mika Sinanan: Could you go to the slide that look at the relevant pending clinical trials? I think that's . . . 'cuz it looks like there may be, over the next couple years, significantly more information about this. Is that right?

Rachel Weber: Yes. So, I'll start with the status of relevant clinical trials. So, there are several clinical trials funded by Novocure looking at the tumor treating fields among different cancers. They all have cool acronyms. Let's find the info here. So, there are currently phase three clinical trials that are ongoing, related to non-small cell lung carcinoma, pancreatic cancer, brain metastasis, and it looks like ovarian. That one, I think, is the phase 2 study is complete and they'll be starting a phase 3 study. There is one phase 2 study that's been completed among patients with mesothelioma and one phase 2 study that's ongoing among patients with liver cancer. So, yeah. There are certainly trials that are in progress among different cancers. There are also additional trials among patients with newly diagnosed glioblastoma. So, on the slide here, slide 57, there are a number of clinical trials among tumor treating fields for newly diagnosed patients, and the completion dates range from soon, so early 2019, and there's one that actually goes out to 2027, and it's a variety of different types of combination therapies with tumor treating fields. There are, likewise, additional trials related to patients with recurrent glioblastoma. Again, some of them are recruiting now, but certainly some of these go out quite a ways.

Sheila Rege: This may be a question more for Jason, on the approvals from commercial insurance, is there any differentiation between the [inaudible], because the study was actually significantly better, even with the optimum therapy with temozolomide with that group, but nobody's really [inaudible]. Nobody's really differentiated that?

Jason Rockhill: I'm not aware of any requirements at this point on MGMT methylation status. We know that that's a marker for responsiveness to chemotherapy, but even that has been challenged somewhat.

Sheila Rege: OK. I remember something that, like, almost 31 months versus 21 months in that group.

Rachel Weber: Yeah. So, in that EF-14 trial, they did look at that. The overall survival was lower in the patients with unmethylated status MGMT status, but there was a survival benefit within each of the MGMT groups that favored tumor treating fields. So, among the patients with methylated MGMT, it was 31.6 months compared to . . . for the tumor treating fields group compared to 21.2 months for the temozolomide group. And among the patients with unmethylated MGMT, it was 16.9 months in the tumor treating fields group and 14.7 in the temozolomide group.

Sheila Rege: So, those with unmethylated MGMT did poorer than those with methylated MGMT. Within each of those groups we did see a survival benefit with tumor treating fields.

Mika Sinanan: I have a question for our industry representative. Has the technology changed over time? It seems that many of these innovative technologies do adjust or they change the characteristics or the array or whatever. So, is there a change over time, or not?

Justin Kelly: Yes. There is. This is Justin Kelly from Novocure. About a year and a half ago, two years ago, we released an updated version of the Optune device, which is about half the weight and half the size of the picture that was included in the presentation. In terms of the transducer array, those are still the same as our original FDA approval, but we are in discussions with some modifications to those, as well.

Mika Sinanan: And as a followup, are those for comfort or portability, or are they actually designed to change the treatment effect?

Justin Kelly: So, my understand of what is current, you know, so for the change to the device itself was more for portability. So, we went from, like, 6 pounds down to 2.7 pounds. So, it's easier for the patient to carry. Relating to the

transducer arrays, my understanding is that the upcoming changes will be more cosmetic, but that there is additional research that will be focused on delivery, but that's nothing that's ready for prime time yet.

Mika Sinanan: Thank you. And I know you didn't in your data look at sort of the social media buzz around this, but I would expect that there is, you know, sort of a rare disease, terrible outcome, very invested families, you could expect that there would be a fair amount of discussion out there about things that people believe with or without evidence actually work. Do you have any sense about that at all?

Rachel Weber: I don't.

Mika Sinanan: Jason, comments?

Jason Rockhill: I think brain tumors, any time there is an incremental or apparent benefit, there is a huge buzz. I can probably look at my phone, since Society Neurooncology Meeting is going on right now, and have three or four emails that are coming out saying this latest data, that latest data, on what's happening in brain tumors. So, yes, I think there is a huge social impact on this.

Mika Sinanan: And so, does that help explain the reason that so many commercial payers are supporting this? I mean, on the basis of even an earlier level, more limited data than we have now, they seem to have made coverage determinations.

Jason Rockhill: I think there is a lot of societal/advocacy group pressure on commercial payers to cover things. I think we're gonna see that more and more. So, yes.

Gregory Brown: But this group is chartered to look at evidence.

Mika Sinanan: I understand.

Gregory Brown: OK. Thank you. Any other questions? I guess I have one, and then we'll take a break. So, across healthcare, a 10% improvement in quality of life is a pretty good benefit for any treatment in most things. Is that?

Rachel Weber: I don't know that I'm qualified to answer that question.

Gregory Brown: OK. So say there was a 10% improvement in quality of life here, OK? So, converting our life years to quality of life years, so $800,000 for a life year,

a 10% improvement in quality of life would give you 8 million dollars for a QALY.

Rachel Weber: So, I'm not an expert in cost-effectiveness analyses, but yes.

Gregory Brown: And we heard from Mr. Kelly that it's actually $21,000, not $27,000. So, roughly 25% decrease in cost. So, if we use that analysis, then we're looking at 6 million dollars a QALY roughly? Does that sound like the math is right? OK. We'll take a break and come back and start our discussion. Thanks everybody. Thank you for the report.

OK. We are ready to resume. So, we will start our discussion and questions amongst ourselves. Anybody want to start with their thoughts?

Tony Yen: I have a question for Dr. Rockhill. So, you made mention that you sit on NCCN? And I was curious, from the NCCN perspective, I was . . . does NCCN look at really efficacy, or do they combine efficacy along with cost-effectiveness when they give their recommendations?

Jason Rockhill: I think they are looking more at efficacy than cost-effectiveness.

Tony Yen: OK.

Jason Rockhill: Yeah. I mean, it's starting to enter in more and more in the discussion, but clearly, the focus is on what's an appropriate treatment, not necessarily how much that treatment costs.

Tony Yen: OK. Alright. Then, I'm just trying to frame this in terms of, like, when I'm looking at the literature over here, I don't really see a . . . at least from my perspective, as a hospitalist and completely not an oncologist, I don't see a wealth of evidence. Can you give me more context as to why NCCN rated this as grade 1 for newly diagnosed glioblastoma?

Jason Rockhill: Because it was a randomized control trial. So, and a lot of treatment in brain tumors is not randomized control trials.

Tony Yen: OK. Thank you.

Gregory Brown: Dr. Weber, could I ask you a question? On the grading of the clinical practice guidelines, you gave nice seven out of seven, but NCCN five out of seven. What did NCCN lose points on?

Rachel Weber: It lost some points on the health questions being specifically described and the views of the preferences of the target population being included. And

finally, it lost a few points on external review by experts prior to publication.

Gregory Brown: Thank you. Come on, this isn't a bashful group. Who has got their thoughts? There you go. Mika?

Mika Sinanan: So, thank you, um, I'll start with the easiest area, the recurrent glioblastoma. For all the reasons that Dr. Rockhill has commented on, the difficulty of what recurrence actually means and, uh, it sounds like criteria that are used but still is a fair amount of interpretation. That seems to be a very soft are, a very difficult are to look at. And even with that, opportunity to create bias, it appears the be no benefit. Certainly no cost benefit, but no true efficacy to tumor treating fields. So, from my perspective, at least with regard to the recurrent glioblastoma, as currently defined, and with the associated other types of treatment that are available and options, the data does not, that we have seen, does not support a change in the coverage decision that was originally made around that area. So, that would be my takeaway on the basis of that area.

Gregory Brown: OK. Anybody else have any?

Kevin Walsh: Do you have an opinion about the harder subject?

Gregory Brown: No, that's OK. We can start with the easy ones. We can start with a really easy one. How about other tumors? Does anybody think there's any evidence on others tumors to even talk about? OK. No. So, OK. So, there's the easiest one. It's gone. Second easiest . . .

Kevin Walsh: I agree with Mika's interpretation of what the evidence tells us about recurrent tumors.

Gregory Brown: Anybody disagree with those thoughts? So, we're two-thirds of the way done. We're not going to, we're not going to cover other tumors, and we're not going to cover recurrent tumors it sounds like. So, now newly diagnosed tumors. So . . .

Sheila Rege: So, going back to our three questions, is it safe, is it effective, and provide value. And so, if I can ask around. I mean, safe, it seems safe. Now, the discussion on effective, and I am going to let somebody else lead that.

John Bramhall: What, it's effective, in the sense that there is a statistically significant increase in duration of life. It seemed to me, I'm tending to go by the JAMA paper, the 2017 study, because it's a randomized trial and was analyzed for us very well. So, it seems like there is . . . there is evidence that there

is an increase in duration of life. I wrote down 21-month mean was our median. My numbers that I'm working from are 21-month survival versus 16-month survival from that study. And I won't go into the economic calculation right now, but that does seem that you would say that was a significant increase. Whether it's a meaningful increase or not, I don't know. I always feel very ill-equipped to deal with these almost human problems of meaningful versus statistical validity. In terms of disease progression . . .

Gregory Brown: OK. Can I ask, can I ask you a question there? So, there's one study. There's risk of bias. They excluded anybody that had progression in the initial treatment. And so irrespective of what they find, even though it's an RCT, the level of evidence that our vendor gave us is low, which means high probability that another study could find a different result. So, saying there's one study that has a statistical difference but low quality with high risk of bias, is that really sufficient for you? Is that what you're saying?

John Bramhall: The quality degradation was attributed to the fact that it's a commercially-sponsored trial. Is that the primary degradation in quality?

Gregory Brown: Well, I think there's multiple issues, but I'm curious . . .

Rachel Weber: So, we rated risk of bias for that trial differently across . . . we provided risk of bias assessments across the different outcomes.

John Bramhall: This is the 2017?

Rachel Weber: Yes, the EF-14 trial. So, for overall and progression free survival there were just some concerns for bias, and those were primarily related to attrition and adherence to the treatment. For the quality of life outcomes, we rated it as high risk of bias, and that was primarily due to the fact that less than a third of the patients provided quality of life assessments. Also, it's a patient-reported outcome in a study where the patients weren't blinded to treatment. So, there is still a potential for risk of bias related to the patient reported outcomes there.

John Bramhall: So, I think you have to say survival is a fairly hard edged . . .

Rachel Weber: Right.

John Bramhall: . . . weapon.

Rachel Weber: And we didn't downgrade in terms of blinding when we were rating risk of bias for the survival outcomes.

John Bramhall: Alright. So, I mean, it's clearly it's a debatable issue, but I think if you're looking at survival, it's a fairly concrete endpoint, and whether or not you are dealing with an awareness of where the therapy was being instituted, or your sham, whatever the variable was, survival is fairly hard. So, looking at the survival data in that study, it struck me that there was a difference between the treatment and non-treatment, but it's small. It's small, and we're going to get into the cost-effectiveness in a little time here. When I looked at it, it looked like it was about . . . if you look at survival only, and you look at the increase in survival that was claimed in that study with the therapy, then it's five months average, five months increase in survival, and if you ran the treatment until the patient died, if that's what you did, if that's what you supported, then it's about a 4 million dollar cost to run it for 20 months at the stated costs that we've been given. So, it just, my simplistic approach is it's going to cost 4 million dollars for a punitive five month increase in survival. I'm not dealing with disease progression here. So, that struck me as relatively expensive for the value that was being obtained, but I did think that the studies suggested that there was a value, so.

Gregory Brown: Does anybody disagree with that?

Kevin Walsh: Could I ask that we, as we proceed through this discussion, could we . . . so we've ruled out recurrent tumor, and there's three, as Sheila mentioned, there are three criteria that we're asked to evaluate. Could we just talk about effectiveness before we mix in the cost, because I think that it gets exponentially more complicated as we do that.

Gregory Brown: Sure. So, effectiveness, does anybody have a different opinion of whether it's effective or not, or whether one RCT is sufficient evidence to prove effectiveness.

Kevin Walsh: I just want to point out that what Dr. Rockhill mentioned about the real inability to kind of determine if it's disease progression or noise, technological noise, and that being a branch point for excluding people from additional therapy, that made the whole thing seem fairly subjective to me. I mean, I understand the premise that we want to get to, but it strikes me that we don't have the technological capacity to do what we're trying to do yet in a meaning, in a dependable way. So, that calls into question for me everything else.

Gregory Brown: So, if I'm hearing you correctly, if we chose to cover in patients without progression . . .

Kevin Walsh: No. Don't, don't frame it that way. Let me say it.

Gregory Brown: OK.

Kevin Walsh: It makes me wonder about the whole premise of the treatment arms, because I don't know who . . . what I heard was, we don't really know who we're treating half the time. So, how, so if we don't know and we can show a few months of increased survival to some people, it gets really . . .

Gregory Brown: So, what you're saying is that difference in survival is essentially random, because we didn't even know who we put in either arm.

Kevin Walsh: That's how I feel.

Gregory Brown: OK.

Kevin Walsh: It seems like we would have more false-positive progressors. So, we're withdrawing the therapy from people who are actually not progressing, because we believe them to be progressing, which in my mind would bias the results to make the treatment look less effective than it actually is, in my mind.

Sheila Rege: So, the other question in terms of is it effective, is effective if the patient is able to put this on for 18 hours a day, is able to charge that battery pack, and Jason correct me, has a caregiver who can help him or her shave his or her head. It, and these are brain tumor patients. And if they take the device home and don't put it on for 18 months, or 18 hours, it's not effective. Now, the studies in an optimal study, there was only, what a 22% noncompliant rate, but the question is in real life, is that, you know, that's with optimal patient selection. So, that, that's kind of my practical focus on the effectiveness question also.

Kevin Walsh: So, where does that take you, Sheila?

Sheila Rege: I don't know. I'm struggling.

Gregory Brown: Well, does that explain a difference? So, if you're going to be compliant with treatment, you have a caregiver who is going to shave your head three times a week who is going to help you put this on 18 hours a day? That's a lot of care. So, those individuals may do better because of their caregiver, not the device. Is that possible?

Jason Rockhill: I think all brain tumor patients require a high level of care whether you add device, keeping track of multiple medications, antiseizure medications. So, I think there's just a large need for the supportive.

Kevin Walsh: So, is it fair to say, then, that you don't think that the addition of the steps Sheila described raises the level of complexity that much?

Jason Rockhill: In my opinion, no.

Kevin Walsh: OK.

Jason Rockhill: They're dealing with so much already.

Gregory Brown: But it's unethical to do a sham? I'm confused there.

Laurie Mischley: While I do think that all these patients are going to receive a level of care, having recently had a study written by the placebo response, I've really been diving into this research. The more invasive, the more expensive an intervention, the stronger the placebo. IV is stronger than IM. There is no way that wearing a heated hat 18 hours a day isn't going to effect the physiology that you're . . . I just am not convinced that the lack of a sham isn't playing a role in some of what we're seeing here.

Chris Hearne: That is a placebo effect.

Laurie Mischley: I am concerned that we're not fully appreciating the potential for a placebo effect here, and I'm not saying that the placebo effect isn't a real physiological translation to tumor reduction that can be evaluated by a blinded evaluator, but the more I learn about the human capacity to influence biochemistry, you know, physiologic change with our perception of an intervention is shocking.

Gregory Brown: It's kind of a ruining of a study, though.

Seth Schwartz: I have some similar concerns. I think we like that we have a randomized trial, because a lot of times we don't have any data, but to have a single randomized trial that has some problems. I think the lack of blinding is a really big one in this situation. I completely agree with Laurie. I think there is a potential for a big placebo effect, and the overall effect that we're looking at is fairly small. So, it's, you know, you're not setting the bar tremendously high for what's a useful benefit. So, a few months, I mean, obviously, to an individual, that's valuable, but in the larger scheme of things, is that a clinically significant difference when you introduce this question about placebo effect and attrition rates and all these other things. So, I'm struggling with how convincing this data is, even though it looks like there is probably something there. It's just . . . it's not sitting right with me that we're seeing a huge benefit. Then, the other question I have is, in terms of how they announced this was done. Was this an intention to treat

analysis, or was there crossover, because we keep talking about crossover, but I'm not exactly sure at what point that was happening and where that occurred along the assessment points. So, maybe our vendor can just help me with that.

Rachel Weber: Yes. These were intent to treat analyses.

Seth Schwartz: OK.

John Bramhall: I agree with the general thrust of the discussion so far, and I also think that focusing on overall survival and progression free survival is only half of the picture here. We really don't have good information about quality of life, and it strikes me that that's at least as important of an outcome in this situation, as survival, and we just don't know much about it at all.

Tony Yen: So, I'm looking at the data very simplistically from my standpoint is that is it effective? It's kind of a binary question for me, and I'm only looking at one part of the data, I'll admit, which is survival, because I think looking at progression . . . and thank you for the guidance, Dr. Rockhill, about kind of the changes that we sometimes see with imaging. That's completely hard for me to interpret as a bottom line. So, by looking at the hard survival data, as John has mentioned over here, I think that to me is the most meaningful part. So, my binary answer is, if I accept the data as it is and pretty much discount a lot of the biases that have been brought out over here, I think there is benefit, but then the next question that I need to ask is, the magnitude of that benefit. Then, the following question, which is the more difficult one, is the cost-effectiveness of this all. For me, I do feel that even with the flaws of the study, I think there is something there. I think there is some survival benefit, whether it's quantified accurately in the study is hard to say, because it's only a single study. There is a number of biases involved there. I think that the progression free survival, that's just too hard to interpret.

Gregory Brown: Mika, everybody else, now, has spoken new, except you, so.

Mika Sinanan: I think that the points that have been raised about the bias, about the open label, about the lack of a sham, uh, raise, and the fact that it's a vendor-supported single RCT is really, for me, makes it unclear that we can interpret this as a true benefit, and I think that's what the level of the evidence that we heard is so low that there is a very wide potential for the measured result in this study to be different from what the true result would be. I think that there is . . . it's a terrible disease with a powerful advocacy group, both among oncologists and among patients and their families who are looking for any hope and any option, and to my mind, that

probably explains the discrepancy between the coverage determinations that we have reviewed and a relative lack of evidence, even before this most recent, I mean, really a lack of evidence before the most recent study. So, clearly a very sympathetic group of people, but this is, to my mind, not evidence that there is truly efficacy there. I get back to Kevin's initial point that the whole premise of the question raised is put into question by the combination of bias and limitations of the way the study was done by a single study that is vendor supported.

Gregory Brown: So, if I hear you correctly, lack of other good treatments in a horrible disease does not mean this one is effective.

Mika Sinanan: Correct. Well, and it doesn't mean that we, from a decision or a recommendation standpoint need to actually support it, and as you pointed out earlier, that's not our mandate. Even more importantly, I think, is the fact that we are . . . we have the potential to actually harm people and to limit the appropriate development of alternatives, or appropriate development of the information, because a lack of coverage is going to drive both the company to reduce their prices to make it more available and for better quality in future studies to actually address the question, which we have said is not answered yet.

Gregory Brown: So, I'll ask a rhetorical question to the group. So, if it's unethical to ask someone to carry a sham unit around, is it ethical to ask someone to carry around an active unit when it's not effective?

Mika Sinanan: For a lethal disease, absolutely. I mean, I think that's . . . we've heard that it's unethical, but I think that's a . . .

Gregory Brown: Well, no . . . again . . .

Mika Sinanan: . . . clinical decision, not a absolute.

Gregory Brown: . . . anyway, it was a rhetorical question, but anyway, I think we've all had . . . Dr. Franklin.

Gary Franklin: I think the . . . one of the most important things here is, it would have been much easier to interpret the difference in improvement if there really was clearcut quality of life information, and it's dumbfounding to me how they could have gone to so much trouble to keep these things on for 18 hours a day but couldn't quite get the information they needed on quality of life, even from surrogates or the patient. So, if they had that in here, and if quality of life did improve, or even stayed great, for the two or four months that we're talking about, that would have really been important

information. So, I don't really understand why they didn't accomplish that, given that this went on over years, and that they put so much resource into keeping this thing on.

Gregory Brown: So, let's go to our safety question, if I can summarize, low risks and dermatological issues, but otherwise, not really a lot of safety issues. Does anybody have a different thought there? OK. Cost, cost-effectiveness, I think we're all on the same page that it's very costly, and if it's marginally effective, the cost-effectiveness is so high that . . .

Gary Franklin: Or ineffective.

Gregory Brown: Oh, yeah, ineffective is zero cost-effective. I mean, if infinite cost-effectiveness in terms of cost per quality adjusted life year if it's ineffective, but.

Seth Schwartz: You know, I'm really struggling with this. I always hate to make a determination based on cost, and in some ways I feel like we're being asked to do that, because there's some questions about effectiveness, and even if there is some, it's limited. We clearly have one cost-effectiveness trial, which is always questionable, because there are so many assumptions that go into them that bring into question what we're really looking, but usually, the concern is that things look better than they should look, because maybe not all the right things are being taken into account. Here, we have the most important aspect of a cost-effectiveness analysis, which is the quality of life piece, completely missing. So, we're not comparing apples to apples. We have a cost-effectiveness ratio that is ten times what we would normally think is acceptable, or eight times what we normally think is acceptable, and the real answer for what the cost-effectiveness is, is probably ten times that. So, I think . . . so I'm just struggling because it seems like by orders of magnitude, the cost-effectiveness of this intervention is not reasonable. And when we have effectiveness data that is at least in question with a magnitude of effect of that, which is small, the fact that we're looking at a ten to a hundred-fold times level of quality of . . . of cost-effectiveness than we're normally willing to accept, it's weighing more heavily with me on this for this intervention than it does ordinarily.

Gregory Brown: OK. Is that everybody else's similar feeling I think? Yeah, I agree with you completely. Our society does not . . . has not been willing to face the tough decision of what is a reasonable cost for treatment in healthcare for a QALY, for a whatever, you know, and we're probably not going to, as this group, be able to answer that question. The . . .

Mika Sinanan: I think that's exactly the subrole of this group is to actually start putting some rigor around that particular question. I mean, when I was reading about this and all of the data that we have suggests that that is what the intention was. So, yes, it's been very difficult, and it is . . . it will always continue to be very difficult, is a person suffering with a brain tumor. How much is the value of a day, a week, a month, two months of their life. That's an existential question, but ultimately, because of the limited resources, and in this case I think because of the lack of data in the ways that you just said, Seth, we are going to have to make some determinations about that, both as you've said from a societal standpoint, but it's got to start somewhere.

Gregory Brown: Well, yeah, no. I hear you. I guess what I'm saying is, we're not going to . . . we, as a group, are not going to say $100,000 per QALY is the line. OK? I'm misinterpreting . . . $800,000, or $8,000,000, or $80,000,000, whatever it is for this treatment, is probably over the line, though, at least is what I'm hearing from most people. Again, if it's not effective, and if we go back to our first question, and we can do our straw poll, or we can go through our worksheet here in just a second, then we don't even get to second and three, you know, the second and third, I guess, is my view, but, OK. Any other comments or thoughts before we go to our tool?

Tony Yen: One of the charges of this group is actually to very explicitly to look at cost-effectiveness, as well.

Gregory Brown: Right.

Tony Yen: And I think one of the roles that I have on this group is actually to really be a steward for Washington State. Am I correct?

Gregory Brown: I feel I have the same role.

Tony Yen: Right. Thank you.

Gregory Brown: Yeah, no. Again, I do feel that's part of our role. I agree. I'm just saying at the same time, I don't think that I, as a member of this committee or even as chair of this committee, have the authority or the voice of the . . . to set what that line is, you know? I can, yeah. Anyway.

John Bramhall: Dr. Rockhill, can I just get a little clarification from you on this whole question of disease progression? Kevin raised the issue, I think in the context of MRI imaging that is confused by a variety of elements, but how much of the degrees of disease progression is attributed, the time the

decision is made that it's progressing to imaging, and how much to the functionality scale, the, the Karnofsky kind of scale?

Jason Rockhill: So, we know that after you treat with radiation and chemotherapy, about 40% of patients will have pseudo-progression. Of those, some fraction, somewhere between 10 to 20, depending on which study, maybe 30%, will have true progression. The others will have a response. So, if you pull out all those people that you think progressed, you should have pulled out equally from both arms, which sides are going to be true progressors and which are going to be pseudo-progression. So, yeah, you're selecting maybe for better responders, but you should have selected from both better responders in each arm.

Gregory Brown: We've got our tool on page 5 here, and we've got our safety outcomes first. We've got listed on the back of our page 5, dermatitis, insomnia, headaches, other adverse . . . serious adverse events. Anybody think we need to add anything else to the safety ones there? OK. So, I guess, for me, in answering a safety question, I mean, that's the next page. We're not going to ask it yet, but the answer to my question is going to be different if I say Optune versus nothing versus Optune versus chemo. So, I would say we're looking at Optune versus nothing, because nobody is being treated with just Optune for the most part, are they?

Jason Rockhill: Yes. Some people are just being treated with Optune.

Gregory Brown: OK. So, then, are we going to compare it to chemo or what's our comparator?

Kevin Walsh: I think the standard of care . . . am I correct? The standard of care is chemo.

Jason Rockhill: For adjuvant therapy, yes, but there are patients that may have a poor enough functional status that they can't tolerate chemo. Getting back to your ethical question, but they can tolerate Optune because . . .

Gregory Brown: Yeah, but most, so I guess my point is, is most patients would get chemo or chemo plus Optune?

Jason Rockhill: Yes.

Gregory Brown: OK. So, the safety issues, so comparing it to just chemo, it would be safer, but comparing it to chemo with Optune or just chemo, there really wouldn't be much of a difference other than the dermatologic issues. Is that correct?

Kevin Walsh: So, the question is compared to chemo, is this technology . . .

Gregory Brown: No. I think it's compared to standard of care. So, if standard of care is everybody's getting chemo with or without Optune, then to me, the difference in safety is there an enough . . .

Kevin Walsh: Optune.

Gregory Brown: . . . of an advantage?

Sheila Rege: We could do it both ways. Mostly, it is done with chemo, temozolomide. So, we could do temozolomide versus temozolomide plus Optune.

John Bramhall: Well, the more general question is, if you . . . whatever the background regimen, if you add this CTF therapy, is there a change in safety. Is that general enough? Just . . . I mean, it's not philosophical. It's real. If people decide to use this therapy versus one that's effective, then there is a danger, but that's too much.

Gregory Brown: No. No. No. I guess the way I'm interpreting it is, if we . . . if you ask me, is there a safety difference between chemotherapy and Optune alone, I would say yes. Chemotherapy has a lot more side effect. If you say, is there a difference between standard therapy, which is chemotherapy . . .

Kevin Walsh: That's not the . . . I don't think that's the way to frame the question, Greg.

Gregory Brown: OK. How would you frame the question then?

Kevin Walsh: Well, if the standard of care is chemo, the question is, in my mind, is the addition of Optune less safe, more safe, you know? What, what's the safety profile of the Optune alone compared to the standard. So, we're not comparing chemo versus Optune. We're comparing the addition of Optune to the chemo.

Gregory Brown: So, so if I understand the question right, then I would say, everybody is getting chemo. They have chemo side effects. If I add Optune, they're going to have a little bit of increase in mild dermatologic issues. So, there is a slight safety . . . so I mean . . . I understand . . . that's how I would . . . if that's how the question is framed, then that's how I'm thinking. So, I just want to make sure we're all thinking the same way.

John Bramhall: What is the incremental risk of using Optune beyond standard of therapy.

Kevin Walsh: Correct.

Gregory Brown: Beyond standard of therapy. So, OK. Then, efficacy, we've got overall survival.

Sheila Rege: Did we ask that? Do we put a little [crosstalk].

Gregory Brown: No. We haven't voted yet. That's the next page. Sorry. OK. I usually get ahead of myself. I'm trying to restrain myself. So, the next one is efficacy. We have overall survival. We have progression free survival. We have tumor response. We have quality of life. We have functional status. So, again, I will summarize, and if people disagree, we think there may be some difference in survival data, whether we think the study, how strong the study is. We don't think we can really discuss progression free survival based on false progression. Are we . . .

Jason Rockhill: Can I just add that it is used all the time.

Gregory Brown: I understand.

Jason Rockhill: But all of us agree that the gold standard, because of all the problems, is overall survival.

Gregory Brown: OK. OK. So, in the same way, tumor response. We don't have quality of life data and similar functional status. So, really, on efficacy, we're voting on overall survival?

Mika Sinanan: That's the only measure we really have.

Gregory Brown: Yep. OK. And then, uh, cost outcomes. We've got direct costs or cost-effectiveness. Should we vote on cost-effectiveness or?

Kevin Walsh: We know . . . we're not being asked to set the standard. The standard has already been set. We're just asking to compare this to that. We're asked to compare this cost to what is the standard cost that's used.

Gregory Brown: OK. So, then let's go to, are there any special populations we need to consider?

Mika Sinanan: Greg, could I ask a question? Jason, do you have a sense about what the magnitude of a new diagnosis glioblastoma patient would pay, what the cost of their care would be from the time of diagnosis to death?

Jason Rockhill: Not with any accuracy. I mean, I could give you a figure right . . .

Mika Sinanan: Take a guess. What do you think?

Jason Rockhill: Somewhere around $200,000 to $300,000, and that doesn't even include cost of housing, transportation.

Mika Sinanan: So, that's including diagnostic studies, radiation . . .

Jason Rockhill: Yeah.

Mika Sinanan: . . . surgery?

Jason Rockhill: I'd put huge air bars on that number.

Mika Sinanan: OK.

Jason Rockhill: It could be even more.

Mika Sinanan: I would expect it would be even more than that. so, I'm just . . . I wanted to scale what the cost, the direct costs and what the cost-efficacy is relative to. So, this is a 300+ thousand dollar disease?

Jason Rockhill: And if we use, you know, the, the cost that people get charged, you know, like, the cost for Optune, I'm sure it's even more than what I, yeah.

Mika Sinanan: Thank you.

Chris Hearne: What are the treatment options for somebody who can't tolerate temozolomide other than Optune?

Jason Rockhill: So, in a front setting or in the recurrent setting?

Chris Hearne: Up front.

Jason Rockhill: Supportive care, different chemotherapy with a different toxicity profile, which is incredibly limited, the ones that work, potentially work, in the brain.

Mika Sinanan: Bevacizumab, would that be?

Jason Rockhill: Yes.

Mika Sinanan: That would be . . . so that's a second line, but . . .

Gregory Brown: Radiation . . .

Mika Sinanan: . . . that would be shown firstline.

Gregory Brown: . . . radiation and surgery.

Jason Rockhill: Yeah, assuming radiation, sorry assuming surgery and radiation to get up front.

Gregory Brown: OK. We will go to the next page. So, we will first say is there sufficient evidence that the technology is safe for the indications considered. So, more safe says that there's more in some is more safe. Less than some . . . or less is less safe. Alright, safety.

Tony Yen: Less for dermatitis, that's about it?

Gregory Brown: We have one, two, three, four five . . .

Josh Morse: Seven equivalent, two less. I am going to ask, though, are you voting for . . . you're not including the conversation about recurrent and other tumors you've already . . . so you're just voting now on . . .

Gregory Brown: We've already basically decided, we don't think there's any . . .

Josh Morse: . . . firstline treatment. OK.

Gregory Brown: We're only doing firstline treatment. Yeah.

Mika Sinanan: So, I'm confused by less. Are you saying it is less safe?

Gregory Brown: Well, I mean, there are dermatologic changes.

Mika Sinanan: OK.

Gregory Brown: I think it is less safe than nothing, but I don't think it's . . .

Mika Sinanan: OK.

Gregory Brown: . . . there's not a little less or a lot of less.

Mika Sinanan: Yeah.

Gregory Brown: So, but that's what I'm saying. OK? Effectiveness. There . . .

Female: I'm sorry to interrupt. I'm just trying to get the notes down right, as I was taking the vote. That was [inaudible]. Correct?

Gregory Brown: No, the comparison is to standard of care.

Female: And the addition of [inaudible]? Right?

Gregory Brown: Yes. Yes.

Gary Franklin: I'm sorry, that's . . . standard of care is debulking, radiation, and chemotherapy, and this is add on to all of that or, or one of those three things might not be done for some reason, but it's still an add on. So, it's just not this compared to chemo. It's this compared to standard of care, which is all of those things.

Gregory Brown: Well, I guess the difference is, in my view, Gary, is that the surgery is essentially once the radiation is essentially once, but the chemo you may do multiple cycles. So, when you're doing the additional cycles of chemo, do you add this or not. So, that's why we're saying standard of care.

Gary Franklin: That's maintenance chemo. That's after the initial chemo.

Jason Rockhill: Adjuvant chemo after combined chemoradiotherapy.

Gregory Brown: So, effectiveness.

Josh Morse: One, two, three, six unproven.

Gregory Brown: I think you're looking at seven unproven.

Josh Morse: Seven unproven, two more in some.

Gregory Brown: OK.

Josh Morse: Was it three more in some?

Sheila Rege: Yeah, more in some.

Josh Morse: So, six unproven, three more in some. Thank you.

Gregory Brown: And then, cost . . . so, the next one is going to make a difference in terms of, are we asking cost or cost-effectiveness? If it's cost, it's more costly. If it's cost-effective, it's less. So, cost-effectiveness. So, nine less.

Josh Morse: Nine less? Thank you.

Gregory Brown: OK. So, in terms of if our mandate is to provide coverage for evidence based treatments and seven out of nine of us are saying it's unproven, is

that . . . are we ready to vote on coverage versus coverage with conditions, or not? OK. Vote for coverage.

Josh Morse: I see nine . . .

Gregory Brown: Out of nine.

Josh Morse: . . . not cover.

Gregory Brown: That's new, recurrent, and all other cancers, all three we agree.

Josh Morse: Got it.

Gregory Brown: OK.

Josh Morse: So, we didn't ask the question about Medicare guidelines.

Gregory Brown: So, Medicare does not have a policy coverage decision. If we look at other CPG's, we have conflicting. NICE, which had the highest quality rating, does not cover for either new or recurrent. NCCN has a 1 for new or 2A or B, you said, for recurrent, but again, there's a conflict. So, we're not going to be able to be . . . so . . .

Mika Sinanan: Can I ask you a question about our recommendations? Do we have the option from the committee of recommending an interval for re-review based on the pending studies on the list coming out in the next five years? Or does that recommendation have to come from the Department of Health? Can we make a recommendation that . . . OK. So, even though we recommend not covered, we could recommend that it be re-reviewed, at least from a data standpoint, in about five years, at such time when at least three or four of the additional studies that are noted should be completed and published.

Kevin Walsh: I understand your point. I think it's unnecessary, because I think that the vendors will push for a re-review when they feel they have data that needs to be reconsidered. I think that's why we're doing this re-review.

Mika Sinanan: Then we'll both make recommendations.

Gregory Brown: OK. We are a little . . .

Female: Are we ready for lunch? I can [crosstalk].

Gregory Brown: . . . yep. I think we are ready for lunch. We can do lunch early and I have 11:18.

Seth Schwartz: Maybe afternoon's work this morning to [crosstalk].

Josh Morse: . . . afternoon work.

Gregory Brown: Yeah.

Seth Schwartz: There's nothing else . . . we, we can't get started on any other topic early in any way?

Sheila Rege: That would be great.

Josh Morse: I don't know . . . Dr. Skelly may be here in the next 15 minutes. I think she was going to be here at 11:30.

Sheila Rege: [inaudible] with Josh?

Gregory Brown: Yeah. Absolutely. No, I've, I've got a flight to catch. I'm going to Chicago for a meeting. So, I'm happy to get out of here early. So, yeah.

Female: Excuse me. I would like to take a moment to introduce Dr. Judy Zerzan, our new chief medical officer. She just snuck in. So, I want to make sure everybody attaches her with a name in case you'd like to chat with her during lunch or something. Welcome Judy.

Gregory Brown: Welcome. Well, since we have all this time, would you like to introduce yourself and give us a little background?

Judy Zerzan: Gee, sure. I can see some of you around, I guess, uh, the table. Yeah. So, I'm Judy Zerzan. I've been here about two and a half months now. I'm a general internist and I came from Colorado. I was chief medical officer of the Medicaid agency there for almost ten years, not quite. I'm originally from the Northwest. I grew up and did most of my training in Oregon, and I did an RDBJ [sounds like] Clinical Scholars program here for three years. So, it is very nice to be back. I have a lot of interest in data. I was a health services researcher for a little while in academics before getting into the Medicaid gig and thinking about payment reform and levers for that. So, I have long from afar admired this committee. In fact, I had tried three times to get Colorado to adopt one. So, I'm quite excited that I can be adopted into such a well-functioning and useful committee, I think, for public service. So, thank you all for your service and being here.

Gregory Brown: OK, just from a process and time perspective, can . . . I have 11:20. Can we reconvene at 12:00. I know we have the public announce . . . for public comments at a specific time. So, we may need to do the agency presentation, the evidence report, and then public comment after so that it's the appropriate time. Would that work? OK.

Seth Schwartz: So, we can't do anything now?

Gregory Brown: Well, we can start . . . yeah. We can get started at 12:00. Again, the problem is . . . well, again, let's just set, I mean, we got lunch. Let's just have lunch and then . . . like I said, the problem is, is because it's a public meeting and we posted what time they can make public comments, if we change that, then they can come back and say you said this time and then you were . . . we never got a chance, so.

We are ready and eager to go. So, we are ready to start our afternoon for our second topic. We are doing PET scans for lymphoma. It's a re-review, and our technical expert is Dr. Rajendran. Would you . . . we'll let him tell about himself in a minute. Would you like to introduce yourself?

Joseph Rajendran: Yeah. I will.

Gregory Brown: OK.

Joseph Rajendran: Yeah. I'm Joseph Rajendran. I'm the [inaudible] of radiology at the University of Washington. I specialize in Nuclear Medicine. My background is radiation oncology.

Gregory Brown: OK. Thank you. We will start with the agency report.

Charissa Fotinos: Excellent. Thank you. Good afternoon. My name is Charissa Fotinos. I am the deputy chief medical officer for the Health Care Authority. I want to start just by saying an appreciation to Aggregate Analytics for what I thought was an outstanding report. This is extremely complex and nuance subject. So, I just want to say that I think you did a really fantastic job. So, thank you all.

This is a re-review. We last looked at this in 2011, about to the date, actually. I don't know if that was planned, but at that time, the limitations of coverage decided that one scan for initial treatment planning was appropriate, and if additional scans were needed for restaging or for progression that could be up to the agency's approval. There was no coverage for routine surveillance. Since that time, there have been more recent literature that's come out, and the request and decision was made

to look at this topic again and really focusing on different stages of treatment and the utility of PET/CT scans, primarily most of the time, unless I say PET alone, I'm referring to PET/CT, because that's what most of the literature was investigating, but looking at initial staging, interim treatment, prognosis both during and at the end of treatment, end of treatment status, end of treatment confirmed relapse, and its role in surveillance. For the purpose of this discussion, surveillance means evaluation of asymptomatic patients in remission.

For key questions, similar to all reviews in patients with histologically proven lymphoma undergoing PET/CT at any time after initial diagnosis. What is the evidence of clinical effectiveness of 18 fludeoxyglucose PET/CT results? What's the evidence of the safety of the PET/CT imaging? What is the evidence that imaging has any differential efficacy or safety issues in subpopulations? What is the evidence of cost-effectiveness?

These are some just images of PET scans. The first is diffuse large B-cell lymphoma, and you can see that the uptake here is quite avid, quite bright. This is a high avidity uptake. The next is Hodgkin lymphoma, also considered an avid uptake but a little less so. Anaplastic lymphoma large cell, quite high affinity in the mediastinum, as you can see. The next is a follicular lymphoma showing just the PET scan alone. Then, the small lymphocytic lymphoma has low avidity, as well. So, it was kinda fun for me to find these pictures and put them in here.

As I read this 200 and however many page report, I came to the realization of lymphomas is much more broad than I learned in medical school a long time ago. There are the types of Hodgkin lymphoma, the most . . . the ones that occur with the most frequency are the nodular sclerosing and the mixed cellularity make up about almost 90, 80-90% of classic Hodgkin lymphoma. Then, that's a pie chart of non-Hodgkin lymphoma subtypes showing follicular lymphoma, diffuse large B-cell, as two of the most common. As I was trying to learn a little bit more and refresh my memory, I read something that there are now about 90 subtypes of lymphomas, and I say that, and I think it's important, as we move through this, in terms of the context of the recommendations the agency medical directors have made.

Our concerns were medium, in terms of safety, efficacy high, and cost medium.

These are the diagnosis codes that were used to pull the information for the utilization across the agencies of the Health Care Authority and Labor and Industry. The procedure codes vary by what type of the body is being

imaged. Then, there is an unspecified body part image at the lower. Then, the modifiers are used either for initial staging or subsequent scans after initial staging.

You can see that there has been at least the last few years some steadying off, but a large increase from 2015 to 2017. Few patients got more than one scan. You could say that's either because we only limit it to one without a need for prior authorization, or people are frugal in using them, and the cost is about $1000 in terms of agency paid amount per scan.

What are other coverage policies? Per our decision in 2011, we cover them under no conditions across the agencies.

Other payers. . . CMS national coverage decision allows for a PET/CT scan for initial staging followed by three more during the course of treatment. They do not allow coverage for surveillance. Regence uses the AIM Specialty Healthcare criteria, or Health criteria, and they break it down a little bit more by type of lymphoma, as to how many scans you can have, but they allow at least one. AETNA has a policy for coverage diagnosis that includes usually staging and restaging. Then, Cigna, as well, covers two to three, varies whether or not it's Hodgkins lymphoma, and they do not cover surveillance scans.

The report will go into much more detail about the studies, but in terms of accuracy and early Hodgkin lymphoma. For initial staging, PET and CT is better than CT alone. Interim accuracy not really any new studies. At the end of treatment, there are more false positives than perhaps was initially thought earlier with the last review. The prognostic accuracy during interim treatment has a good negative predictive value. So, if it's negative, that's helpful, but if it's positive, not so helpful. The prognostic accuracy after the first treatment is neither sensitive nor specific. Inter-rater reliability is moderate to substantial. Though there were some pediatric studies, the conclusion that the evidence was insufficient to make a recommendation or informed decision.

Thinking more clinically pertinently a prognostic influence, using the PET/CT to inform prognosis at the time of initial staging, it's not clear that there is evidence to do that, but I would venture that we'll hear form our expert that most staging does start with some sort of imaging. Whether or not used to upstage or downstage, there are mixed results. The decision as to the study, as to whether or not people actually change their results were not compelling, and there were not patient-oriented outcomes. However, there were some utilities in terms of informing treatment escalation. When the PET scan was positive and additional treatment was

employed, thee was improved five year survival; however, at the cost of increased Grade 3 and 4 toxicity with a number needed to harm of about 25. I would say that's a perfect place for shared decision-making . . . informed decision making. In terms of using it to inform treatment de-escalation, PET adapted therapy when the PET scan is negative, showed that there was little difference in terms of omitting radiation when the PET scan was negative, which, given that the likelihood of survival is high, it reduces the risk of secondary cancers due to radiation. So, if radiation can be avoided, that's a good thing, though the followup was not long enough to really look at secondary malignancies. There was not much information on the toxicity difference, but presumably one could think that might play out that way.

For advanced Hodgkin lymphoma, similarly, interim and end of treatment used to assess for treatment escalation in the face of a positive PET scan, really not any difference that was significant in terms of survival or toxicity. In terms of changing treatment due to an interim scan with a PET negative scan, again, survival times were not diminished when radiation was left out. So, you could say there was utility there. In terms of relapsed/recurrent Hodgkins or non-Hodgkins lymphoma, really insufficient evidence to speak to relapse at that point, though there was mention made that when relapses were done along with the development of clinical symptomatology suggesting a relapse, then the scans were much more useful and predictive.

Looking at aggressive non-Hodgkin lymphoma, accuracy of the diffuse large B-cell lymphoma, in terms of diagnosis, there are mixed findings, staging not really updates from the last report. Interim and end of treatment testing for accuracy alone, quite a wide range of both false positive and false negative making it not necessarily accurate for interim staging, and then surveillance it has a low positive predictive value. In terms of prognostic value, again, a wide range of sensitivity and specificity and the end of treatment if PET positive that is associated with a lower progression-free and overall survival.

In terms of the prognostic influence, initial PET scanning with diffuse large B-cell lymphoma did lead to about 10% of patients being upstaged. So, the evidence was from observational studies and felt to be of low quality. Interim negative adapted therapy, again, there was no difference in overall survival without radiation when used in early stage, so again, might be useful to help not expose someone to radiation that may not prolong survival. Then, relapse surveillance, again, when it was used along with clinical symptoms, then there was improved detection of relapsing non-Hodgkin lymphoma. I will say that these studies were complex. They were

not consistent in the types of lymphoma they looked at. So, trying to parse out by each study what the [background noise] lymphoma and which stage was looked at is done in a report, but for the purposes of this, I sort of generalized, based on the most common lymphoma types.

In terms of safety, the estimated exposure from a PET/CT is about 25 millisieverts. So, you can see that we're exposed naturally over the course of the year to about 2 millisieverts of radiation. Then, if you say three or four scans during the course of active treatment, 100 millisieverts, that would be the annual dose at which any increasing cancer could be expected, which these folks have cancer. So, it's not an insignificant safety concern, but it's relative to other things.

There are no studies to inform the difference of impacts on subgroups. Cost-effectiveness studies were either of poor quality or evaluated limited use cases and really aren't useful to draw substantive conclusions.

So, the way I tried to sort of think through this is a very busy slide, but across the top, I tried to put the three buckets, as it were, of lymphomas, each for staging, interim treatment, or evaluation, end of treatment, prognosis, and then surveillance. So, looking at Hodgkin lymphoma, avid tumor, there is actually some evidence that it's useful for the diagnosis, in terms of accuracy. Aggressive non-Hodgkin lymphoma and diffuse large B-cell lymphoma, mixed evidence as to the ability for staging. Then, the T-cell lymphoma, extranodal marginal in the small lymphocytic lymphoma, really not, non-avid tumor and really were not specifically called out in that, though I would say for staging, I would . . . and we can, when I'm finished, we'll hear from our expert, if any therapy or planning is done without some sort of initial look of where the PET/CT scan in any of these lymphomas. IN the interim, there is evidence of moderate strength that suggested Hodgkin lymphoma there is clinical utility. There is [background noise] evidence as far as aggressive non-Hodgkin lymphoma and the diffuse large B-cell lymphoma. As to the clinical use of it, in terms of either escalating or not proceeding with radiation, there is not really evidence to support interim use in the red box, either, at the bottom of interim. In terms of end of treatment, PET/CT in prognosis . . . I apologize both for my cough and that some of the colors are not accurate, but Hodgkin lymphoma, when I actually looked at this again, there is some mixed evidence, as opposed to insufficient, that there may be some clinical benefit, aggressive non-Hodgkin lymphoma was not as clear in terms of evidence support for a benefit. Then, the T-cell, again, not enough evidence to really support either way. Then, for surveillance, it was pretty clear across all lymphoma types that it's use for surveillance in the absence

of clinical symptomatology is not recommended. There's not enough evidence to support the utility of that.

Gregory Brown: So, if it's not avid, then FMG isn't going to go there. So, it's of no value. Correct?

Charissa Fotinos: If it's not avid, is there, yeah. What I was, if it's not avid, you can see bulk, but you're not gonna see any uptake. Is that correct?

Joseph Rajendran: Yeah. That's correct. Yeah. The FDG is based on glucose metabolism. So, it's functional imaging compared to CT. CT will give us information about the bulk and the size of the tumor for staging and other things, but there may not be much uptake in these tumors. So, that doesn't mean that they're not malignant. It is how the biology of the tumor works. Some are, like, carcinomas also . . . some carcinomas are very avid for FDG and it all depends on how well they are having the glucose metabolism, glycolysis. That's what is happening in the tumors. So, here, the PET/CT itself and the role in this non-avid tumors, non-FDG avid tumors is kind of . . . it's still not very clearly established, because it's not going to help, like, the Hodgkin's disease or aggressive basal lymphomas.

Gregory Brown: OK. So, could you go back to . . . so, the red is not . . .

Charissa Fotinos: The red is not . . .

Gregory Brown: . . . supported. The purpose has insufficient evidence. Then . . .

Charissa Fotinos: Let me qualify. By non-supported, it means there is not evidence either way. It does not mean that there is evidence that shows it's not effective. It's just, I probably should have left it insufficient. We don't know that the utility is as present as it is in some of these other types of tumors.

Gregory Brown: What's the difference between mixed . . . I would interpret that as mixed evidence. So, if you've got . . . mixed evidence is some support it, some don't? Some of the evidence [crosstalk].

Charissa Fotinos: Yeah. So, they're supposed to say insufficient. I should have, I, I got too crazy with my colors. I apologize, but, this was just, I was so confused by all of this, but I would, at this point, say insufficient and not supported, I would consider those somewhat the same. Either there wasn't enough information in the report and literature to say we should do it for this, or we shouldn't do it for that, as opposed to don't ever do it, but there is one could argue utility in seeing if the size of the tumor is changing.

Gregory Brown: I guess what I'm seeing here is, it's only the 2x2 in the upper left corner that you would say are appropriate indications?

Charissa Fotinos: No. End of treatment, there is some prognostic information on Hodgkin that should be, you know, let's just, let me, let's forget that. Let's use this number slide. OK? So, here's the summary in which I think is more explanatory than that was. So, there are multiple lymphoma types. There are evidence that supports the use of both improved accuracy and diagnosis in staging of some lymphomas but not all. There is evidence to support the use of PET/CT at interim and at the end of treatment periods, both to help determine the intensity of treatment and to inform prognosis for certain types of lymphoma, again, recognizing there are many types. Evidence does not support the use for routine surveillance to assess recurrence in asymptomatic persons. Really, the whole context in which I approached this was, thinking about it from either a provider having to fill out a form and check all the boxes of which tumor it is, which stage it is, what kind of avidity it is, and our agency trying to make themselves crazy understanding what to approve for when. So, in terms of our recommendations, we essentially are following the NDC recommendations to allow up to four scans per active occurrence of lymphoma allowing for the initial diagnosis or staging, and then really leaving it up to the provider to determine, based on lymphoma type, what is and isn't appropriate. The notice there about when scans should be done after chemotherapy and radiation. I took that out of some literature. Our expert can help inform us as to whether or not those are the right numbers, but I think similar to the conversation we had this morning, you don't want to do things too early, because you may get false positives. Then, recommend that a scan is covered for relapse in the presence of clinical symptoms, but surveillance is not covered. These, again, are consistent with the national coverage decisions for Medicare, although they don't specifically call out relapse but do say you can request additional scans, if indicated.

Gregory Brown: Thank you. We are not scheduled to do public comments until 12:50. So, that's about 25 minutes.

Female: Nobody signed up here, so.

Gregory Brown: Well, yeah, but we . . . I think at 12:50 we should get on the phone, but any questions here, or do we want to go to our evidence report or?

Sheila Rege: Yeah, I have . . . yeah, go ahead. Sorry. I have questions for our clinical expert. I do like leaving it up to the treating physician. Can you comment

on false-positives, false-negatives, especially at the interim treatment point?

Joseph Rajendran: The false-positive means that there is uptake of FDG in the tumor, and then, when they chase to make a diagnosis, a biopsy, or other things, then it comes out as just in [background noise] tissue or other things. The FDG [inaudible] PET/CT there is always, when you do the interim, um, interim PET/CT . . .

Kevin Walsh: Excuse me?

Joseph Rajendran: Yeah.

Kevin Walsh: Could I ask you to speak into the microphone, please? Thank you.

Joseph Rajendran: OK. I'm sorry. So, the FDG PET/CT, at the end of treatment, there is always some uptake. That's why we usually give some time for [inaudible] cancer or other things when you do it within a month or so. There is always some positive uptake. That is all because there are a lot of things taking place. If it is a chemoradiation therapy, there is a lot of inflammation going on. Then, there is also apoptosis that is going on. Apoptosis is a result of treatment is an active process, and that utilizes glucose for its metabolism, but that means there are programmed cell death that is going on as the result of therapy. That is not a bad sign, but that always complicates, because we, as clinicians and also imagers, are used to looking at something that is positive. When it is positive, we usually put a negative connotation to that and say that this is . . . the tumor is still there. Not all positive . . . false-positive tumors may have negative connotation, but the problem is, we have to, when we are using that to escalate or deescalate tumor therapy, then one needs to be careful about that thing. In [inaudible] cancer, we don't repeat it more . . . before 12 weeks or so after therapy is completed, but in this case, when you do an interim PET, it is very difficult to wait for that length of time, but there are some other markers that will be available, but we are only talking about the FDG PET at this point in time. The false-negative can be . . . it's usually not a very frequent occurrence in lymphomas, but because lymphomas are very FDG avid, we would have known that at the first scan itself that it was very avid or not, and it's very rare for it to become FDG negative, false-negative during the course of the therapy, because a lot of things are going on in this process. Also, the times when FDG can become false-negative is usually in squamous cell carcinomas the majority of the time, because there is a lot of necrosis that goes on in those tumors, like, anything other than lymphoma, there is a lot of necrosis. The necrosis is as the result of blockage of the blood cell plate itself. Although lymphoma is kind of similar

to other solid tumors, there is not much angiogenesis that is going on. So, that is where you don't see that much necrosis in these tumors. So, it's a little bit of a complex biology. Did I answer your question?

Sheila Rege: yes. This is Sheila Rege again, and any comments on . . . I know there was on the interim, there was some issue about limited stage versus extensive stage on the interim PET imaging. What do you usually do in your practice? Have you seen any in your practice?

Joseph Rajendran: When you say limited stage, what exactly?

Sheila Rege: Like Hodgkins or lymphoma?

Joseph Rajendran: Yeah. I mean, it's the same thing, I was talking to the medical oncologist, the lymphoma specialist a couple days ago. Then, he mentioned the same thing. I mean, they do the interim PET, and then based on that, then they change the management. They go to the next line of therapy based on that. It has come a long way, from a long time ago. Somebody makes a diagnosis, and then they get six cycles of chemotherapy in respect to what was happening, but now we are in a position to use this type of tumor markers, like, FDG, PET, which is good, but again, we need to be cautious about how we are going to use that thing.

Mika Sinanan: Thank you. Could you go back to slide 21? It's the summary slide. So, in the third bullet point, this talks about interim scans at the end of the treatment period to determine . . .

Charissa Fotinos: Oh, add at. There should be an at, and at the end of treatment period.

Mika Sinanan: . . . and at . . .

Charissa Fotinos; I combined them.

Mika Sinanan: . . . to help determine intensity of treatment, the next treatment, or the effectiveness of the treatment that they just completed.

Charissa Fotinos: So, if it's interim, it would be helping to determine the need to either escalate or hold or not proceed with the next treatment. If it were the end, and there were residual tumor, I would assume that that would inform next steps if there were still remnants. So, in that sense, was it interim and end, it would potentially improve, inform prognosis and future testing. Does that make sense?

Mika Sinanan: So, this is an action step where it could change the treatment.

Charissa Fotinos: Yes. Correct.

Mika Sinanan: And, I presume, on the second bullet point, it would also, by determining the staging and accuracy of diagnosis, it would also be an action step in changing the treatment?

Charissa Fotinos: You may choose different therapy based on something you weren't aware of. Yes.

Mika Sinanan: And then, the final point, I'm not sure I understand where the burden would be. Do you mean by different types of lymphoma?

Charissa Fotinos: Right.

Mika Sinanan: Different coverage decisions?

Charissa Fotinos: Yes. Different numbers of scans and . . .

Mika Sinanan: So, we have to have a uniform standard across all lymphomas or just across Hodgkins versus non-Hodgkins?

Charissa Fotinos: Well, see, that's partly why I showed that confusing slide. I mean, we could, we can do it however you want. What is not necessarily tenable from an agency standpoint is to list a number of lymphomas and then say, this one gets one scan. At this point, this one gets one scan at this point and this point. So, from a implementation perspective, that would be extraordinarily burdensome, and it would just cause you all to fill out more forms. That said, certainly we can focus only on the lymphoma, the non-Hodgkin lymphoma, leave all the rest out and say we don't know. So, no, and we're just going to allow that number for, for this. I think we wanted to, at a minimum, align with the national coverage decision parameters. Again, because of the number and type of lymphomas are so many, and the nuances of where in the course of treatment and at the end these scans occur, it seemed at the end, because of the . . . because the research is changing, and they're becoming more useful, it seemed more sensible and practical to leave it up to the decision of the provider at that point. We can put limits around it, if that's what you feel the evidence says more appropriately, but from an implementation standpoint, it's doable, but it would be extraordinarily complicated.

Mika Sinanan: So, that's why on the next slide, you don't distinguish non-Hodgkin lymphoma from Hodgkin lymphoma, and just say said number of scans for a diagnosis of lymphoma and then leave it up to the clinician to determine . . .

Charissa Fotinos: Clinician to help . . .

Mika Sinanan: . . . when to do those?

Charissa Fotinos: . . . exactly, and hope that the clinician is adequately informed to make a decision at the appropriate points, but just looking at, we rarely got requests to do more than one per person when we looked at our utilization. So, it's . . . and we wouldn't have refused people if they would have asked, because we're not going to second-guess a radiation oncologist or an oncologist. So, the fact that it's only used once, we were not particularly concerned about, you know, a massive increase in utilization. We'll track it if that's what the committee ends up supporting, or if you have something different. We'll obviously track it, but again, the nuance and complexity just, I couldn't find a straight line between yes and no. The evidence says only do this, not do that. You may be convinced otherwise after the report.

Mika Sinanan: Thank you.

Joseph Rajendran: Also, one additional point, adding to the complexities, some of the low-grade lymphomas, like the follicular lymphomas, they start off as non-FDG avid. Then, they transform. Then, they become into an aggressive form of malignancy. That's why the spectrum is kind of very void and broad. It's very difficult to give a binary decision. That's where the one diagram, there is a lot of overlap in the middle. We are making every effort to understand the biology and then see how they respond to chemotherapy. What we are talking about is traditionally the anti-DNA directed chemo and radiation therapy, but with the immunotherapy coming into the picture, that is also causing additional complexities here, because when a lymphoma [inaudible], they become metabolically active by rapid proliferation. They are also expressing receptors for the cell types, like B-cell lymphoma, CD20 antigen are expressed. So, there may be other . . . in the case of follicular lymphoma, there may be other markers that are positive. We had two agents, [inaudible]. They both target CD20 antigens. That may, at some point, will also be used, but it will be in the future, but at this point, we have to live with this vague thing. In nuclear medicine, we frequently come across some intermediate zone, which is kind of always complex. We started off with pulmonary embolism when we used to a VQ scan. Then, we always had that. People always say, you know, you should call it . . . why don't you have a binary decision, positive or negative. It's kind of very difficult at this point. When overall the treatment of cancer itself is evolving, we are almost . . . we have come a long way, but we still, in the process, are where breast cancer treatment was about 60, 70 years ago, or even 100 years ago when [inaudible] radical mastectomy was the

mainstay of treatment, it took a long time for people to change their philosophy of management and how they evolved into simpler form of therapy, because our understanding of the biology has come a long way, too.

Charissa Fotinos: I would just add one more comment, Dr. Sinan, to your last question. If you look at the studies, there were not studies that were uniform across either the chemotherapy regimens, how long they were used, how they were used in conjunction with what. So, again, trying to pull out from there, do we, with this regimen, because that studied showed that it worked, we'll give it for that one but not for that one. So, again, just from an implementation perspective, into the grayness, was a challenge.

Mika Sinanan: I have a question for Sheila, actually. Do you, or do you think that oncologists track the number of PET scans that are done? I mean, how do you know, except for a denial occurring, that you've gotten to three of four? Or is that . . . does your EMR tell you? Ours certainly does not.

Sheila Rege: No, but I think we always just know that Medicaid only covers it for the initial screening. So, we don't even try it, and if we have doubts at the end of treatment, head and neck cancers, you definitely wait 12 weeks. After lymphomas, I tend to wait six to eight weeks, just to kind of let everything cool down and make sure that the bone marrow is not an issue with chemo. The interim is where I struggle, because that's where you, you're continuing the chemo and you can . . . you don't have the luxury of waiting. There have just been so many false-positives and false-negatives, but yeah. We do track, because at one time Medicare actually had something where we could only do three in a lifetime or something.

Charissa Fotinos: I think it was four.

Sheila Rege: It was four? It was, yeah. So, we do . . . patients know. They'll say, I already had that, because when we start, we tell them we're going to hold that.

Gregory Brown: OK. Thank you. So, we have, well, 13 minutes or whatever until the public comments. Why don't we get started. There's nobody signed up for public comment here. My guess is nobody is on the line, but just because this was publically posted as an open meeting at 12:15, we'll take a break to make sure there's nobody on for a public comment. Then, we'll resume the evidence report. [30:00]

Andrea Skelly: I'm Andrea Skelly from Aggregate Analytics, and we're pleased to share with you our fun times in this report. I would like to take a moment to publically acknowledge Noel Weiss from the University of Washington who

helped us with some of the methodological issues that we faced in this challenging report. As you've heard from both the agency, Dr. Fostinos, and our clinical expert, this was a very complex and challenging topic to try and boil down. So, I hope you'll bear with me a little bit, as we go through some of the nuances, and I am hoping not too many of the nuances get away from us.

As you know, it's an update to a prior report that was done in 2011. The prior report used a rapid review technology where selective sources were evaluated and only selected systematic reviews were used for the basis of the report. There is a lot of new evidence, as you've seen in the report, since that time, and our objective was to update what the 2011 report did, mainly in terms of the diagnostic accuracy aspects but then to add on more clinical utility related data that has come into being since then.

As you know, there is a continuum of medical studies that can be done. The first report and our report did not address the first level of medical studies, which is basically looking at the technical efficacy and analytic validity. Basically, is it a feasible type of test. The 2011 report, we focused on the diagnostic accuracy aspect. We updated those to some extent in the contextual question for our update report, but our focus on the report is on the more clinically related aspects, the clinical validity and use of the test for diagnostic thinking efficacy, therapeutic efficacy, looking at patient outcomes, and clinical utility, as well as cost-effectiveness.

By way of background, Dr. Fostinos' slide is certainly much more accurate and complex than mine, but much more pleasing. As you've known, there are a lot of different types of lymphomas, even within the major types of lymphoma. We don't need to discuss that any further.

I would like to make a distinction between diagnosis, at least how we use it in this report, and staging. From our perspective, diagnosis relates to the initial diagnosis, which includes a biopsy that is really the only way that you're going to get at a definitive diagnosis for this type of lymphoma. That said, PET/CT, I understand from our clinical experts that provided input into the report, might be used to help identify where the best place for a biopsy might be.

Staging, then, after the initial diagnosis, is done using the Ann Arbor criteria, which started in 1971 as a very basic criteria, and in 1989, CT was added so that you could evaluate maybe more distribution of the tumors, and over the last couple decades, the ability to evaluate the metabolic aspects and add to the morphologic characteristics has come into being. So, now PET/CT is now a standard part of the staging process for PET/CT,

for lymphoma. As you know, PET uses the radioactive tracer and that abnormalities can concentrate that radioactive tracer to create a hot spot, and the distribution of these then informs the staging criteria, as you see here. Stage I or II is usually above the diaphragm. Stage III is now above and below the diaphragm. Then, stage IV is in multiple sites and multiple areas.

With regard to treatment, there is a whole range of treatments. There are some standard treatments recommended by clinical guidelines. However, many of those are now being supplanted by other types of therapy, including immunotherapy. So, that has evolved. It's tailored based on the type of lymphoma, the disease stage, the age, and if there are other coexisting medical conditions that need to be considered, and the aim is to be able to balance a high survival with decreasing the amount of toxicity, especially early in treatment. PET/CT has become an integral part of evaluating the evaluation to treatment, the response to treatment, usually in conjunction with clinical examination symptoms and possibly other types of testing like blood work, and there is always a need to monitor toxicity. In the past bit of time, there has been an emergence of the PET adapted therapy, as our clinical expert was discussing. Using PET usually at the interim or at the end of treatment to identify individuals who may be at higher risk or lower risk of progression or relapse to help inform management, which could include escalation of treatment, de-escalation of treatment, discontinuation of ineffective treatment, or consolidation of treatment and anything in between.

By way of background, you are already familiar that it's part of nuclear medicine imaging and that the 18-FDG uptake is taken up by abnormal areas. The current standard of care is to use PET in conjunction with CT. That could be done separately. PET could be done separately from CT, but most areas use now a combined PET/CT scanner for initial staging and for reevaluation at critical points and/or after treatment, but again, from our perspective, the way we've defined diagnosis, it's not related. We have not looked into the diagnosis.

Gregory Brown: Can I just ask a general question of our expert, or?

Andrea Skelly: Sure.

Gregory Brown: Is there any significant difference between the separated or integrated PET/CT scanner?

Joseph Rajendran: When the PET imaging was first developed, it was only a single PET image available. So, what has happened was, we have to look at the PET images

separate and then CT separately, and then mentally, we use to fuse. That has changed now with the two scanners placed in tandem, but the main difference is that it need not be a full-fledged CT scan, high-dose diagnostic CT scan. It can be . . . it is only done . . . it's a low-dose CT scan done only for an attenuation map creation. Then, you fuse these two images so that they are easily identifiable and there is no mental fusion going on. So, that is the advantage, but you can hardly see any standalone PET scanner these days. We used the last one when FDG was developed about 30 years ago at the University of Washington. We used to have it but not anymore.

Gregory Brown: OK. Thank you.

Andrea Skelly: With regard to the use of PET sort of in the interim, there is discrepancy across clinical guidelines about its use and currently some indicate that they would not use interim PET to change treatment just based on the interim PET alone but contingent upon consideration of clinical aspects and other patient presenting aspects. There are some data to suggest, as you saw in Dr. Fostinos' slides, that PET may assist with prediction of prognosis later on.

As you've learned, nuclear medicine has evolved substantially from the older days of gallium scanning where you can just see amorphous blob of stuff in the abdomen compared to now PET/CT where you can more readily identify the margins and the avidity of the lesion. So, you have both anatomy and function. You are able to evaluate to evaluate in the same type of equipment. Not only has the equipment evolved, but so has the interpretive criteria. The interpretive criteria are very important. PET/CT can be somewhat subjective, and over the years, they have attempted to . . . groups have attempted to increase the objectivity of assessment early in 2000 and before visual evaluation, just comparing the intensity of uptake from the mediastinal blood pool was used to evaluate end of treatment. More recently, some quantitative methods from a conference in Lugano, Switzerland, called the Deauville 5-point scale, had been used and are basically what are currently used in most of the studies that we have seen here and in clinical practice, from my understanding, and it's used as a basis for evaluating response to treatment both at the interim and end of treatment stages. The criteria are still evolving. There are opportunities to look at maybe the standardized volume uptake that may change from baseline, and during the course of treatment at the end of treatment. So, things have evolved. I say this because it adds to the heterogeneity and complexity of the studies that we've reviewed, and that some of the criteria that were used in some studies were the visual criteria later on, as the Deauville 5-point scale came into being. They started to

incorporate that. So, you have a lot of heterogeneity within the studies themselves.

So, here's the Deauville 5-point scale in its most basic, general format. Basically, it includes two reference points, not only the mediastinal blood pool, but the liver, as well, and you are on a scale of one to five, one being best, five being worst. The score you get helps inform and create them, distinguishing them . . . the opportunity to distinguish between whether or not you are in complete remission if you have low scores of one, two, or three, and no avidity, regardless of what is seen on the CT. Partial remission, score of four or five and decreased uptake versus baseline and no progression on CT stable disease. No changes really, and then progressive disease where you have increased intensity versus baseline and/or new foci of tumor. So, the Deauville scale, the 5-point scale, is the primary things that's used.

Gregory Brown: Excuse me. I think I'm going to interrupt there. I've got 12:50. So, if we can unmute the microphones. Hello. This is Gregory Brown. I'm the Chair of the Health Technology Clinical Committee. We are discussing reviewing PET imaging and lymphoma. It is a re-review. We are wanting to know if anybody is on the line for a public comment. I'm not hearing anything. So, OK. Sorry for that interruption, but we have met our public . . . open public meetings criteria. So, OK. Please resume. Thank you.

Andrea Skelly: OK. No worries. So, as I mentioned, studies may have used different criteria for PET positivity, which again, adds to the complexity and heterogeneity of the different studies. The other thing to point out is that the Deauville criteria were primarily developed around traditional therapeutic regimens. Some of the newer regimens now are trying to rethink some of the criteria for PET positivity. As Dr. Rajendran mentioned, some of the newer agents, the immunomomodulary agents may impact the way FDG is taken up, and that then, in turn, influences the interpretation. The other aspect of that, that was mentioned, is the timing relative to treatment. If there is still inflammatory process that's involved, you may get PET that is being uptaken when there really isn't as active a lesion as one might presume based on the level of activity. There are also some limitations to PET, some of the older images. The resolution was maybe only 6 to 9 mm that may then lead to some false negatives, and you may then not necessarily be able to say, with impunity, that the tumor is all gone. Then, as was mentioned before, there are a number of false-positives that can occur with inflammatory changes. So, the timing and the type of treatment, all of those things potentially go into some of the false-positive results.

As I mentioned, this is a very complex topic, because not only are we dealing with a number of different types of lymphomas, the literature that we were asked to evaluate is all over the map in terms of when PET and CT are done. So, again, we're not looking at initial diagnosis. We're looking, starting with anything after the initial diagnosis, biopsy proven, and this is the body of literature that we looked at. In terms of the language, some of the older studies would call the interim path a different thing, and we tried to be as standardized as possible in the terminology, but there are maybe some differences, because the terminology is [inaudible]. Again, the literature and the guidelines vary with respect to how useful PET is at the interim stage in particular, and as was mentioned previously in terms of the flow of things, generally patients will have a firstline of chemotherapy. An interim PET will be done at some time. In the literature that we're reviewed, it's anywhere between two and four, sometimes six cycles of therapy. Then, there may be the decision to randomize patients to continuing treatment or to escalate treatment, or to de-escalate treatment based on PET/CT findings. Then, they would maybe go on to an end of treatment PET at the end of the firstline of treatment to evaluate tumor response to the treatment. Then, there may be consideration of whether they do no further treatment, they consolidate treatment, or maybe they need to do salvage therapy. Then, you can also have a set of interim PET scans during that point, as well.

For our purposes for the report, relapse evaluation is when there is clinical suspicion of recurrent disease or relapse disease and surveillance among symptomatic patients in complete remission. If you're interested and you need further stuff to sleep, in the appendices, we have outlined what we could from the studies about when they did PET based on this very general algorithm.

Moving onto the contextual question. The contextual question was basically again to update any information on the diagnostic accuracy and diagnostic performance of PET CT.

The key questions, you're already familiar with, looking at the clinical efficacy, safety, differential efficacy and safety, and cost-effectiveness.

The PICO criteria for this report are anyone with basically a biopsy-proven lymphoma, 18-FDG PET is the intervention. Then, we looked for studies that either compared it to other imaging, to CT, to clinical followup, and we really would like to have found some studies that compared it to a no PET/CT strategy, realizing that that would be a very difficult opportunity, that really would give us the best information. The primary outcomes that we evaluated were overall survival and progression free survival or event

free survival, whatever is reported, as a result of the clinical decision making after the PET scan, as well as adverse events attributable to the PET/CT and cost-effectiveness outcomes.

We've already talked about the timing. For study design, we focused on the highest quality studies, those that we felt were at the lowest risk of bias, and for economic studies, those that reported ICERs were full economic analysis.

Each individual included study per PET adaptive studies was evaluated based on criteria you see listed here, which were modified based on the Cochran Review criteria and made specific to this review. Each individual study then contributes to the body of evidence and the overall strength of evidence the risk of bias is only one criteria to evaluate for the overall evidence quality or strength of evidence. Consistency, in other words, the degree to which different studies come up with the same conclusions is another part of it. Directness, then precisions, and publication or reporting bias are all considered in the overall strength of evidence. So, it's not just risk of bias.

In the systematic review process, this is where we, again, look at the efficacy using RSAT's, effectiveness for observational studies, harms, economic studies. We assess those. And then, we come to an overall strength of evidence of very high, moderate, low, or insufficient, depending on our confidence in the literature that we see for a specific outcome.

In terms of the results, we examined over 2400 citations and for the included publications for the key questions, there are 662. There are another 38 that were included for the contextual questions. So, there is a lot of literature to go through. We'll talk about each of those, as we go through the different things.

For the contextual question, I would like to preface a few things before we talk about that. First of all, as you probably got the impression from Dr. Fostinos' presentation, there was a lot of heterogeneity, not only in the accuracy parameters that were reported, but also in the studies that reported them, and the quality of those studies. So, rather than get bogged down in the specifics of the sensitivities and specificities, I think it's more productive for us to maybe look very generally through those and get to the clinical piece. It really is the meat of the report. In your executive summary, tables A through D, I believe, give you excruciating detail about what is found for the diagnostic accuracy parameters, but there was substantial heterogeneity in study design in treatments that

were used and reference standards that were used, timing on PET, intended use of PET, as well as types of lymphoma. So, to try to draw conclusions across all that is just not feasible.

So, for Hodgkin lymphoma, the accuracy for initial staging appears to be fairly high. That's one of the potential highlights. Diagnostic accuracy measures then also varied quite a bit, as you see, for differing timings of PET. We didn't have much information on pediatric staging. We had one small study that looked at pediatric patients, but there really was not a good set of data to draw firm conclusions about it. Again, there is a lot of heterogeneity.

For non-Hodgkin lymphoma, the sensitivity and specificity appears to be a bit different, a bit lower. Again, rather than spending lots of time looking at some of this, again, the ranges are quite substantial, in terms of the accuracy for the different types of non-Hodgkin lymphoma. The DLBCL is the most common, and that's where we had the most data. As mentioned previously, there are a number of false-positives that seem to be a little bit more prominent in the non-Hodgkin lymphoma data than what we had seen in the Hodgkin's, but again, there are so many caveats to that. The negative predictive values, as Dr. Fostinos pointed out, generally have been very good and something the clinicians found have been very important. When we get to . . . the only pediatric other type of lymphoma we have got to, there was only one small study of 34. So, it's very difficult to really draw a lot of conclusions about the accuracy of PET in this particular type of lymphoma in children.

Indolent non-Hodgkin lymphoma . . . indolent non-Hodgkin lymphoma tends to be very slow-growing and has some different characteristics based on what we found in the literature, in terms of its accuracy, maybe not so much as initial staging, but later on, it doesn't seem to be used as much for the indolent, unless, as was pointed out early, it tends to transform into a more aggressive form. So, in terms of reliability, the 2011 review did not talk about that. The bottom line is, in terms of reliability for the eight studies that we looked at, most of it was based on the Deauville 5-point scale and the reliability ranged from moderate to substantial. On pediatric patients, it ranged from fair to substantial. Again, this is all on the full report. There was one report that also discussed that the inter-rated reliability may depend on the criteria that were used, which makes sense, but also the reader experience with oncology.

So, in terms of the rest of the report, the meat of the report, here's the organization that we will go through. We'll look at initial staging for each type of lymphoma, interim assessment for each type of lymphoma, end of

treatment for each type of lymphoma, etc. Then, we'll get to safety differential, effectiveness, or safety, and economics.

Here is the body of evidence that we used. Again, given our intent to focus on the studies that may have the best data with the least potential for bias, we focused on the RCT of PET adaptive studies, because A, that's where the literature seemed to be most robust and where we could draw some level of conclusion. So, that means that there are a number of observational studies that are in your report that are not represented in these slides. We're perfectly happy to discuss those with you; however, most of them did not link the PET/CT results to changes specifically in treatment. So, specific changes were not enumerated, and they weren't linked to the outcomes with interest, the overall survival and progression free survival. So, I just wanted to let you know ahead of time. The PET adaptive studies are those that explicitly describe specific changes in management in response to the PET results. The number of patients that were impacted by that changes, as well as describing the prognosis, what happened to those patients in terms of overall survival and progression free survival.

So, even though there were no studies that evaluated a PET/CT strategy versus a no PET/CT strategy, we felt that the randomized control trials of PET adaptive studies provided, again, the best evidence with the least potential for bias.

I think it's important to provide some context for how we approached this particular report. One of the important aspects about any medical testing is to consider how useful is it. So, the value of a medical test really relates to its ability to identify individuals for whom there is an appropriate and effective treatment. That's really the clinical utility and clinical efficacy of a test. From our perspective, PET impact on the clinical decision-making could only be assessed indirectly. In other words, in the absence of studies comparing a PET/CT strategy to a no PET/CT strategy, this . . . we had to use this indirect approach. That involved looking at PET/CT outcomes as function of PET/CT in combination with the treatments that were received on the basis of those results. So, in other words, our approach was to consider the overall survival and progression free survival in relationship to the modifications of treatments that were received and the attempt to decrease the amount of toxicity. In other words, finding effective treatment with the lowest toxicities may be where the most value of PET may lie in identifying patients for whom the appropriate treatment is given. So, in other words, the value of PET for assisting with decision comes to escalate, de-escalate, continue or discontinue therapy, is indirectly assessed based on the impact of PET/CT adaptive treatment.

So, taking initial staging first, we'll probably be able to go through it pretty quickly with that. There were really no PET adaptive studies and only observational studies that were available. Again, your full report has more information than what I will share with you. The bottom line is that very few of them look at our outcomes of interest, progression free survival, or the overall survival. There were only two studies, and the evidence was considered to be insufficient. Both of them were . . . one of them was very small. One of them was a retrospective cohort with lots of potential for bias, and even though there were no statistical differences between PET/CT and conventional methods for staging, again, we felt that there was insufficient information. They did not provide how any information on how specific treatments were modified based on the staging. The bulk of the evidence for clinical effectiveness for initial staging came from 18 different observational studies. As you see here, they reported changes in stage, whether it was upstage, whether it was downstage. Very few of them really reported any specifics on how management was specifically changed, either whether it was upstage or downstage. Some postulated theoretically what they would do. Some provided . . . very few provided information on what they actually did in response to a change in stage. I think the bottom line here is that where patients were upstaged versus down-staged using PET/CT, the changes varied from 8 to 50%, and the actual change in management also varied, but again, we don't have any further data what happened downstream from that.

Moving on to interim PET, again, interim PET could be done after any number of cycles and any number of different therapies across the different studies that we included. So, there was a lot of heterogeneity. Some studies randomized patients who had positive findings to escalation of treatment. Some studies randomized patients with PET negative findings to de-escalation of treatment, or continuation of treatment. Some studies did both. Some of the studies that we included for PET-adaptive treatment were randomized control trials of an induction therapy. So, the study designs are all over the map and that adds to the complexity of all this. So, I'm gonna try to boil it down the best I can.

So, for interim PET, in patients with early stage Hodgkin lymphoma, looking at escalation of treatment, again, this may not be the standard of treatment, but escalation of treatment, in patients who have an interim PET that was positive, one can see that the overall survival was slightly higher with the escalated treatment. It may have not been statistically significant, depending on your perspective. The question is, could it be clinically important at 6 per 100 individuals. If we take a look at 5-year progression free survival, there was a statistically significant better progression free survival with the escalated treatment. We classified this

as moderate strength of evidence. Historically, based on sheer database information and clinical guideline information, the survival . . . history of survival . . . 5-year survival is about 93%. So, these are highly curable lymphomas.

If we take a look, however, at the toxicity related to that escalated treatment, we can see that across the board the escalated treatment was associated with higher toxicity versus those that did not receive the escalated treatment. So, obviously, there is a clinical tradeoff. Better survival, more toxicity. If we take a look, then, at the studies that looked at de-escalation of treatment, there were two of them, and basically, the overall survival was similar in both groups. The progression free survival was less common with a de-escalated treatment. Basically in these studies, they eliminated radiation therapy from the protocol in order to de-escalate the treatment, and it was only statistically significant in patients who had an initial favorable prognosis. So, again, that's another nuance that is difficult to really draw conclusions across, but it's unclear if the differences may be clinically important. They may be very small, except for, again, the patients who had favorable prognosis to begin with.

In terms of the toxicities, there was little data to draw any conclusions about the de-escalation, and there was likely insufficient time to really evaluate any secondary malignancies due to radiation therapy.

So, in summary, for early Hodgkin lymphoma, interim PET may be of most value for identifying patients in whom escalation of treatment may be beneficial. There was some evidence of higher progression free survival, and overall survival. Also, there was greater toxicity, which needs to be considered. The value of PET/CT for de-escalating treatments is, unfortunately, less clear. The differences were small and it was very difficult to really indicate that we had identified the correct patients for that.

If we now moved to advanced Hodgkin lymphoma and escalation of treatment, 3-year survival across two different studies was similar overall survival, not statistically different. It was statistically similar to progression free survival. There may be a clinically important difference in one study for progression free survival for the escalation of treatment. So, this is sort of the opposite of what we saw in the early-stage Hodgkin lymphoma.

In terms of toxicity, there really were not any statistical differences between the escalated treatment in these individuals, and the overall survival and progression free survival at five years were not statistically different. Toxicities, again, were not well reported for the advanced stage.

For advanced stage Hodgkin lymphoma de-escalation and survival, 3-year survival and progression free survival, were similar or slightly better with the de-escalated treatment, maybe suggesting that you could de-escalation treatment without compromising survival. If we take a look at the interim PET and the de-escalation at five years, it appears that there were only small differences between survival both overall and progression free survival when treatment was de-escalated versus the comparator. So, again, maybe one can de-escalate safely. Here are the historic 5-year survival rates, which, again, are high.

If we take a look at the de-escalation and the toxicity related to the de-escalation, mostly, you see that there is lower toxicity related to the de-escalation of treatment across the different trials and the different types of treatments that were given. They were less common in the groups receiving the de-escalated treatment. So, again, the value of interim PET may be for advanced Hodgkin's stage lymphoma, maybe to identify those in whom you can de-escalate treatment. The value for identifying patients in whom you can escalate treatment is less clear.

For relapse or refractory, the evidence was based on three very poor, very poor observational studies and was considered insufficient to draw any meaningful conclusions. As is the case with most of the observational studies, patients with PET positive findings generally did not have as good progression free survival or overall survival, as those that had PET negative findings.

If we look at aggressive non-Hodgkin lymphoma, again, DLBCL being the most common. We have two trials, and the results across those two trials differed, but they used very different treatment regimens, and they were not standard regimens, and they were very different study designs. So, it's very difficult to draw any conclusions with regard to those two studies. There was a third study in patients who had non-bulky, in other words, they didn't have a bulky mass or tumor, DLBCL, in early stage, and the progression free survival and overall survival were quite high, but there was no difference between those that got radiation therapy and those that were de-escalated to no radiation therapy. In terms of toxicity, again, you can see that there is higher risk of treatment related toxicities with escalated treatments. Again, they were using a different protocol, a very aggressive protocol and one RCT. Treatment related mortality was really fairly high. The strength of evidence for this was low, and they really did not provide . . . other studies did not provide any information on toxicity. So, in summary, for the aggressive non-Hodgkin lymphoma, the value of interim PET to identify those for escalation is unclear across the two RCT's, but again, they were very heterogeneous studies. There is limited data

from the one RCT to suggest that perhaps radiation therapy could be omitted from an identified patient with the negative interim PET.

If we take a look then at end of treatment PET evaluation, there, again, is very sparse information. We have two studies that we could evaluate . . . or one study that we could evaluate overall survival and progression free survival, and patients who had a large nodal mass on baseline were PET negative had similar outcomes in both groups, slightly better with the de-escalated treatment, but not significant for the progression free survival, and the omission of radiation therapy did not apparently affect survival but toxicities were not reported. Again, time may be an issue in terms of time to take . . . for some of those to be manifest.

In terms of overall survival for end of treatment PET for aggressive non-Hodgkin lymphoma, only one small study is actually a complete study. It was a subanalysis of a randomized trial. The data really were insufficient, even though the overall survival and progression free survival were lower for end of treatment PET. Patients with clinical evidence of disease and those who had persistent PET findings had lower overall survival and progression free survival. So, again, insufficient information for the end of treatment PET.

If we go on to take a look, then, at studies that evaluated either relapse evaluation or surveillance, there, again, were a paucity of studies looking at the things that we were looking for. There was one retrospective cohort that looked at a probability of overall survival, and basically the overall survival was similar for patients who were asymptomatic and evaluated periodically who were in remission compared with those who had active surveillance . . . compared to those that only had it when clinically indicated. Again, another study, a retrospective cohort, looked at routine surveillance versus whether there was a suspicion. Again, the yield was, on this report, no statistical difference in progression free survival and those that routinely were imaged versus those that had it for clinical suspicion of disease. Again, insufficient evidence. There were no statistical differences in median survival, but the sample size was very small for this study that looked at routine surveillance in aggressive non-Hodgkin lymphoma. If we take a look at . . . there's a series of publication by Taghipour that looked at whether or not scans . . . repeat scans were done with clinical suspicion of disease or without clinical suspicion of disease, and whether treatment had changed, and the bottom line is, is that in patients with clinical suspicion of disease, there was a higher yield of true positives and fewer false positives, and that the change in clinical management was less than 10% in patients who were asymptomatic but over 30% in patients that presented with symptoms.

So, the need for additional testing during relapse, high false-positive rates reportedly led to additional perhaps unnecessary testing that could either include additional radiographical types of testing or greater need for biopsies, greater need for other types of tests, and you can see that in one study, which may not be a typical way to do things. There was a study that compared PET/CT versus ultrasound with chest radiography. There was a greater need for mediastinotomies when you looked at the PET/CT versus the ultrasound chest radiography. Again, the strength of evidence is low, but there may be some repercussions of increased testing with routine surveillance and false-positives.

In terms of safety, as you learned, the radiation exposure varied from study to study. In one study, again, the PET/CT study compared to radiography and ultrasound, obviously there is going to be a higher radiation dose delivered. There are two observational studies. Again, there is not really much that we can say about the types of studies other than that additional studies do lead to additional radiation.

The effective dose on PET/CT, the cross studies, ranged from 14.5 millisieverts to 26.1 millisieverts in adults, and from 6.4 to 8.6 in pediatrics. Those were estimates based on 10-year-olds and 15-year-olds. The Radiologic Society of North America and America College of Radiology estimate the effective dose at 25 millisieverts, as a reference.

There were no studies looking at differential efficacy or safety or effectiveness.

In terms of economic studies, two studies were identified, one very poor quality comparative effectiveness study was evaluated looking at staging. They concluded that based on Brazil's gross domestic product, a threshold of three times that product PET/CT would be cost-effective for initial staging, but again, it was very poorly reported, and their methodology was very unclear. For surveillance, there was one study that looked at evaluating asymptomatic patients for DLBCL for surveillance. They concluded that it was not a cost-effective strategy to evaluate these patients routinely for relapse of disease.

So, in summary for initial staging, PET/CT is routinely used and a part of the Ann Arbor criteria. In general, it's more common to upstage across the 18 studies that we evaluated, but there is lots of variability. There are only limited data from two observational studies looking at survival, and the data were insufficient.

With regard to surveillance and relapse evaluation, overall survival and progression free survival appeared to be similar whether you did it for clinical suspicion or routinely in asymptomatic patients, but the data were insufficient. CT may not be superior to clinical followup alone at identifying relapses and/or leading to changes in management based on the five studies that we have. In general, routine surveillance of asymptomatic patients is not recommended either in the clinical guidelines or by the authors of the studies that we evaluated, and it may be best for individuals in whom there is a suspicion of relapse.

So, in summary for the initial staging, there was insufficient evidence for interim PET, but again, the caveat is, is that it has become a routine part, and the studies that we looked at were probably earlier studies and again were all observational.

For interim PET, if we look at early Hodgkin lymphoma, the value of PET may be to identify patients in whom escalation of treatment may be most valuable. It was less clear for de-escalation of treatment. If we look at advanced Hodgkin lymphoma, it was sort of a flip, de-escalation appeared to be where the value for PET is in identifying PET negative people who would be candidates for that de-escalation. If we look at early stage aggressive Hodgkin lymphoma, there may be value in findings patients for whom de-escalation is appropriate. For advanced Hodgkin lymphoma, the ability of PET to direct treatment is not clear. In terms of end of treatment PET, there are limited data from one study that suggests that it may be beneficial in both interim and end of treatment situations to identify PET negative individuals with whom de-escalation of treatment may be appropriate.

In terms of summary, there is limited evidence on summary. There is moderate radiation with each scan and, of course, that's cumulative with additional scans. Effect of radiation doses in children, of course, are very different, and there is a potential for longer term effects with more repeated scans, and that becomes a more important issue with younger individuals. False-positives may tend to lead to additional unnecessary testing, either diagnostic testing via imaging or biopsy. Routine PET CT is not superior to clinically indicated imaging for identifying relapse.

Cost-effectiveness, one poor study really does not provide sufficient evidence to describe cost-effectiveness of staging. In terms of cost utility analysis of surveillance of DLBCL of asymptomatic patients, it was not found to be cost-effective.

Again, I would remind us, as we wrap up here, and I realize it's been kind of long and drawn out, but most of you seem to still be awake, most of you. Evidence per PET value is really indirect. We don't have any direct studies to help evaluate that. the use of PET is evolving. The criteria for PET is evolving and has evolved. Again, I would remind you of the substantial heterogeneity across the studies included in this report, not only in terms of types of lymphoma, types of treatment, criteria for interpreting the PET/CT images, but also of any of the nuances of the staging, favorable or unfavorable, the different stages. So, there is a lot of heterogeneity. So, generalizing across these studies is difficult, and it is unclear what the consistency might be. So, all of the studies were . . . all of evidence bases were downgraded for consistency, because we really can't know that. The role of false-positives and other limitations of PET across these studies was not explicitly reported and not clear. The evidence for staging, surveillance, and evaluation of relapse studies, again, was based on observational studies. There was only one RCT, which may not be the typical case. It was the one that was looking at the comparison with ultrasound and chest radiography. In terms of prognosis, there is a lot more information in your full report. Generally, patients who have had PET-positive findings at interim PET tend to have worse prognosis, worse survival, but there is limited evidence in pediatric patients and in patients with indolent non-Hodgkin lymphoma, and there were no PET-adaptive studies in either of these.

So, my little gecko friend says it's time for me to be quiet and see if there are questions among those of you who are still awake. Good. No questions.

Joseph Rajendran: Just one comment, in the continuing evolution of this treatment, more and more centers are now trying to omit the initial diagnostic CT scan, as a standalone thing. So, they are willing to, and they are comfortable moving to PET/CT, as the only modality for staging without additional things. So, that further reduces the radiation dose to the patient. So, I just wanted to tell you that. It's kind of getting into common practice now.

Andrea Skelly: Thank you.

Joseph Rajendran: Because, PET/CT can give information about the size of the tumor, as well as the metabolic activity. You don't need contrast-enhanced CT that adds to the toxicity and other things.

Gregory Brown: So, what you're saying is there is a potential safety benefit of eliminating . . .

Joseph Rajendran: Yes. Yeah.

Gregory Brown: . . . that initial. OK. Yeah.

Joseph Rajendran: It is again, as with any evolution, it takes time for the philosophy to change.

Gregory Brown: Yeah.

Mika Sinanan: So, thank you for your summary. That's a lot to digest. I would take it that the PET positivity FDG uptake is not necessarily . . . is not easily correlated with biologic activity of the tumor or necessarily its responsiveness to anything. I mean, that . . . you said earlier that it could be inflammation that's causing the PET positivity versus tumor. So, it could be confusing on what's driving a positive scan, and even if you saw positive scan, it was related to tumor that doesn't necessarily predict what the responsiveness is. It just tells you that there's something that's active there.

Joseph Rajendran: Yeah. You know, again, it depends on which PET we are talking about, the initial PET when it is active, when it's definitely active, as was mentioned.

Mika Sinanan: Before any treatment.

Joseph Rajendran: Before any treatment, the standardized uptake value that is what the . . . the SUV is always very high when there is, like, Hodgkin lymphoma and other things, except in indolent situations. After therapy, there are two things we look at. One is the reduction in the level of uptake that is the reduction in the SUV values. Second is whether there is persistent uptake amount. That second part is still evolving. That is the one that causes the false positive situation, because not all of them, all of the FDG uptake is related to tumor activity in those situations. Earlier on, prior to therapy, the same thing may be going because there is epitosis even otherwise, even prior to therapy there is inflammation and how much of that one is usually less than 10% of the uptake being due to that kind of inflammation and other things even without treatment, but when you give therapy, it is kind of reverse. There is more resolution of the tumor, itself, and that means low activity of the tumor proliferation. That means less glycolysis, which results in reduced uptake of FDG. So, it kind of flip-flops.

Mika Sinanan: So, these patients are being followed clinically. They're being followed by laboratory studies. They're being followed by other types of radiographic studies, and they're being followed by PET or PET/CT?

Joseph Rajendran: Yes. PET is kind of, especially after staging, they go through treatment and then it used to be always six cycles given and then at the end only the PET

[inaudible] anything else used to come in, but now, the interim PET is introduced to see if there is a way we can modify the intensity of therapy. This is especially important when you are combining chemotherapy and radiation therapy in bulky diseases, and if the PET is negative, they are becoming more and more comfortable to omit radiation. It is important, again, in younger individuals and pediatric situation.

Mika Sinanan: Thank you. That's helpful, but what underlies, I think, the question that . . . as I understand it, that we're trying to answer is, what is the incremental benefit versus the incremental risk of adding the PET/CT to everything else that's being done, all the laboratory studies, clinical evaluation, the vital sign measurements, etc. So, can you talk about that?

Joseph Rajendran: Yeah. I can talk a little bit about that. The main thing is that there is no single entity or test that can follow or track the response to therapy at this point in time, except direction and size. That you can either do it clinically or using ultrasound or other means, but the incremental advantage is the change in the metabolic activity. That, you cannot, you don't get it in other situations. That is where . . . you know, they tried this interim evaluation using regular diagnostic quality CT scan, and it was not very helpful at that time, as a single entity. That is when PET/CT came into practice. Then, it was definitely given that thing. The advantage is not only to de-escalate or escalate therapy and also change in the treatment regimens. That's what they do at our center. The second thing is avoiding radiation in bulky tumors.

Mika Sinanan: Right. And you said that we . . . that it's become a standard of practice, and yet, what we have heard is that there is a lot of observational studies, a lot of confusion, at least a lot of variability among both the results and among the definitions. So, there is a delta between what the evidence would suggest and what is current practice now. Is that fair to say?

Joseph Rajendran: Yeah. That is correct. Yeah.

Mika Sinanan: Is that because you had . . . the oncologist had a need for something in addition to what they have, and they have filled that gap with PET/CT, even with its shortcomings, as an explanation. Or is it because their experience would suggest that the data that we have seen, the objective data, is not a fair representation of what the performance of the test is?

Joseph Rajendran: The latter I would agree.

Mika Sinanan: So, it's more the latter? It's not that they're just trying to fill a need? It's actually that they believe it's better than what the evidence would suggest?

Joseph Rajendran: That's the thing, because use the advantage of actually doing something that is more functional in nature compared to anatomic imaging like ultrasound or CT alone.

Mika Sinanan: But again, the assumption then is that the function is coming entirely from the tumor. Right? Not inflammation and that it's not necessarily an apoptotic effect. It's actually tumor activity or growth.

Joseph Rajendran: Again, that depends on if you are doing it at . . . the initial PET will help both of that, but there is predominant tumor activity and then as you use therapy, the tumor activity reduces. Then, whatever you are seeing . . . the uptake is not as hot when you see there is persistence of an inflammation or epitosis. You can clearly see that when you are able to do that. Persistent uptake could mean that there is . . . that is where the problem came. The event after that, the node in the mediastinum, and then they wanted to make a diagnosis and say that it is negative or not negative. That is histologically.

Mika Sinanan: Right. I mean, I think that's the key question. Suppose you have an initial lymphoma that's hot, you treat that patient with standard treatment. You do a followup PET/CT, and the activity is exactly the same. Then, the question is, did it not work? Do we have the wrong diagnosis or is the tumor activity down, inflammation up, and it simply looks like the same, but it's a different biologic activity?

Joseph Rajendran: Again, we are not looking at it the same way. If it is due to inflammation and epitosis, it is less than 10 to 20% of what the initial uptake is. I can tell you . . .

Mika Sinanan: It will always look less?

Joseph Rajendran: Yes. Yeah.

Mika Sinanan: OK.

Joseph Rajendran: It will always look less. If I tell the SUV value, initially, it will be in the range of 40. It's a unit-less measurement. When you give therapy . . . see lymphomas are very sensitive to chemo and radiation. You know that. So, when they respond, the SUV drops to less than five or so. You can make that same argument, but again, the medical oncologists are fairly

comfortable in even switching to other form of chemotherapy, the second line chemotherapy.

Gregory Brown: Dr. Fotinos, did you have a comment or question?

Charissa Fotinos: I just wanted to point out the recommendations that we had were just for adults. So, that's probably obvious, but I wanted to clarify that.

Sheila Rege: And if I may speak, in a prior lifetime, I actually did a PET fellowship with one of the . . . Michael Phelps at UCLA. We actually sat down and tracked how head and neck cancers looked on PET and stuff, but the way it's used, and unfortunately, you're right. Oncologists believe it. They go through two cycles of chemo, say ABBD with a high risk Hodgkin's, and if the PET is negative at that point, we may do radiation but a lower dose. And if that is positive, they go onto a really high dose of chemo. So, I think what happened with PET is, it got incorporated in a clinical medicine into our guidelines before we had a lot of the data. We're all worried about false-positives, but we're even more worried about disease recurrence.

Mika Sinanan: And there's no way to interpret this information that we're seeing now and say, as a result of the PET diagnostic benefit, the incremental benefit from PET that we have impacted survival, per se, because there are so many other moving parts.

Sheila Rege: Right, because we're actually . . . survival has not gone down. Survival has been the same or better, but we're treating less. So, we have less side effects, because these are young adults in their 20s and 30s. So, you know, that's the criteria.

Mika Sinanan: They're being more selective in treatment.

Sheila Rege: Correct.

Mika Sinanan: With the same results?

Sheila Rege: Right. And when you look at SUV, an SUV of inflammation is eight to ten. It's a low number. An SUV of a tumor, if you get 25, 30, you feel fairly comfortable that's a tumor. So, that's the standardized uptake, so at value. So, even though they have inflammation, we . . . there is standardization there.

Gregory Brown: Done with questions? Comfortable [crosstalk]?

John Bramhall: So, you raise the issue . . . you raise the issue of a false-positive, and in particular, there is a study that we looked at for Hodgkin lymphoma where the decision is . . . really, the benefit of the decision is either to escalate, fine. That could be the result of a false-positive. My question is, the other arm of the decision is to de-escalate on the basis of a negative PET. What is the incidence or the risk of a false-negative PET happening? Is it possible to have that?

Joseph Rajendran: It's always possible, but it is not, as I eluded to earlier on, it is the false negative thing is not very common in lymphoma, as opposed to a solid tumor, like a squamous cell carcinoma of the head and neck, because there is a lot of necrosis that goes on there. So, a negative uptake means just necrosis, but there may be active tumor or something like that, but it's much less in lymphoma. That's why they are very comfortable trying to de-escalate by avoiding radiation therapy, which is even for localized radiation, although it's localized, they are still trying to avoid that in young adults, young individuals.

Mika Sinanan: So, the negative determination is [crosstalk].

Joseph Rajendran: You're on pretty solid ground to de-escalate the amount of radiation.

Mika Sinanan: OK. Thank you.

Joseph Rajendran: And also in terms of patients who are going for autologous stem cell transplant, the positive PET and the long-term prognosis is also worse when they have that, but that's something that is evolving. Again, these are . . . we put the . . . the cart before the horse so to speak in so many ways, but because of the heterogeneity in the patient population and then the pathology of the tumor has forced individuals to look at ways to . . . that's why they just pull some newer technology that is coming in, but again, it's a difficult situation with such a heterogenous population. That's what is causing the whole confusion, too.

Mika Sinanan: Thank you.

Gregory Brown: OK. Are we ready to start a discussion?

Mika Sinanan: Can I ask one, one other question? What is the current cost of a PET/CT?

Gregory Brown: $1000.

Joseph Rajendran: Yeah. That is what is reimbursed, I believe. Yeah. I don't know.

Mika Sinanan: That includes the professional fee?

Joseph Rajendran: Oh, yeah. the professional fee, I mean, is kind of a, you know, how it works.

Mika Sinanan: I understand. I'm just . . . what would you say?

Joseph Rajendran: Yeah. It's, yeah, that is in addition to that. Yeah.

Gregory Brown: OK. We've had a request to have our break now, which I think is a good break before we start our discussion. So, I've got 1:42, ten minutes. Does that work? OK.

OK. I think we're pretty close to our quorum. So, I would ask to start with, are we going to, in our discussion, are we going to follow the recommendation from our medical director of not trying to do it for each step of, or each indication and each different type of lymphoma? Or does anybody want to do it that way? I'm not hearing anybody wants to do it that way. OK. So, thoughts? I don't know. Is there an easy way out, Mika? You got an easy one to start with?

Mika Sinanan: Well, yes. So, I would certainly agree that any decision we offer has to be actionable, has to be something that is a clinically effective solution. So, what has been offered of offering recommendations, which are deployable in a real world environment is a given, I think.

Gregory Brown: I'm not hearing from the initial report that there is a big concern about overuse. So, OK. Anybody want to summarize their thoughts on kind of safety, efficacy, and costs? Let's leave out cost right now. I don't think there's any data on cost on any of these. Right? So, kind of a non-issue in terms of . . .

John Bramhall: Well, if we, so if we're doing lumping, that's just what we're going to do. We're going to lump together a lot of cell types for some of them the data are not as convincing as for others, but I personally am impressed by this Andre Study, which is a big study on Hodgkin lymphoma. I don't know whether we want to split Hodgkin and non-Hodgkin. That's starting the splitting process. I think we've agreed to just lump everything together. So, I'm very impressed with the ability of the PET information to decrease the subsequent radiation dose for these relatively often young otherwise healthy in a beneficial way. So, I'm impressed with that. So, if I'm impressed with it, that means that I think that we should . . . I'm in favor of this scan. I'm in favor of the PET study. I think it works within some patients in a positive manner. The cost of it, the economics, it's $1000. I'm going to say it's trivial. It's not trivial when you add it up. I get that, but

for an individual patient decision, it's a relatively small sum of money for a diagnostic test that may be quite beneficial. So, I'm enthusiastic just in sum. I'm enthusiastic, and I tend to agree pretty much with the medical directors' recommendation, which seems very sensible and very pragmatic to me.

Gregory Brown: OK. Others.

Kevin Walsh: I appreciate Charissa's reality check about implementation. That was helpful, and I agree. I think that there is potential benefit in de-escalating therapy. I don't see any outcome data that compels me. There is not a huge cost. So, I'm supportive.

Gregory Brown: Tony, you're shaking your head yes?

Tony Yen: Yeah. I generally feel the same. That seems to be the one clinical utility that I can observe from this is for de-escalation, but then, as Kevin's comment is, I'm not too sure what that really leads to. I think, intuitively, that means that people with have less toxicity, and actually, the cost would be less overall, I think, but I don't have any clear data that shows that.

Gregory Brown: Anybody have a different view? I guess if we're unanimous then there's no point in anybody . . . so, I'm not seeing any other views. So, we all appreciate the possibility of de-escalation treatment, less radiation, less chemo, less side effects from both of those. OK. The safety issues are false positives and extra procedures or extra treatment based on that, but, I mean, and again, those are going to be varied by different types, and if there is up to 90 different types of lymphoma, trying to sort that out, I mean, I don't think that can be our role pragmatically. That's, I think, you said, Charissa, that's perfect for shared decision making. That's where that comes in. OK.

And in terms of cost, I mean, I didn't hear any evidence on cost with any of this. So, I guess, the one other question and that is, as you just said, yours was just for adults not for pediatrics. So, do we, I mean, I guess, from my perspective, de-escalating pediatrics is even more important for secondary cancers and other things. So, do we want to just have one coverage for all adults and pediatrics, or do we want to split them up or?

Sheila Rege: Pediatrics, they usually are in clinical trials, but I wonder about, I mean, 18 is our cutoff, but often I find a 16-year-old doesn't want to go travel to Seattle Children's Hospital. So, they often, 16 and over, but that's . . . I don't know. That's placing and, maybe say pediatrics consider on a case-by-case basis.

Gregory Brown: Well, I mean, it . . . the policy, as is, allows the patient and their oncologist to decide, up to four for a given episode. So, I mean it . . . does anybody see any reason to exclude pediatrics from this policy?

Seth Schwartz: I think my only struggle is that I haven't really seen any data on it. I mean, I subjectively don't have any issues with it, but I just didn't see any data on the effectiveness for this imaging technology in kids.

Gregory Brown: To me, I think, Sheila, you hit it early on when you said that this was incorporated very quickly when it came out. So, it's almost a standard of care issue, and we are chartered to do things based on evidence. There is no direct evidence, because there's no trials. It's all indirect evidence. At the same time, without compelling evidence to make a no coverage decision in something that's a standard . . . I don't want to say standard of care, but certainly common clinical practice, would seem to be.

Laurie Mischley: What percentage of lymphomas occur in younger children, like, under 16, the usual cutoff? Do you have a sense?

Sheila Rege: I don't do a lot of pediatrics. So, I don't know for sure. It's usually the 20's and 30's, though. That's the normal age group. Every once in a while, you'll get a 16-year-old, and we treat them often as adults, but most of them younger, they go into trials, big trials, because this is radiation and chemo on developing organs. I mean, it's, you know?

Gregory Brown: We're not making that . . . our decision doesn't affect that, so.

Sheila Rege: I understand the evidence based, and I struggle with that, too.

John Bramhall: Well, but I mean, it's . . . if you look in the terms of pharmaceutical interventions, I mean, an awful lot of the medications that are used routinely are not supported by specific pediatric trials. It doesn't absolve your argument, but I think we work routinely with medications that have only been tested and demonstrated in the adult population and have been extended into pediatric use. So, it's a pretty common weakness of our own sort of research system.

Seth Schwartz: Well, again, I don't object to that, and I'm not saying that I think we should exclude kids necessarily. I'm saying that for this . . . for us making this decision, we really haven't see any data. That was my only point.

Gregory Brown: I certainly agree. I think we mostly agree. Do we want any more discussion, or are we ready to go to our tool?

Charissa Fotinos: May I ask one question, I'm sorry, before? In the agency medical directors' decision, we put up some timeframes in terms of waiting, and I would need the expert's help in determining if those were reasonable or those should be changed if we are trying to reduce the false-positive piece.

Gregory Brown: So, the recommendation was up to four scans per active occurrence of lymphoma and then scans should be done no sooner than three weeks after chemotherapy and eight to twelve weeks after radiation or combined chemoradiation therapy. Are those, Dr. Rajendran?

Seth Schwartz: That doesn't seem to include the initial scan, the initial staging scan. If it says needs to occur after chemotherapy.

Gregory Brown: So, we would amend that to add a staging scan and then three additional . . .

Seth Schwartz: Up to three additional scans.

Gregory Brown: . . . up to three additional scans? Those numbers are [inaudible]? Yeah. He seems to think the timing are fine. So, OK. So, like I said, I think we're getting the cart before the horse here. So, let's do our tool. Safety issues, again, we've talked, I mean, the false-positive and false-negative that can lead to under-treatment or over-treatment with procedures and radiation exposure. Does anybody want to add anything? I guess we're not quite ready to vote yet. Does that cover everything, as far as everybody is concerned?

Seth Schwartz: Radiation from the CT component was the only other thing we talked about.

Gregory Brown: Correct. Yep. Efficacy. What we have listed is overall survival, event free survival, progression free survival, clinical decision making. I guess the efficacy or effectiveness that I heard that's not listed is, you may have the same survival but with less chemo and radiation, and therefore adverse events. So, that would certainly be an efficacy benefit, I think. So, I would add that to the list of what we're looking at.

Mika Sinanan: Also introduced as a safety issue, because there are safety issues with that additional treatment that does not offer benefit.

Gregory Brown: OK. And again, we don't think there's any evidence on cost. So, there's nothing really to add here in there. OK. So, we are ready to vote. I'm sorry, the last one is a subgroup. Are we leaving . . . we're not separating out peds. Is that correct? We're just gonna leave it as one and, OK. I guess

the answer for that is we don't have any evidence to show that pediatrics is different than adults. So, we'll leave them as one group. Then, the first . . .

Josh Morse: OK. Just to remind you that your previous decision did not separate that either.

Gregory Brown: OK.

Josh Morse: The decision [crosstalk].

Gregory Brown: Sure. OK. Safety. So, again, how is the question, well, how is the question . . . so, if you're looking at it as PET/CT is safer, more in some than none, PET/CT because you can de-escalate, you would say more in some. Is that how people understand the question? It seems like a little leading, but I don't know how else to ask it. We're unanimous on that, I think? Sounds good.

Josh Morse: Nine more in some for safety.

Gregory Brown: And in terms of efficacy, it's kind of the same thing. If we're saying you get same survival but fewer side effects in de-escalated treatment, that that is more in some.

Sheila Rege: I said equivalent, more in some.

Josh Morse: Six more in some and three equivalent.

Gregory Brown: Cost-effectiveness, or cost outcomes, effectiveness, is . . . we don't have any data, I don't think.

Sheila Rege: I thought it was more in some, because I was looking at reduced treatment. That's why I came up with more in some.

Josh Morse: Two more in some and seven unproven.

Gregory Brown: OK. So, any more discussion before we go for our coverage decision? OK. Not cover, cover with conditions, or cover.

Josh Morse: And you're voting on the conditions, as presented by the medical directors? Is that correct?

Gregory Brown: Well, we'll . . . if we do with the conditions, then we'll wordsmith it, because we started a little bit, but, yeah.

Josh Morse: OK.

Gregory Brown: So, I think we're unanimous in the cover with conditions.

Josh Morse: So, I'll just remind you, normally you would do a straw vote at this point.

Gregory Brown: OK.

Josh Morse: Is what you've done and decide you're going to do coverage with conditions and develop your draft, and then you [crosstalk].

Gregory Brown: That was a straw vote, folks. OK. That's fine. You had it up there a minute ago. There we go. So, I heard a friendly amendment from Seth earlier that we were going to cover with conditions, initial staging scan, to three scans per active occurrence.

Seth Schwartz: You don't want to say following the initial scan, because we're gonna include the initial scan. So, it should be an initial staging scan plus up to three additional scans with the condition of greater than three weeks after conclusion of chemo.

Kevin Walsh: Did I hear you say people were moving more and more to not doing a PET/CT or not doing a CT?

Joseph Rajendran: Not doing the diagnostic contract CT.

Kevin Walsh: Thank you. So, then I . . . I'm supporting Seth's desire to include staging. So, do we have to take the caveat out that it should be done no sooner than three weeks after chemo and . . . to allow the . . .

Sheila Rege: I think we can leave that.

John Bramhall: Yeah, just put followup scan.

Sheila Rege: Followup scan . . . the followup scan should be no sooner than three weeks after chemo.

Gregory Brown: I guess I would also, just for clarification, I know we were using PET for PET/CT for brevity in the report, but for the recommendation, I would say PET/CT for lymphomas just to again make it . . .

Seth Schwartz: And I think the one other area that's vague here, as you say, no sooner than three weeks after chemotherapy, but we're talking about initiation of chemotherapy, right, not conclusion of chemotherapy? I think

chemotherapy is vague, because there could be multiple cycles of chemotherapy, so up to three weeks after what?

Sheila Rege: Any chemo, because what if they go into salvage chemo. It just causes false . . .

Seth Schwartz: I think that's fine, but I think it's vague as it's currently written is my point. We should just be more explicit about what we mean.

Laurie Mischley: It could say three weeks after you start chemo.

Sheila Rege: Or after the last chemo.

Seth Schwartz: But is that really what we want? Is that the way it works out? Don't they sometimes do several cycles and then assess progress?

Sheila Rege: You want your chemo done and then your body to recuperate so there is no inflammation before you do your PET. So, it's the last chemo. It doesn't matter how many cycles they are doing.

Seth Schwartz: Is that true that . . .

Gregory Brown: Then we're not allowing the interim?

Joseph Rajendran: This is for [crosstalk]?

Sheila Rege: Not interim.

Joseph Rajendran: Sometimes, they may not . . . in the three weeks of the completion of the cycle . . .

Gregory Brown: You lost a P- in PET.

Seth Schwartz: So, it's the commission of a cycle, but not . . .

Joseph Rajendran: When you state chemotherapy, that means they may . . . six cycles may become . . .

Seth Schwartz: That's my point. So, that's my point. So, I mean, if the standard was six, then we're saying you can assess them in the middle and see that they have had a complete response. They don't need, necessarily, the complete [crosstalk].

Joseph Rajendran: Yeah.

Seth Schwartz: So, I just think, it's vague as it's written. So, I mean, as it's written now, I would initially read that, I would think after six cycles of chemo. So, I think it just needs to be clear that if it's . . .

Gregory Brown: So, is it . . .

Seth Schwartz: . . . three weeks after any cycle.

Gregory Brown: . . . any chemotherapy cycle?

Seth Schwartz: It just needs to be . . . I just need to be clear. I'm not exactly sure [inaudible] terms.

Gregory Brown: The cycle after the last chemotherapy cycle, and I would change that to scans may be done instead of should be done. We're not telling them to do it. We're allowing them to do it.

Seth Schwartz: Yeah, say may be done, because you're saying that if they're going to be done, they should be done greater than three weeks after the completion of the cycle. They may choose not to do them, but you don't say it may be done three weeks after, because then it seems like the three weeks is the option.

Mika Sinanan: Scans, if indicated, should be done? Scans, if indicated, should be done no sooner than . . .

Seth Schwartz: Before changing that, I think what we're talking about is allowing the choice to do the scans to be at the discretion of the treating physician. So, if we had a second bullet point that said followup scans can be done at the treating physician's discretion. Then, the next bullet point is, scans should be done no sooner than three weeks after the conclusion of therapy.

Tony Yen: But how would you simplify it . . . scans can be done no sooner than three weeks after completion of chemotherapy, because that's . . . is that what you're trying to drive towards, Seth?

Sheila Rege: But then that's . . . but what if you're . . . what if you've gone one cycle of chemo and then you say [inaudible], and now you're trying to go into a higher dose chemo versus radiation? You're not done with the entire cycles.

Seth Schwartz: I just think we need to be, I think there's some confusion even amongst us what we're talking about. So, it makes this . . . this is not clear. I think the points are that you can do the initial staging scan. Subsequent to that, you

can do up to three that are at the discretion of the treating physician when those occur in the overall span of treatment.

Tony Yen: I think I understand you, and I'm actually listening to your language very carefully, and what actually makes sense to me is that it can be done three weeks after the last cycle of chemo . . . the last cycle.

Seth Schwartz: But we're not only talking about the last . . .

Tony Yen: It's not should . . .

Seth Schwartz: . . . but we're not only talking about the last cycle. I think the point is, it can be done at any point during the treatment, but relative to an individual cycle of chemotherapy, it should be done at least three weeks after the completion of the previous cycle of chemo, or the . . . so, in other words, they may be getting . . . plan for six cycles of chemotherapy. You may choose to do the scan after the third cycle, but you should wait three weeks after the third cycle is complete before you do the scan.

Tony Yen: OK.

Sheila Rege: or, you could just say, there should be an interval of three weeks between the patient having received chemotherapy and eight to twelve weeks. So, just make it interval. There should be an interval. That's what you're trying to say.

Mika Sinanan: This is exactly the point of how complicated it gets. So, if it's three and a half weeks or two and a half weeks, I think the issue is four scans. We're authorizing four scans. Use your best clinical decision making to do four scans in the lifespan of this incidence of the disease. Whether they do it at that timeframe is a clinical decision based on the characteristics of the patient. What we're trying to do is to drive them to a better . . . I mean, there's a guidance, right, but do we want to put that in a policy?

Charissa Fotinos: From a utilization standpoint, our greatest challenge with the PET scans is them being done too soon after chemo. So, one of our big goals with this policy was to clarify this very point, because many of them are being requested before they hit the three weeks, or even less. Then, they're wanting more scans. So, this is a particular point of utilization to get under control, because the false-positive rate is higher if you do it too soon. So, if that helps at all.

Sheila Rege: And that's because the flow, you finish the chemo and then you tell the patient he's gonna get a PET. It goes into a loop, and it gets preauthorized, and it gets denied. So, then it . . .

Mika Sinanan: But in the order set at that visit, right?

Sheila Rege: You do it. Then, if it gets approved . . .

Mika Sinanan: Then, the patient shows up too early to get it.

Sheila Rege: Right. Then they get it before you know they've gotten it, because, you know, the hospital system kinda just moves. Then, you go, oh. You weren't supposed to get it that early. So, I think something about the interval between PET imaging or some . . .

Laurie Mischley: It sounds like what the conversation is about is, to Seth's point, you can talk about provider discretion. When used to assess response to chemotherapy, a scan should not be done any sooner than three weeks. That doesn't define which chemotherapy or how. When being used to determine response to radiotherapy or radiation therapy, however you want to say it, scans before 12 weeks, or whatever, you should wait at least 12 weeks. So, it doesn't say which cycle or when in the course. It's just use your judgment, but you gotta wait and order for it, and how you . . . I mean, that might be another way to parse it out and add both.

Sheila Rege: Somebody needs to wordsmith that.

Gregory Brown: So, just what I heard from you earlier was that you say you may do radiation with a third chemo cycle.

Sheila Rege: Well, usually we wait. We hold off, and then we decide.

Gregory Brown: I guess what I'm saying is you don't want to be in a situation where you're in the middle of multiple cycles of chemo, but you do a radiation. Now, you have to wait eight to twelve weeks from that. OK. So, you don't do that clinically.

Mika Sinanan: I think the language that Charissa just used is very clear.

Sheila Rege: Can you repeat that?

Charissa Fotinos: These are the [inaudible] scans to be done at the provider's discretion. When used to assess a response to chemotherapy, scans should not be done any sooner than three weeks after completion, however you want to

say that. Then, when used to assess response to radiotherapy, scans should not be done sooner than 12 weeks after completion of the last dose or however you'd say that.

Sheila Rege: Eight weeks.

Charissa Fotinos: Eight weeks? OK.

Sheila Rege: Yeah, eight to twelve. I'm good with that.

Josh Morse: If we're going to say no sooner than eight to twelve, maybe we should just say no sooner than eight.

Sheila Rege: Yeah. There's too many sooners.

Gregory Brown: Leave that. Then, I'd hit a return and get another bullet point.

Mika Sinanan: After the cycle.

Gregory Brown: And then, I'd say when used to assess response from radiation, you know?

Sheila Rege: Radiation therapy. Then you can take away anything after. So, within a period of up to eight weeks.

Mika Sinanan: After completion.

Sheila Rege: After radiation. Correct. And then just, or no. I guess, or combine makes sense. That's good.

Gregory Brown: I would put a comma after chemotherapy in the first bullet point, the first chemotherapy. No, of the first bullet point, the first . . . there you go, right there, and then the same way on the second bullet point after radiation therapy, comma. So, it's a clause.

Sheila Rege: And if you want to put a line about per occurrence of lymphoma at the discretion of the treating physician. That's what she had implied, I think, we leave it. I don't think we need it. I think we're good.

Gregory Brown: I think you've got an extra space between than and eight. That's why you get your purple underscore. Right. You've got two spaces. That's why you're getting . . . there you go. My mother was an English teacher. Sorry. You normally don't find such English in an engineer surgeon combination. Can we see the bottom then?

Josh Morse: There's more, because surveillance is not covered.

Gregory Brown: OK. So . . .

Seth Schwartz: And we want to add the bullet point of, or at the treating physician's discretion or something of that effect.

Gregory Brown: But we think that's implied. Right? Yeah? So, you get your initial staging scan followed by up to three scans, you know? Well, if it's a relapse, then it's a new active occurrence, right? Right. But again, it needs something clinical to trigger it, not just a surveillance scan.

Mika Sinanan: This is not intuitively clear. I think you could . . . we should say under relapse, relapse is considered another active incidence. Relapse will be considered another active incidence of the disease or something like that.

Sheila Rege: Only treatment is needed.

Gregory Brown: Well, I mean, you may have clinical suspicion to get your study and not find anything. So, then treatment is not going to be indicated. So, I don't know that, I mean, but basically, you're saying to . . . we're trying to define relapse is what I'm hearing you say?

Mika Sinanan: No. Up top, we've got per active occurrence, but that's not clear. Does that include all relapses that occurred with the original one, or is the relapse a separate issue? That wasn't clear to me.

Sheila Rege: To me, it was clear, because if it's a relapse, then you start another course. Like, all our bundled payments, it starts another episode.

Mika Sinanan: OK. So, it'll be clear to people who are using . . .

Sheila Rege: Most . . .

Mika Sinanan: . . . this?

Sheila Rege: . . . I think most oncologists . . .

Gregory Brown: You guys are implementing it. Is it clear to you guys?

Charissa Fotinos: We understood what we meant, but if people who are . . . the ones that have to order it and get it for their patients . . . if you don't, then we need to fix it.

Gregory Brown: Well, yeah.

Charissa Fotinos: Because if it's confusing to providers, it needs to be fixed.

Mika Sinanan: Or say, we'll use it as a basis for arguing about . . . or misinterpreting.

Gregory Brown: We do transcribe these meetings so that we understand . . . there would be a context if they want to appeal it. You can come back to this. Anyway.

Sheila Rege: The only clinical symptom, sometimes we do CT scans, and we find something, and then we want to do a PET, and they may not be symptomatic. So, I'm OK leaving it that way, but just realize that may be a question that comes up to the agency.

Gregory Brown: Say that one more time.

Sheila Rege: So, sometimes, we do a CT scan and we'll find something, and we're not sure. Then, as the treating physician, you try and get a PET scan, but the patient doesn't have symptoms, so . . .

Gregory Brown: So, why are you getting the CT scan?

Sheila Rege: Some doctors still get CT scans.

Mika Sinanan: Because they've got lumbar spine pain, and they find a lump, and they previously were treated for lymphoma.

Sheila Rege: But then, that's symptoms. So, that's symptoms. So, I think I'm OK with the way it is.

Charissa Fotinos: [inaudible] . . . because there's not due process.

Sheila Rege: You could say, presence of clinical symptoms or imaging evidence of relapse or something.

Charissa Fotinos: That's truly how it should be. I would put those words in there.

Sheila Rege: I'm OK with this.

Gregory Brown: So, when relapse . . .

Sheila Rege: And you'll get back to us if you have problems.

Gregory Brown: . . . is suspected in the presence of clinical symptoms or other imaging findings?

Josh Morse: Imaging findings suggestive of . . .

Sheila Rege: Suggestive of recurrence.

John Bramhall: I think we like it to have its own meaning. Right?

Sheila Rege: Findings suggestive of recurrence. Findings suggestive of recurrence. Would that help the agency with . . .

Charissa Fotinos: I think that would be helpful.

Tony Yen: But is that supported by the literature or?

Sheila Rege: Suggestive of recurrence? No. We didn't hear any literature on that. That's clinical practice. So, that's the problem.

Gregory Brown: so, instead of subjectable, it's subjective.

Josh Morse: Suggestive of.

Gregory Brown: That's correct spelling, it's just the wrong word.

Laurie Mischley: Is routine CT surveillance done right now after completion of cancer treatment, just to see if something comes back. Is that . . .

Sheila Rege: Some physicians do.

Seth Schwartz: It's recurrence, not occurrence. That should be recurrence, not occurrence, the last word.

Gregory Brown: There we go.

Sheila Rege: But there was no imaging. There was no data on that, so.

Tony Yen: Yeah, but that's common practice, folks will just image without symptoms? I have no idea.

Gregory Brown: Well, I mean, what I'm hearing is that it's an incidental finding in some other test than someone whose got a history of lymphoma.

Sheila Rege: Say you have right upper quadrant pain, and we do a CT scan on you, and they see something, and they say, oh, yeah, lymphoma. There's a node there.

Mika Sinanan: If you walk in the Emergency Room by the wrong door going to work, you'll end up with a CT scan.

Gregory Brown: So, actually, at our retreat, we talked about taking a break. So, we have to do laps for five minutes then come back. Yes, we do. We said we wanted to . . . so, anything we can talk about that's a different topic. We've talked about our other one. We've got our evidence report on the request for re-review of the CyberKnife. There we go. We can hand out parking permits. We can hand out our forms to sign and parking permits. And I don't need a ticket, because I'm flying. I'm in a different lot.

Should we reconvene for our vote? Would everybody like to vote? OK. Put your card up then. Get off your phone, doctor. OK. It is unanimous, cover with conditions.

Josh Morse: Nine cover with conditions.

Gregory Brown: Then, now that we have this, this is consistent with the National Coverage Decision from CMS. So, we are consistent with them.

Josh Morse: OK. And guidelines?

Gregory Brown: The guidelines were conflicting. So, I think we're consistent with at least some of them.

Sheila Rege: Very true.

Josh Morse: OK. Thank you, very much.

Gregory Brown: Thanks everybody. So, we will see you in January. No March meeting.

Josh Morse: Excellent. Great job. Thank you.