Washington State Health Care Authority

Washington State Health Technology Clinical Committee Meeting

Treatments for chondral defects of the knee

September 20, 2024

DISCLAIMER

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Sheila Rege	Sounds good. Good morning, everybody! Hey, my name is Sheila Rege, like the Rege music, and I'm a radish on colleges practicing, and Benton-Franklin County. Gonna be asking with new members for a 1 or 2 sentence from each of our committee members. So welcome to the Washington State Health Technology Committee meeting. As we know, the HTCC was established to make coverage determinations. And these determinations are followed by State purchased programs, Medicaid, Uniform Medical Plan, Department of Labor. Now I want to say our strength as committee members is our diversity of knowledge and we're eleven and we're a mighty eleven, and we have to use our experiences, expertise, knowledge and to make these determinations we also have a clinical expert who's a non-voting member and attending these meetings is, is very important, because when one of us is missing, we lose that perspective, especially if topics are carried on. And we are going to go ahead and start, I'm gonna hand it over to Josh and we're gonna go ahead and start with an introduction, I believe Josh, with new members and an update. Thank you.
Josh Morse	We'll go through our typical introduction.
Sheila Rege	Maybe roll call 1st to make sure all of us can speak as panelists. I forgot that.
Josh Morse	Yeah, let's do that. Thank you.
Val Hamann	Okay, we'll start with John Bramhall.
John Bramhall	Yes, hey, I'm present. I was having some difficulty. I, I'm here, good morning. Thank you.
Val Hamann	Clint Daniels.
Clint Daniels	Good morning. Yes, I'm here as well. No conflicts with this topic either.

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Val Hamann	Janna Friedly is not here today. Chris Hearne.
Chris Hearne	Morning. I am here today.
Val Hamann	Conor Kleweno.
Conor Kleweno	Yes, here.
Val Hamann	Laurie Mischley is not here. Evan Oakes.
Evan Oakes	Here, everybody. Nice to see everybody.
Val Hamann	Now Sheila Rege. We know you're here. Jonathan Sham is not here. Jonathan Staloff is not here. Tony Yen.
Tony Yen	Here.
Val Hamann	And then I we do have a clinical expert today, but I have not seen them. There is a couple of individuals in the attendees that do not have a specific name, so if Michael James is one of those attendees could you please raise your hand, and I can promote you? Okay, perfect. Then, Michael James, if you want to introduce yourself, please.
Michael James	I'm Mike James. I'm an orthopedic sports medicine surgeon in Oregon, and I'm serving as a medical expert this morning. My expertise is in knee reconstructive procedures particularly cartilage restoration. Did my fellowship at the University of Pittsburgh where I became fairly familiar with MACI and osteochondral allograft procedures, as well as other cartilage restoration techniques.
Val Hamann	And that concludes roll call.
Josh Morse	Great thanks, Val. And can you hear me?
Val Hamann	Yes.
Josh Morse	Okay. Okay. So some meeting reminders, this meeting is being recorded. Transcripts will be generated for this. We have chat disabled and if it's not disabled technically, we're not using it. So please don't use the chat for any reason today during the meeting it adds confusion and just complicates our communications. The raise hand feature is another feature that we're using in a very limited fashion, and Val will ask you to use the raise hand feature, I think, only during the public comment period. Some background on the program. The health technology assessment program is administered by the Health Care Authority. The program brings evidence reports to the Health Technology Clinical Committee to make coverage decisions for selected medical procedures and tests based on the evidence for safety, efficacy, and cost effectiveness. As Dr. Rege noted multiple agencies in this process to identify topics and implement the policy decisions. And they include the Health Care Authority which runs

the Uniform Medical Plan and the State Medicaid or Apple Health program. The Department of Labor and Industries and the Department of Corrections is also using the determinations from this process. These agencies implement the decisions from the Health Technology Clinical Committee within their existing statutory frameworks. The purpose of the process is to ensure that medical treatments, devices, and services that are paid for with state healthcare dollars are safe and proven to work. The program provides resources for State agencies that are purchasing healthcare and through this process we develop scientific evidence based reports on the selected medical devices, procedures, or tests that come to the HTCC. Our program staff support the HTCC to make determinations for the selected devices, procedures, and tests based on the available evidence.

There are multiple ways for anyone to participate in this process. The link shown here is to our Health Care Authority site for the health technology assessment program. We publish information about how to sign up to receive notices from the program. Anyone may comment at various stages through the course of a review on topics that are proposed for review on key questions, on draft and final reports, and on draft decisions when they're published. And anyone is welcome to attend these meetings of the Health Technology Clinical Committee, these are public. And anyone may sign up to present comments either in advance or today during the meeting. Additionally, anyone may nominate a topic for review or for update, or what we call rereview. Today's agenda after we do some introductions this morning, and this update include previous meeting business, and that is the minutes from the last meeting, which was July 26th. We then have a question for the committee about updating the cochlear implant policy, and we will walk you through the questions there. And then we'll get into the new topic, which is a partial rereview and some new, newer technologies for treatment of chondral defects of the knee. There is a public comment period. There's a limited time available. For day of signups, we will use the raise hand function at that time and we will monitor for raised hands there for a few minutes. So this the rest of this describes the process. Attendees who are scheduled for public comment will be temporarily reassigned as a panelist and provided the option to unmute and turn on their camera. You will get a notice, and you'll have to select that when that occurs. We ask that you please limit your comments to the time that's been allotted, and we do monitor the time. When you're finished providing public comment, you'll be assigned as an attendee. There'll be a pause in the rejoining the meeting. We ask that for anybody providing a public comment, that you provide your name, and please declare any conflicts of interest. We will show this again during the public comment period.

After today's meeting we will publish the minutes and the transcripts, as well as any draft determinations generated today, and draft determinations from the committee are open for public comment for 2 weeks. So future meetings currently scheduled include November 15th where there is a rereview of vertebroplasty, kyphoplasty, and sacroplasty. The draft report, I believe, is published right now. The meeting after that is the Health Technology Clinical Committee retreat. We are currently working on reserving space for that meeting in Seattle and the date for that is January 10th. In March we have 2 topics teed up for the 21st of March hyperbaric oxygen, which is a

	targeted review of one condition treated with hyperbaric oxygen, and along with that as a rereview of continuous glucose monitoring. And then currently scheduled for May is a review of frenectomy. This is new and information is not yet published on that topic. Key questions just closed on hyperbaric oxygen, and on continuous glucose monitoring. So draft report will be then, or the final key questions will be published soon followed by draft reports here soon. Okay, and if you have any questions here's my contact information and our program inbox. Thank you. Dr. Rege.
Sheila Rege	Great. What we will do is Val, if you could count or, or name us starting with our newest members. Or, no, actually, let's go with our, let's go with our other the existing members so our new members know how to introduce ourselves. And what I'd like is your name, your specialty, and whether you have any conflicts with today's topics which are cochlear implants, and chondral defects. I'll have Val call us out so we can introduce ourselves.
Val Hamann	Yeah, we'll start with John Bramhall.
John Bramhall	Hey, good morning. Do you want an introduction, or just an acknowledgement that I have no conflict?
Sheila Rege	No, just a little introduction, because we have some newer members, and I'd like them to know who we are before the in-person retreat.
John Bramhall	Sure. You bet. So, John Bramhall, I am anesthesiologist by training I was for a long time, 30 years at Harborview in the basement doing anesthesia for trauma and other things, and working with Dr. Kleweno on a frequent basis, which was a great pleasure. I was also an administrator associate medical director for Harborview. I've stepped back from that last month and now I'm simply emeritus professor at the University of Washington in clinical anesthesiology. And the reason I step back is because I'm moving into a little bit more of a busy position, Sheila, you know all about this with the medical association, so I'm pleased to be here on this committee.
Val Hamann	Clint Daniels.
Clint Daniels	Hi! Good morning. I'm the Chiropractic Supervisor for VA Puget Sound. Sorry. My dogs just took off running across the room. And no conflicts with either of the topics today.
Val Hamann	Chris Hearne.
Chris Hearne	I am a nurse practitioner. I work for Hospital medicine at Swedish Medical Center in Seattle, and I have no conflicts.
Val Hamann	Conor Kleweno.
Conor Kleweno	Yes, I'm an associate professor at the University of Washington, and the chief of the orthopedic trauma at Harborview. My practice is all orthopedic trauma primarily. I

	don't have any direct financial conflicts with this topic, although I do see it in practice to some degree, and I think we are all in withdrawal for not having Bramhall at Harborview anymore.
Val Hamann	Sheila Rege.
Sheila Rege	Sheila Rege, radiation oncologist in Tri Cities. I also teach at the WSU School of Medicine. Involved in AMA and WSMA, where Dr. Bramhall is going to be a fearless leader soon. Been involved in the RAP and CPT committees of the AMA, and again have no conflicts with these 2 topics.
Val Hamann	Tony Yen
Tony Yen	Hi! I'm Tony Yen. I'm a hospitalist, I practice at Evergreen in Kirkland. I have no conflicts with either of these topics.
Val Hamann	And our newest member, Evan Oakes.
Evan Oakes	Everybody in Evan Oakes. I'm a family physician by training. I am currently the chief health officer for HealthPoint which is a federally qualified Health Center, serving mostly King County. And I have no conflicts with this, and happy to join.
Josh Morse	Welcome, Dr. Oakes!
Val Hamann	And that, yeah, that's everybody for today.
Sheila Rege	Perfect. Now I think we the next step would be the previous meeting minutes review. We can project that and I will take a motion for approval. I also wanna say that in the absence of Janna I have asked Dr. Conor Kleweno and Dr. Tony Yen to help me with spotting any, you know kind of methods of making us more efficient, or if I miss a hand raised. I'll take a motion for approval.
Conor Kleweno	I motion.
John Bramhall	I second.
Sheila Rege	Any discussion? Otherwise, how would you like the voting, Val? Can we just say I or would you like a poll? This be a good.
Val Hamann	You can just say, I, today.
Sheila Rege	Okay. Everybody in favor, please say aye.
Tony Yen	I.
Clint Daniels	I.

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Chris Hearne	I.
Sheila Rege	I.
Conor Kleweno	I.
John Bramhall	I.
Sheila Rege	Anybody opposed? Please speak, now. Okay. That's approved. And now we're going to move to cochlear implants. And this is just an administrative, kind of a recommendation the committee has to give. So, Josh, if you would project that.
Josh Morse	Yes, I think Melanie Golob will be.
Melanie Golob	Here. Yeah, I'm on it.
Sheila Rege	Oh, Melanie. Sorry.
Melanie Golob	No, no worries at all.
Melanie Golob	Let me get that pulled up. Okay. And hopefully, everyone can see my screen. There we go. Okay. So as Dr. Rege pointed out, this is planned to be an administrative update, just because, the coverage, it doesn't really align with the FDA approved limitations anymore. So just a little background on what happened when the decision was made in 2013. There was no data comparing bilateral to unilateral for less than 12 months. So again, the issue is the age limitation. So there wasn't at the time data comparing bilateral to unilateral for less than 12 months, and the FDA approval at the time was for greater than 12 months that has since changed. So again, this is just kind of a background of what happened at the time, what the discussion was. The age minimum doesn't affect the unilateral implants and the unilateral implants were out of scope at the time and there was some concern expressed about the accuracy of hearing measures for those very young children, just because it's hard to do hearing tests on young babies, because you don't, you don't have a clear way of communicating with them. So what has happened since then? Again I mentioned that FDA approval that was in March 17th, 2020 and it changed that age limit from 12 months, and it lowered it to 9 months. And the basis for this particular decision in 2020 was a retrospective analysis of 84 participants as well as a literature analysis conducted by the manufacturer. And again that decision from 11 years ago the HTCC decision listed age 12 months or older, which is in conflict with the current FDA approval. So based on that we're proposing 3 different options either removing that age restriction bullet which would be kind of the easiest thing to do, and then that would align the age limitation with the FDA approval, we could rereview the topic or we could retire the policy. And so, as you can see, this is the current coverage determination, I've used strike through to indicate the bullet that could be removed and that

particular bullet is what is currently seen as in conflict with this last bullet, which is the device is used in accordance with the FDA approved labeling. So to reiterate, removing that bullet would align coverage with the FDA approved age limitations. And in terms of utilization for this procedure it's very low, less than 15 procedures a year at a cost of less than 5,000 per year, and that was looking at the timeframe of 2017 to 2022. I listed out the CPT codes that we looked at, and just restricting to that age limit that is of concern, that less than 12 months. So age 0 to one. So based on that, and, Sheila, I'll let you decide how you want to do it. I think Val is prepared a voting slide, if that's how you want to do it. But we could vote on which is the best path forward for aligning the coverage decision with the FDA approval.

Sheila Rege — Thank you. That was a very comprehensive review. So in summary, this determination. And let's put the determination coverage determination in front of us. Was made prior to 2020, when the FDA lowered the age limit from 12 months to 9 months. And so it has been brought to our attention now that that is in conflict. So the 1st bullet, age 12 months or older, is in conflict with the last bullet device used in accordance with the FDA approved labeling. So the way to bring that make this consistent or accurate, would be to the 1st option to remove strike what's proposed by staff, strike through. The committee could say, we want to rereview this or retire this which and we've, we've been given if they retire it, or rereview it how, how many dollars, or how many patients are at risk. In my opinion they're just looking to make it consistent and accurate. I like the you know, removing the age 12 months or older, because the FDA with new data may change the age to a different age in a in a future, or, you know, kind of so, so that would be my leaning, but I'm open to discussion. I'm also open to a motion to go to vote.

Conor Kleweno — Yeah, I'd like to motion to go to vote.

Tony Yen — I second.

Sheila Rege — Okay, any objections to that? Hearing none, let us go ahead and vote. This would be a good time to test the ttpoll.

Val Hamann — Yeah, great. So if in another browser or mobile device, again, do not leave the Zoom meeting. If you go over to ttpoll and follow the instructions that you were emailed again. Do not share that information. And once that I see 7 connections in there, I will be able to launch the poll. We currently have 5 connections.

Sheila Rege — I'm in there, but it doesn't give me the option. Am I doing something wrong?

Val Hamann — No, yeah. I have not launched that poll yet. You should be seeing a slide that just says voting question cochlear implants vote using the instructions emailed to you. We're waiting on one more connection before I launch that. Okay, we have 7. So I will launch that. And that poll is open. We have 7, and I will share my screen. So we have 7 to remove the age restriction bullet.

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Josh Morse	Great. Thank you.
Melanie Golob	Thanks. Val. Alright, thanks everyone that is concluded. I believe so, Sheila, back to you.
Sheila Rege	Right. At this point we are actually slated for a break. It seems a little early to break. So I don't know if we can move forward with the chondral defects of the knee.
Josh Morse	Oh, I think we can. I think we can move ahead.
Sheila Rege	That'd be great.
Josh Morse	Take a break after the medical director's presentation.
Sheila Rege	Yeah, that would be really good. And then we'll just have to make sure we keep to the 8 the 9:20 for the open public comment, Josh, I will let you lead and get things organized to have the presentation.
Josh Morse	Gotcha.
Sheila Rege	Up.
Josh Morse	Okay. Maybe I spoke too soon. Oh, no, Ji Young
Ji Young Nam	I, Josh.
Josh Morse	Dr. Nam is here.
Ji Young Nam	Can you hear me well?
Josh Morse	I can hear you. Yes.
Ji Young Nam	And I was trying to.
Sheila Rege	Thanks. Thank you, Dr. Nam. We, yeah, we can hear you and thank you for doing this.
Ji Young Nam	Then I'll start my PowerPoint sharing, and I'll start the presentations. Thank you. And can you see my slides.
Josh Morse	Yes, can see your slides.
Sheila Rege	Yes.
Ji Young Nam	Good morning, everyone. My name is Ji Young Nam, and I'm an associate medical director at L and I. And I'll be providing presentation for the treatment of chondral defects of the knee today. And for chondral defects, it is often caused by trauma,

overuse, or other conditions and it is associated with increased risk of developing osteoarthritis over time and it can significantly impact the quality of life. And for the treatments for the chondral defects of the knee, it aims to repair, restore, or replace the damages of tissue with healthier cartilage and microfracture is often used as a 1st line procedure, because it has proven advocacy and safety profiles, and it is minimally invasive. And microfracture also is often considered as the standard comparator to other procedures, such as OATS and MACI. And this chondral defect treatment can be considered for people who are younger than 55 years old to avoid total knee replacement. The scope or the evidence report includes individuals at any age with chondral defects of the knee and interventions can be divided into 3 categories which is 1st marrow stimulation procedures like microfracture, or drilling and OATS and OCA, which is osteochondral placement, and MACI, which is cell based restoration procedure. And for efficacy question, validated measures of patient reported outcomes were included and intermediate outcomes, like MRI images or pathology findings were excluded because knee symptoms and functions from the chondral defect often do not correlate with pathology findings, or images findings. And 1st and second generation ACI are not included because they are no longer common use in clinical settings.

HTCC reviewed the topic of OATS and OCA in 2011 and they determined that OATS and OCA to be a covered benefit with conditions for the knee joint, and the conditions were age younger than 50 or order at the, at the discretion of the agency. Single focal full-thickness articular cartilage defect excluding malignancy, degenerative and inflammatory arthritis in the joint. And Agency Medical Director Group has medium concerns for efficacy and safety and high concerns for cost. And after evidence review our concern, because of our defect treatment was downgraded from high to medium because of the few reported adverse events in the evidence. The key questions are efficacy, safety, and cost effectiveness of the treatment for the chondral defect of the knee. And this is our current State agency policies. For example, for MACI is a covered benefit with the conditions for Uniform Medicare plan and it is not a covered benefit for labor and industries. And this graph shows the agency combined cost and encounters for the treatment of the chondral defects of the knee. The combined cost, the agency combined cost in 2023 was $1,050,000 with encounter number of 492. And this utilization data was retrieved using the target procedure calls including microfracture, drilling, OATS, OCA, and MACI on the date of service, plus minus one day. And this graph shows the average payment per individuals. In 2023, the average payment was 1,500 for Medicaid, $10,000 for UMP, and $3,600 for L and I. And this chart shows the number of individuals with at least one related service. In 2023 Medicaid had about 57%, UMP had 32%, and then L and I had about 10% of the number of individuals with at least one related service.

Now back to the evidence report. There were 3 RCTs and 2 NRSI comparing MACI to microfracture. And these RCTs show the greater effectiveness, and response to MACI compared to microfracture with moderate certainty of evidence. And certainty of evidence was rated using the GRADE approach based on consistency, directness, precision and study limitations. Overall the included studies, consistently showed

favorable outcome of MACI compared to microfracture. And there are some study limitations, such as small sample size and different patient selection criteria of the included studies. And for OATS, a total of 7 studies which are 5 RCTs and 2 NRSI were identified comparing OATS to microfracture and it showed the over comparable effectiveness between group, using the patient outcomes. And this figure shows the meta analysis of 3 RCTs using the lysholm score resulting comparable effectiveness outcome between OATS and microfracture. And the mean defect size of the chondral defect was about two and four centimeters in this 3 RCTs. The certainty of evidence was low to very low for these matters comparing OATS to microfracture. And studies, comparing 1st line MACI or OCA to second line procedures which are often done after failure bone marrow stimulation procedures showed either greater or comparative effectiveness of the 1st time MACI or OCA compared to second line MACI or OCA. And these 4 NRSI had highly scope bias resulting in very low certainty of evidence. And we concluded that because the evidence base is insufficient at this time, it was insufficient to make a recommendation for 1st line procedure at this time.

And lastly, evidence for cell-free implant and AMIC were considered. There is one RCT comparing cell-free aragonite implants to microfracture or chondroplasty. And it showed greater effectiveness in response in cell-free implant group. And this study deemed to have high school bias because of the lack of information in the randomization domain, and also it has differing baseline differences in disease, severity. And AMIC is a procedure in which collogen membrane covers the microfracture treated area. And there was 1 RCT including 47 participants comparing AMIC to microfracture and it showed a greater effectiveness in AMIC group. However, this study deemed to have highly risk of bias for several reasons such as no intention to treat analysis and missing data outcomes.

For a safety question the evidence was limited because only a small number of studies reported harms. And based on the available evidence, we concluded that MACI or OATS likely have comparable to microfracture. And for a cost question, there is no evidence available for MACI compared to other procedures. And for cost consideration for MACI, there are 2 major considerations. First. it's 2 stage surgical procedure, 1st one is harvesting the chondrocytes and then 6 to 8 weeks later implantation of the chondrocytes. And also it requires longer rehabilitation period with intense rehab. And there is one cost effectiveness study comparing OATS to microfracture from one single institution and, in short, mixed rehab before the return to play outcome. OATS appeared to be more cost effective over time based on this study. And this paper summarizes the other payers. There was no Medicare, national or local coverage determination for chondral defect treatment procedures. And there are 4 payers which have the coverage decision for MACI which are covered with certain conditions.

And for guidelines there is no clinical practice guidelines for MACI identified at this time. And this conclusion, inconclusion, we, the agency medical director group recommend for the treatment of the chondral defect of the knee to be a covered benefit with conditions. And the conditions based on our evidence review are symptomatic single or multiple full-thickness articular cartilage defects of the femoral

condyle and/or patella at least 3 square centimeters in size. Documented closure of growth plates in adolescent individuals. Age younger than 50 or older at the discretion of the agency. Body mass index of less than 35. And excluding malignancy, degenerative, or an inflammatory arthritis in the joint. For OATS and OCA, we also recommend them to be covered benefit with conditions. And these conditions are identical to the conditions for MACI except for the chondral defect size. For OATS procedure we recommend cartilage lesions that are between 2 and 4 square centimeters in size. And for cell-free implants and AMIC, we recommend them not to be a covered benefit at this time, because of the limited evidence which are one RCT for each procedure, and the study had high risk of bias. And this concludes my presentation, and I recommend any questions. Thank you.

Josh Morse — Thank you, Dr. Nam.

Sheila Rege — Thank you very much. That was a really good summary. Sorry, I was trying to print some of your material to run to the printer. Any, any questions for Dr. Nam?

Ji Young Nam — Yes, Dr. Conor.

Conor Kleweno — Yeah, thank you for that great summary. I can make the assumption, but I just thought it'd be helpful for you to specify why you had the diameter specifications for the MACI versus the other ones.

Ji Young Nam — So for MACI when we review the evidence, there was defect that was for the study population included in RCTs and NRIS, especially for the RCTs. The mean defect size was 3 to 5 squared centimeters. And based on our evidence review we thought that it's sufficient to make a recommendation for the diameter recommendation at this time, and in terms of the evidence base. There are 3 RCTs and one RCT had low risk of bias which it was the Summit trial done by the Saris, et al. team, and that's the had the inclusion criteria of participants with chondral defect size higher than larger than 3 square centimeters so our diameter recommendation for MACI came from the evidence review, as just as a reference.

Conor Kleweno — Great. Thank you.

Ji Young Nam — Thank you.

Sheila Rege — Any other questions?

Ji Young Nam — Dr. Bramhall.

John Bramhall — Yes, so again, thanks for that review, very helpful. And you may not be able to answer this question. It's a little indirect, but it relates to the cost slide that you showed. And it looks to me like in 2023 the data it shows the Uniform pays 10 times the rate or the cost for a patient who's got Uniform is 10 times greater than the Medicaid cost, and I

know it's not directly related to your sort of evidence base. But do you have a feeling for why, that might be? It's pretty spectacular price difference.

Ji Young Nam — It's quite a difference. And I we think that the main reason might be that as you see our state agency coverage policy, MACI is a covered benefit with conditions for Uniform medical plan, and it is not covered benefit for Labor and Industries and in terms of the Medicaid, there is no specific policy for fee for service at this time, so we think that large portion of that might be from the MACI being covered with conditions or not among our State agencies. But I will see if other agency medical directors have more insights on that. Thank you.

Sheila Rege — If there's a no more questions I would recommend we go to a break till 9 o'clock. And when we come back, is it okay to start with the agent, that the Oh, what do you call it? The.

Josh Morse — Public comment?

Sheila Rege — We won't do the schedule and open public comment, we'll go to the evidence report. If that's okay with committee members, but I will take a motion to continue and move right on to the committee report. What do what give me a motion. What do people want?

Josh Morse — Dr. Rege, we do have our public commenters that pre-signed up. Here. If you wanted to take a break and then do the comment period at 9.

Sheila Rege — Instead of 9:20?

Josh Morse — That might be on track. Yeah, and we can make a check at 9:20 to make sure nobody else's has arrived for that.

Sheila Rege — Okay, let's do that. Till 9 o'clock. Bye.

Josh Morse — Okay.

Sheila Rege — My clock shows one more minute.

Josh Morse — So Sheila, Val may have an update on the signups. We do have some of the signup people here, but I don't think we have them all.

Sheila Rege — Yeah, I think it's probably safer to keep that 20 min past the hour. If, If we are all willing, maybe we could start with the evidence report. And we'll take a break at about, in in 20-25 min. If that's okay with everybody? Let's go ahead.

Shivani Reddy — Hi everyone. I'm gonna go ahead and share my screen.

Sheila Rege — Thank you so much.

Shivani Reddy

Can you see the slides. Okay, great. So my name is Shivani Reddy, I'm from RTI International. And we'll be reviewing the Health Technology Assessment on treatments for chondral defects of the knee and we had an excellent team who participated in this HTA. An outline for the presentation. We will review the policy context for this HTA, and then an overview of articulate cartilage of the knee and procedures, methods, results, and conclusions. The State of Washington Health Care Authority chose this topic because of high concerns of safety and medium concerns for efficacy and high concerns for cost. We included the following treatments to review. Mai, matrix induced autologous chondrocyte implantation, or MACI, osteochondral autologous transplantation, or OATS, osteochondral allograph transplantation, OCA, and microfracture. One procedure that was initially in the topic was autologous chondrocyte implantation or ACI. We ultimately excluded, and we will discuss our rationale in the method section. Our focus for this presentation will be MACI and OATS or OCA. As we will discuss later, microfracture was often considered the standard of care for a lot of these studies for chondral defect repair. We did identify additional procedures that were modifications of microfracture or newer devices that are not yet widely used in clinical practice. But they do have FDA premarket approval and breakthrough device status so we will touch on this emerging evidence.

This is an overview of knee cartilage. Articular cartilage is the cartilage that lines the surface of the bones that meet at the knee joint. Articular cartilage is made up of hyaline cartilage or type 2 collagen which gives this cartilage it's tensile strength and elasticity. It appears like glass microscopically, and is smooth and lubricated so it reduces friction as the bones glide against each other in motion. Cartilage is poorly vascularized, and innervated, if damaged, the cartilage has limited ability to repair and regenerate smooth hyaline cartilage. The majority of damage articular cartilage is replaced with fibro cartilage composed primarily of type one collagen, which is stiffer and more prone to wear. Some common causes of articular cartilage defects include acute trauma, which is more common in younger populations, anatomic abnormalities, such as malign, developmental defects, such as osteochondritis dissecans, which is a disease where a piece of subchondral bone and overlying cartilage detaches and it's most common in patients 10 to 20 years old. And then there's chronic degeneration. If chondral defects are not repaired, they can lead to an increased risk of osteoarthritis as well as an earlier onset of osteoarthritis. Symptoms include pain, a catching or locking sensation and impaired function. And in studies using validated measures of quality of life, the quality of life of patients with chondral defects was similar to those patients with osteoarthritis awaiting knee replacement. Why repair chondral defects of the knee? As we talked about in the previous slide, untreated these defects can lead to significant limitations in pain, function, quality of life. Another important point is that the only alternative is a knee replacement. So the control repair acts as a stopgap measure before knee replacement. Additionally, patients with chondral defects tend to be younger and knee replacement is generally not recommended for patients less than 50 years old due to likely need for revision during the patient's lifetime. There are 3 categories of treatment for cartilage, articular cartilage repair: bone marrow stimulation techniques including microfracture which aims to induce a healing response from the body to fill the defect with new cartilage. Osteochondral restoration

involves transplanting cartilage tissue into the chondral defect. And cell based for generation involves culturing the patient's own cartilage cells for transplantation.

We'll start with microfracture, which is a bone marrow stimulation, technique. This is a procedure that aims to induce a healing response to generate new cartilage. In this procedure a small sharp pick is used to create channels down to the subchondral bone. mesenchymal stem cells, then can migrate from the bone marrow to the bone surface and create new cartilage. However, only a small amount of hyaline cartilage is generated in this procedure. There's still a large amount of fibro cartilage, and as we discussed before, the cartilage is stiffer and less durable than hyaline cartilage. There is a newer procedure called autologous matrix induced chondrogenesis or AMIC. In this procedure a microfracture is performed, and then the site is covered with a collagen membrane to enhance repair. Microfracture is the most commonly performed chondral defect process in the United States. It is a simpler technique which does not require specialized expertise so it is more widely available than other procedures. It is minimally invasive and has a lower upfront cost compared to other procedures. Microfracture is often considered the standard of care comparator for other chondral defect repair procedures. So when we review the evidence, you will see that microfracture is often the comparator for other procedures.

The next procedure are OATS and OCA which are restoration procedures. They aim to fill the chondral defect with cartilage that better resembles hyaline cartilage. And they can treat deeper lesions that include cartilage as well as defects that reach below the surface of the bone or subchondral lesions. This graphic depicts OATS, in OATS a piece of hyaline cartilage is harvested from a non-weight part of the patient's own knee and then transplanted into the defect. Surgeons are limited by the amount of cartilage they can harvest from the patient, so OATS is generally reserved for smaller lesions. In OCA the source of cartilage is cadaveric tissue so this allows surgeons to fill larger defects. The one of the potential harms is graph versus host disease. These procedures generate a greater amount of more durable hyaline cartilage than microfracture. MACI is a cell based regeneration technique and it's a 2 stage procedure. In the 1st stage chondrocytes or cartilage cells are harvested from a lesser weight, bearing part of the knee and then transplanted on an external porcine or synthetic scaffold. The cells are then cultured outside of the body for 6 to 8 weeks. In the second stage the scaffold with cultured cells are implanted back into the chondral defect. MACI procedures generate more durable hyaline cartilage than microfracture, and OATS or OCA. However, MACI procedures demand higher skill and more resources and the upfront costs are more expensive than microfracture or OATS.

How do surgeons choose if and which particular cartilage repair is most appropriate? They consider patient factors, including age as we talked about on the previous slide, younger patients tend to be favored for these procedures to delay the need for knee replacement. Activity level, so if a patient is less active or sedentary, they may receive less benefit from the intervention. Comorbidities, such as osteoarthritis, obesity, and other comorbidities can decrease the chances of success. Limb alignment refers to various deformities which cause malignant of the joint, and put increased load on the

femoral condyles and this poses an increased risk of failure of the chondral defect repair. The characteristics of the defect also guide decisions of which procedure may benefit the patient most. There's the size of the defect which is evaluated by MRI and or arthroscopy. The depth of the lesion, so is the defect confined to the cartilage, or does it extend to the subchondral bone just below the cartilage. The location of the lesion can also impact the decision of whether or which procedure to use such as whether the defect is on the femur or the patella femoral compartment. This slide gives a rough overview of which procedures align, with which defect characteristics. Microfracture and OATS are used for smaller lesions while MACI and OCA are used for larger lesions. OATS and OCA are used for defects that reach the subchondral bone and microfracture and MACI are for cartilage defects without subchondral bone involvement. The evidence for the size and depth of defects that pretend to the operations primarily comes from single arm studies within group changes, and one arm of a comparative study and nonsystematic reviews and expert opinion. All of which were not included in this review. We also want a caveat, that the cut offs of 2 and 4 cm was common in the literature, but different authors did use different cutoffs to determine large or small. And the range of sizes considered for each procedure is evolving as one of our external peer reviewers indicated.

Regulatory approvals for surgeries that do not involve an external product there are no specific regulatory requirements, so microfracture and OATS. OCA follows the rules of tissue donation and products used in cartilage repair procedures are regulated by the FDA Center for Biologics and Evaluation and Regulation or CBER. And are categorized as human cells, tissues and cellular and tissue-based products, HCT/P. The porcine scaffold use in the MACI procedure is the one product currently approved by the FDA through the 351 HCT pathway requiring evidence of efficacy and safety. There are newer products, including the cell-free implants, or Agili-C and chondro-gide AMIC that have received FDA breakthrough device status. We found no guidelines on the use of articular cartilage repair procedures from orthopedic societies and this was confirmed by our orthopedic consultant, and external peer reviewers. We did identify NICE guidelines from the UK which approved mosaicplasty, which can refer to either OATS and OCA. And I think the difference is that they can, it treats a much larger area. The last HTA of cartilage repair was in 2011, and looked at OATS and OCA only, and it also looked at joints other than the knee. As Dr. Nam reviewed OATS and OCA, were covered with conditions, including age less than 50 and full thickness cartilage defects. There was no prior decision on microfracture lightly, because this is considered a standard of care and there's been no prior coverage decision on MACI.

Let's move on to our methods. Our key questions are what is the effectiveness of the treatments for chondral defects, including bone marrow stimulation and repair of osteochondral restoration and cell based regeneration? What are the harms of these procedures? And what is the cost effectiveness of these treatments? This figure illustrates our analytic framework. We are looking at a population of patients with chondral defects of the knee only. The interventions or the procedures microfracture, OATS and OCA, and MACI. We focused on patient-centered outcomes of knee symptoms and function, as well as harms. The next few slides review our inclusion and

exclusion criteria for this review, using the PICO's framework. We included individuals with defects of the knee only. We also included all ages. Osteochondritis dissecans is a indication for chondral defect repair surgeries and it's primarily a disease of children and adolescents. From our scoping call we decided to include children, as was as well as adults. For the intervention of we include interventions of microfracture, OATS, OCA, and MACI as well as the products that have FDA breakthrough device, designation. Additionally, we looked at second line procedures after a failed procedure. So, for example, if a patient failed a microfracture and then a MACI was performed second line compared. If you just did, the MACI first. And this reason this was included to inform the committee's decisions about coverage for repeat surgeries if you decide to include it. We specifically excluded 1st generation and second generation ACI, and ultimately included 3rd generation ACI. In 1st and second generation ACI the cultured cells are in a liquid suspension versus a scaffold. And that liquid suspension is injected into the defect. In 1st generation ACI, the defect is then covered with a periodical patch harvested from the patient. In second generation ACI college and membrane is used as a cover. 1st generation ACI has been largely phased out, due to improved outcomes for 3rd generation. And in the report we cite research. For this, for example, there was an RCT comparing 3rd to 1st generation and over half of the patients in the 1st generation group failed, due to graph hypertrophy compared to the MACI group, where only one patient experienced graph hypertrophy. And this trial is actually stopped early, due to the disproportionate failure of 1st generation group. And then none of the collagen membranes used in second generation are FDA approved in the US. Competitors that were the same, for all procedures were conservative therapy, such as physical therapy and joint injections, chondroplasty or debridement, knee replacement and sham surgery. For OATS and OCA and MACI, microfracture was an eligible comparator and for MACI we included OATS and OCA as a comparator. We should note here that again that microfracture was the most common.

Our outcomes for effectiveness included symptoms and function using validated knee specific measures as well as response to treatment. treatment failure, and re-operations. We wanna note that the outcome of response was defined differently across studies. In general response was defined by a change in score of a validated measure. The different measures were used, and the threshold defining response varied. We found variability and definitions for treatment failure and re-operation as well. We excluded intermediate outcomes, such as imaging, like MRI and pathology, outcomes. And we included standard outcomes for harms and cost. We did not include cost studies with non-US cost inputs to increase the applicability of the results. We included RCTs and NRISs, or non-randomized studies of interventions for this HTA. We did require the NRISs to have a comparison group. We excluded single arm studies as discussed during the scoping phase, including single arm studies in the and including single arm studies in the review would have increased the volume beyond what was feasible within the resource and schedule constrains. And then these PICOs were also posted for public comment for which we receive no comments regarding this exclusion criteria. The validated measures reported by the included studies are shown here. Most included measures included both symptoms and function. For example, return to

daily activities, work or sport, and the Tegner Score focused on function only. We searched 2 databases and clinical trials.gov., performed risk of bias assessment for individual studies, synthesize narratively and quantitatively, if there are minimum of 3 studies. We use the GRADE framework to assess certainty of evidence for each set of studies with the same comparison and outcome. So a high grade indicates, we are confident in the results, and future studies are not likely to change our assessment. In contrast, low or very low of grade means we are less confident, and future studies could change the effect estimate.

We'll move on to a summary of our findings. In this slide we present the search yields for eligible competitors. So in the 1st column we have the comparisons and the total number of studies identified for that comparison. And then in the other columns we report the number of studies we found for each key question. So, for example for MACI versus microfracture we identified a total of 5 studies and all 5 studies reported effectiveness outcomes, 4 studies reported safety outcomes and no studies addressed the cost key question. We found the greatest number of studies for MACI compared with microfracture and OATS compared to microfracture as well as 1st line versus second line procedures. And so for this presentation, we'll focus on these comparisons, and then we'll touch on cell-free implants and AMIC. Our top line summary is as follows. MACI may be more effective than microfracture, with moderate to low certainty of evidence. OATS is possibly more effective than, or of comparable effectiveness to microfracture with low certainty of evidence. 1st line MACI or OCA may be more effective than performing these procedures as second line procedures with low certainty of evidence. Harms, for all comparisons are probably comparable, but few events in many studies, but there are a few events in many studies or they were just not reported, and this is low to very low certainty of evidence.

Sheila Rege — Dr. Reddy, could I interrupt? This is this is excellent. I just wanna make sure, though, that because it's 9:20.

Shivani Reddy — Sure. Yeah.

Sheila Rege — That we a goal for public comment. It's a good time to stop. You just could give us a top line summary, and then we'll go on to your thank you very much.

Shivani Reddy — Okay. Okay. Okay. Sounds good. Gonna end my share here.

Sheila Rege — But this is I mean, this was a really good. I'm very impressed. So thank you. Dr. Reddy.

Val Hamann — Okay, for the public comments today I am seeing a couple of groups that did sign up ahead of time. For anybody else that was not signed up, could you please raise your hand so we can identify anybody new that would like to speak today. Again, anybody who did not pre sign up, we cannot accommodate any type of presentation materials today. And we will start with. Great. Thank you, Dr. Clinton. I have you on the list. We'll start with Vericel today. So I will promote them to panelists. And they.

Sheila Rege — And again, if you would, when you in your introduction, also mention conflicts, whether anybody has paid for your way here or you're doing, you know, kind of what capacity you're doing this presentation on behalf of.

Val Hamann — And Dan. And Andrew, did you want to present your slides? Would you like me to or do you have those ready?

Andrew Kocher — I, I, this is Andrew. Thank you very much. I do have them ready. And I'd be happy to present from my computer. If that's okay?

Val Hamann — Yep, that works great, and just as a heads up I will give you, you have 6 min today between you and Dan. However, you would like to split that up, and I will give you a heads up at the 1 min mark and then again at 30 seconds, so feel free to start when you're ready.

Andrew Kocher — Excellent. Thank you very much, and thank you very much to the committee for the time to speak today I will go ahead and do a brief presentation and then turn it straight to, to Dan at that point. So thank you again very much. So, looking at MACI, from the Vericel perspective. Excuse me, so.

Sheila Rege — Andrew, can you identify your conflicts if you're employed by? Go ahead.

Andrew Kocher — Yes, absolutely so in the medical science liaison for Vericel as an employee of Vericel. Yes in consistency with my disclosure to the committee. Thank you very much. I appreciate that. Almost forgot to mention.

Sheila Rege — Thank you.

Andrew Kocher — So MACI is an autologous cell, cellular scaffold product. It's indicated for the repair of symptomatic, single or full thickness, cartilage defects of the knee, with or without bone involvement in adults. And it's the 1st FDA-approved product that applies to processes of tissue engineering to grow cells or scaffold, using healthy cartilage from the patient's own knee. And so there were some great images, and very appreciative of the discussion that's happened so far, so just to provide a little visibility into what the, the membrane looks like. On the left we have the type 1, 3 collagen membrane and then you can see below in the image the, the dual sided nature of the bilayer aspect of the membrane with a couple chondrocytes that are attached via cytoplasmic projections, and then on the right we can see how that is delivered through the delivery of the satellite model, and being decanted into the OR and just what that looks like within the OR experience itself for the MACI being delivered for the time of surgery. So, looking at the surgical procedure. So there are 4 key steps. Following the biopsy as mentioned, it's sent to the laboratory in Cambridge, Massachusetts. At that time it is expanded, takes about 3 weeks or so for the cells to, to grow and be seated onto the membrane and then shipped to the, the surgeon. At the time of implantation we have custom cutters that can be used to outline the defect that defect once outlined and is debrided down to, but not through, the subchondral bone, and this

prepares for the implantation of the MACI. The same size cutters, then placed over the membrane. So you have a match between the membrane and the prepared defect, and then ultimately the membrane is that's been prepared is glued into the defect, using fibro and glue. The knee is cycled, and then that can is the extent of the MACI procedure itself. Looking at it from an arthroscopic perspective. It's a very similar procedure in terms of arthroscopically using a custom cutter to outline the defect. It's then to debrided again down to, but not through the subchondral bone. The, the corresponding cutter for the membrane. Again, as with the open technique, it's to match the same size as the arthroscopic cutter, and then the membrane is deployed and implanted again with the use of fiber and glue, via a V shuttle into the defect for, for implantation in that prepared defect. So looking at, there's been lots of great discussion on data looking at a couple key studies. Really a, our clinical trial, the Summit trial. Looking at the two-year outcomes again, I know it's been mentioned, but just to, to briefly touch on the fact that MACI demonstrated it was demonstrated to be safer and more effective based on a superior clinical outcomes over MACI, and was statistically and clinically significant in the primary endpoints of KOOS pain and function that was out to 2 years, and then in an extension study out to 5 years of the of the clinical trial, the, the clinical outcomes of MACI versus microfracture that we're seeing that 2 years were maintained out to that 5 year time point.

Looking at some additional data and, and looking to our colleagues in Australia with their MACI experience again culture chondrocytes, autologous chondrocytes on a type 1, 3, collagen membrane in ten year outcomes. The clinical effect of 5 years was sustained out to 10 years, and we see that across the various KOOS subscales. And then looking at additional from, from Australia, additional studies from 11 to 16 years, with prospective clinical looking at what's been reported from a patient reported outcome perspective certainly. We see that data, but looking at it from a clinical perspective in terms of the limb symmetry indexes with single hop distance, triple, hop for distance, knee extension, peak torque knee flexion, torque. So, looking at those clinical measures we can see that for those achieving those we're, we're in the 80%. An extension peak, torque in the in the high, 70%. Further looking at a satisfaction that we see 93 and 93, 83, and 73 in terms of patient, satisfied with pain, undertaking ADLs, their participation in recreation activities and participating in sports activities. And then, looking at the final couple, slides just again, looking at a little bit of the longer term, outcomes one graph survivorship so we see 5 year graph survivorship being reported in the literature at around 90% ten-year graph survivorship around 82%. And in 88 to 90% in terms of patients satisfaction at 10 and 5 years respectively to speak to the durability of, of the repair tissue that's seen. And then looking at the minimal, clinically important difference which the for the VAS pain which is indicated.

Val Hamann 1, you have 1 min remaining.

Andrew Kocher Thank you, which is in which is indicated at 2.7 on the MCID. We see that being reported in the literature for Aci and MACI, and not seeing that for, for other technologies, so moving on to the final slide and the final just looking in a cost efficacy analysis over 10 years, and looking at MACI from the perspective at a at a $50,000

threshold, that we see MACI in various models of cost, efficacy and failure rate. Being modeled as cost effective within an analysis. And so with that, I'd like to turn it over to my colleague Dan Doyle.

Val Hamann — And you have 30 seconds.

Dan Doyle — I appreciate your time. I'm Dan Dole, Associate Director of National Key Accounts for Vericel. It had been brought up earlier that you guys were gonna take a look into some of the other Medicaid's to see who's covering MACI. I wanted to point out that Iowa. Indiana and Ohio have all, added MACI at 105% of whack. Thank you for your time. Today.

Andrew Kocher — Thank you all very much.

Val Hamann — Thank you so much, and we will move on to Dr. Clinton next, and then we will have Dr. Jones. And Dr. Clinton feel free to start when you are ready, and you will have 4 min. Are you there, Dr. Clinton. If you're speaking, we're unable to hear you.

Sheila Rege — We've confirmed Dr. Clinton as a panelist?

Val Hamann — Yes. It looks like Dr. Clinton is going to try to connect via their phone. So. Let's just jump over to Dr. Jones. I will promote you, and then we'll try again for Dr. Clinton. Okay, Dr. Jones, feel free to begin when you're ready, and you will have 4 min.

Ty Jones — Hello! Hi, I'm Dr. Ty Jones, I'm a medical director at Regence, supporting the HCA, and I'm also a sports medicine physician. I would like to supplement some information the evidence draft from a health plan perspective and also from a sports med perspective. First, some supplemental information of what local health plans are doing. I noted in the evidence draft and slides in the slide other payers that no policy was identified for Kaiser, Premera, Cigna, and Regence for microfracture drilling. I wanted to explain that this is because these health plans do not preauthorize these requests, which means they're automatically approved and reported to the help plan. So if they're commonplace, noncontroversial procedures that are covered without a medical necessity review. In addition to microfracture and drilling, I found that Kaiser also doesn't require authorization for OATS, meaning it too, is covered without a medical necessity review. They do have criteria for MACI, however, and one of those criteria is that the physician provide documentation to support why, an alternative cartilage, such as OATS is contraindicated in order to authorize MACI. In other words, they request the providers and members please consider OATS before MACI and OATS isn't the right procedure to please provide a reason why the member's needs must be met by this other procedure, which just a reminder it is 2 separate surgeries, and is probably at least twice the cost and also Regence does also cover OATS and uses the same criteria.

My second comment is request that we'll make administering an HTCC decision much simpler for all involved. So I work with or I do work with Regence's team to

appropriately interpret HTCC decisions when they come through, and clarity early can be really helpful. So. I see in the agency medical director's recommendation to exclude members with degenerative arthritis and the joint from having these cartilage repair procedures, so OATS and MACI's this is an excellent recommendation in that repairing a chondral defect in any with the background a significant wear and tear is unlikely to result in a meaningful clinical improvement. But I know the different help plans interpret what the presence of osteoarthritis even means in the context of approving these procedures. So even going so far as using different grading systems of what that osteoarthritis so Cigna would say that Kellgren-Lawrence grade one or 2 osteoarthritis would be okay but if it's 3 or above that, you're excluded from coverage for MACI Regence policy states that surrounding degenerate changes must be outerbridge grade 2 or less for MACI to be considered medically necessary. So a whole other system and Kaiser's policy states that there must be no evidence of osteoarthritis at all without specifying what system they're using. So seeing that there are multiple interpretations of the same concept in the health plan policy space, I requested an HTCC determination that specific in its definition of what degree of osteoarthritis would be considered a non-covered indication would support ease of interpretation for providers and administrators. And I recommend that when drafting those non-covered indicators that the committee, yeah, so please be specific. And if you could use a, a Kellgren-Lawrence system or an outer bridge scale or an objective statement, such as MRI findings of partial or full thickness cartilage regions outside of the deficit or the defect would be a contraindication or simply any radiologic science for any arthritis at all. I feel like I've driven this point home. Just please be very explicit, and what it means to have a degenerative changes in the joint. Thank you. That's it for me.

Val Hamann — Great. Thank you so much. I am having Dr. Clinton be promoted to a panelist, so we'll try that again. So, Dr. Clinton again you have 4 min and feel free to take it away when you're ready.

Camille Clinton — Okay, is it working this time.

Val Hamann — It is.

Camille Clinton — Okay, sorry about that. So I'm Dr. Camille Clinton. I am an orthopedic surgeon. I'm employed by Evergreen Health. I've been in practice for about 16 years. I have a fellowship in sports medicine. And my practice essentially at this point, focuses primarily on knee arthroscopy, reconstruction, and knee replacement, primarily knee surgery. I have no conflicts of interest. So while you may see procedures, I am not in any way linked to Vercil or the company. I so I, I know you've gotten a lot of information about different cartilage replacement procedures and those are all procedures that that I use when I'm approaching a patient with the cartilage issue. As was just mentioned these aren't appropriate procedures for patients with arthritis. These are procedures for patients who generally are younger and have an isolated chondral defect in some cases perhaps more than one, but they do not have arthritis. And when you're looking at the different cartilage replacement options we have for patients, the, there's kind of a flow chart as a physician I go through as you know,

we're, we're making our clinical decisions. And so the 1st thing you look at is the size of the lesion, and, and so procedures like a microfracture which are cheap and, and quite, you know, easy, straightforward can work well, but under very specific conditions. So they work best for young patients less than 30, very small defects, and in general the function over time or the results over time tends to decrease. So you're never getting normal cartilage in that area and so functionally that that tends to decrease over time. The other issue with microfracture, is that there's evidence that if you've done a microfracture, then if that microfracture fails, subsequent cartilage are less likely to be successful. So again can be appropriate for small defects when we're looking at larger defects in my mind, microfracture is just not the best choice. The outcomes aren't as good, frankly, and you potentially decrease your success rates of other procedures. So when we're looking at, then you're basically left with MACI versus osteochondral graphs and if there's a bony defect osteochondral graph is a great option. If there's no bony defect, MACI can be a very good option for people. An excellent option, in fact it, it uses a patient's own cells which is a benefit potentially, especially when you're looking at larger defects. In a place like the patellofemoral joint, where the anatomy or conquer of that joint can be difficult to match with an osteochondral defect, MACI graphs can be very, very helpful. MACI do not burn any bridges, so if you do, an osteochondral graph, and that fails, you have limited somewhat more limited options after that you don't have that same issue with a MACI graft. And then, from a practical standpoint, while MACI is a two-stage, which is, is what it is.

Val Hamann — You have. You have 30 seconds.

Camille Clinton — Okay, when you're looking at an osteochondral graph for larger lesions, you need to have a matched graft and they're fresh frozen, they're fresh so there's a time limit and a time window on when to use them. For so, so for patients and a lot of our patients that are, you know, manual labor patients are really young patients it's extremely difficult, from a practical standpoint for them to have a 2 week window in which their surgery needs to be scheduled. So MACI is also much easier to use in these patients. And I would say in my patients have had excellent outcomes of people getting back to function, work and you know, pain free life, sports, etc.

Val Hamann — Thank you, and that concludes your time. If we have any other members of the audience that are wishing to speak today as we did have another group, it looks like someone else has raised their hand. I will promote them to panelist. And if there are any others while we're having this individual come over, please raise your hand, and we will be prepared to promote you in a bit. If you could please let us know your name. That would be great, as we're just seeing numbers at this time.

Carolyn Garziano — Yeah, I'm, I'm sorry about that. My name is Dr. Carolyn Graziano.

Val Hamann — Great. Okay.

Carolyn Garziano — I'm the director of strategic reimbursement for Smith and Nephew.

Washington State Health Care Authority

Val Hamann	Would you like me to present your slides, or would you?
Carolyn Garziano	And, sure, if you can do that. Just a couple of quick slides. I'm not gonna take up much of, of the committees time.
Val Hamann	Okay. Great, and you will have 4 min today. So and I will give you a heads up at the 30 second mark. So.
Carolyn Garziano	No, thank you.
Val Hamann	Feel free to start.
Sheila Rege	And appreciate you declaring your conflicts. Thank you.
Carolyn Garziano	Thank you. I appreciate your time. I just wanted to say overall, it was really an excellent review of technology. The point that I wanted to bring up in, I think that Dr. Clinton, ahead of me said a lot of this we still have gaps to be addressed. In both the evidence development, and the unmet clinical needs in this space. So I, I really appreciate the opportunity to comment. If you can just go to the next slide, the main point I wanted to bring up was so again, I represent Smith and Nephew CartiHeal Agili-C. We are the cell-free implant and while the focus of this HTA was on all the other sort of existing procedures, we, we did get on your radar. And I think the reason why we ended up on the radar is because we do have a compelling 251 patient study out there, comparing our cell-free implant to microfracture debridement. So when you look at and there's there is a slight typo on this particular slide here but the point I wanted to make is that the cell-free implant goes beyond all of the other procedures out there in the fact that it's used to treat centimeters basically ou know, 1 cm squared to 7 meter squared in the presence of both subchondral and up to moderate OA and again Dr. Clinton was bringing out points that a lot of these procedures are done younger people, no OA, there isn't a lot of options for, for patients that are maybe really too young for a knee replacement, but have chondral defects. The Agili-C product and procedure again, it allows you off the shelf, easy sourcing without tissue matching barriers, without some of the time of the time and cost of the other products out there. Last slide, just talk a little bit about the main study. And again we realize that we really have just one large RCT here. We were very pleased that you saw moderate confidence of evidence for effectiveness, and the patient reported outcomes responder as MACI. Our 4 year manuscript has been submitted and should be published shortly. We have 5 year data that is complete is in process. Abstract has already been submitted. So there's compelling evidence worthy of CartiHeal Agili-C as a treatment option in select patients while more evidence is developing. And again it it meets that unmet need for the smaller 2 larger subchondral lesions with subchondral involvement and up to moderate OA. Thank you.
Val Hamann	Thank you, and just wanted to do a final call for anybody else in the audience who wishes to speak during the public comment portion. Not seeing anyone so that's all of the individuals we had pre-signed up today.

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Sheila Rege Great, and we have public comment scheduled for another 15 min, so maybe we'll take a break again. And right at on the top of the other we'll ask again. Dr. Reddy, would you mind coming back and on with your presentation?

Shivani Reddy Sure.

Sheila Rege Thank you. Sorry about that.

Shivani Reddy No, no, that's fine.

Sheila Rege Okay.

Shivani Reddy See if I can. Are you seeing my slides now? Great. So some overall across all the studies, most had an age inclusion criteria ranging from 18 to 50. A few studies were conducted in adults that extended up to 55 or 60. One study was performed in patients under 18 exclusively, and 7 studies included adolescents and adults. And I, I just wanna point out that the, there was a closed plate requirement for 2 of those 7 studies and nothing else reported anything about skeletal maturity. The mean age of the participants range from 15 to 53. And this isn't on our slides but I do, because defect size has come up a couple of times, I do wanna say the inclusion criteria for these studies were quite broad anywhere from 1 cm to 10 cm. But the average mean defect size was between 2 and 5. Sorry I'm having a little technical issue here, okay.

So we'll 1st look at our results for MACI compared to microfracture. We identified 5 studies, 3 RCTs and 2 NRSIs for the comparison of MACI and microfracture. These studies were conducted between 2000 and 2018, with sample sizes ranging from 30 to 254 participants. And follow up for these studies from 2 years to 5 years. Most of these studies were conducted outside of the US and 2 studies were rated as high risk. 4 studies that reported funding were funded by industry. So this included 2 RCTs and 2 and NRSIs. In this slide, we present an evidence map over results across outcomes. So you're gonna see this slide multiple times in our presentation. So I'm gonna take a few minutes to orient you. So the y axis is our outcomes. The X-axis is, whether the results favor MACI, microfracture, or are comparable. The color of the bubbles represents the strength of evidence. So green represents moderate, which is the highest certainty of evidence we observed in this HTA. Yellow is low certainty of evidence, and red is very low. Sorry about that. Couple other things about this. So the solid colors here represent the certainty of evidence for RCTs and the speckled pattern is for NRSIs. We did combine any adverse events and serious adverse events for the harm row, and we presented the lowest certainty of evidence. The text inside the bubbles are the number of studies and the total number of participants for that outcome. So in this figure we see that MACI was more effective than microfracture for patient reported outcomes and response for both study designs with a higher with a certainty of evidence of moderate for trials. All other outcomes had low to very low certainty of evidence. MACI had fewer re-operations than microfracture among NRSIs and all other outcomes were comparable, including treatment failure and reoperations for RCTs and harms. This slide summarizes comparativeness findings for MACI versus microfracture.

As we presented on the prior slide, there was greater effectiveness of MACI for patient reported outcomes. For most of the patient reported outcomes the results were clinically as well as statistically significant. Response to treatment was also greater with risk ratios of response ranging from 1.3 to 3.4. Treatment failure was comparable, as well as re-operations for RCTs. NRSIs reported greater effectiveness of MACI. In terms of harms, any adverse events were comparable for both study types. Only RCTs reported serious adverse events, which were also comparable. However, the caveat is that few harms were reported across studies. The most common adverse events were knee pain and swelling, which can be common after many orthopedic surgeries. The few serious adverse events reported septic arthritis and deep vein thrombosis. So there was one of each from different studies.

Moving on to OATS versus microfracture. We identified 7 studies comparing OATS to microfracture, 5 of which were RCTs. The sample size ranged from 25 to 203 and there was a range of follow up from 2 to 15 years. One study was conducted in the US. 4 had some risk of bias and funding sources were not reported for any of these studies. This is the evidence map for OATS versus microfracture results. As a reminder of the Y axis or the outcomes, the X axis is procedure. Yellow is low certainty of evidence, and red is very low certainty of evidence. Solid colors are RCTs and speckled our NRSIs. For outcomes of response and treatment, there was greater response to OATS and 3 RCTs and lower treatment for OATS in one NRSIs. The remaining outcomes were comparable for other outcomes with low to very low certainty of evidence. For the one cost effectiveness outcome we were unable to determine which procedure was more cost effective. We were able to perform a meta-analysis of 3 RCTs reporting the Lysholm score, a patient reported outcome that asked questions about both knee symptoms and function. We found a mean difference in score of 3.6 points. There was a wide confidence interval that crossed the null. In terms of other effectiveness outcomes there was one small trial that reported a greater response to treatment for OATS compared to microfracture. One NRSI reported fewer treatment failures for OATS. And among trials, treatment failures, and re-operations were comparable. Harms were similar for each procedure, though there were few events reported in most studies, as we discussed with MACI. The most common adverse events for OATS versus microfracture were knee pain, joint swelling and crepitation of knee joint and they were greater in the microfracture group. And there were no serious adverse events reported. There was little data on subgroups. Among the trials smaller lesions were associated with greater effectiveness in the microfracture group compared to larger lesions. While in the OATS group there was no difference in outcomes by defect size. For one NRSI, the OATS group also had greater effectiveness than microfracture group for younger ages and smaller lesions. We identified one cost effectiveness, study. The effective effectiveness data inputs were validated measures that were derived from 3 RCTs. And the cost included the cost of the initial procedure, operating room procedures and staff cost of failure which included cost of return, evaluation, visits, repeat MRI imaging and a second procedure, if indicated. The specific cost estimates came from a single academic institution which may not represent costs for different settings. We found mixed results. The cost effectiveness depended on which patient reported outcome was used to measure. So microfracture had lower cost per

point improvement using the Lysholm score the HSS score. But OATS was more cost effective using the Tegner score or the metric of return to sport. And this is another look at the evidence map for OATS versus microfracture.

The last comparison we're presenting is 1st versus second line procedures. We identified 4 and NRSIs comparing 1st line and second line procedures. This refers to procedures of MACI or OCA comparing the effectiveness and harms of performing these procedures first versus performing them after failed microfracture. The sample sizes for these studies range from 26 to 167 and there was a range of follow up from 3 to 8 years. 3 studies used US data and all were high risk of bias. 2 studies explicitly reported no financial support and one was supported by a foundation. The 2 procedures that were compare, the 2 procedures that were compared 1st line to second line were MACI and OCA and we'll go over them in the next slides. So this cross hatch pattern that you see here indicates the MACI procedure and the speckled pattern represents OCA. There were fewer treatment failures and re-operations if MACI or OCA was performed upfront as the 1st line procedure. 1st line MACI procedures had greater improvements in patient reporter, reported outcomes compared to MACI compared to if MACI was performed after the bone marrow stimulation. Patient reported outcomes were similar for both 1st and second line OCA procedures and there were no harms reported in the 4 studies. The remaining comparisons that had few studies are listed here. Some of these comparisons are less likely to be observed, due to defect characteristic. So OATS and OCA are generally used for defects with subchondral involvement, and microfracture, or MACI may not be considered. OCA and OATS are used for different size defects. And OCA is especially hard to study because it requires a match donor, the patient needs to be on call when the tissue becomes available, and the tissue is only viable for a short amount of time.

And some procedures are newer and haven't developed a large evidence base and aren't widely used in practice yet. But they do have breakthrough device so we're gonna review them briefly. We found one study, an RCT evaluating cell-free implants or Agili-C compared to a chondral group of microfracture and chondroplasty. The total number of participants was 251, and the study was industry funded. As a reminder Agili-C is a procedure in which the cell-free implant plugs the chondral defect. And this is made out of Oregonite, which I think is similar to coral. Agili-C has moderate certainty of evidence for patient reported outcomes in response to treatment. Treatment failure was comparable between the 2 groups with low certainty of evidence. And there were few harms. There were fewer harms in the cell-free implant group, with low certainty of evidence as well. We do want to note that because this is a single study of evidence, we can't assess consistency of the results and according to the GRADE framework, you do not downgrade for consistency in a single body in a single study body of evidence. This approach to consistency is considered one of the weaknesses of the GRADE framework. So we did not downgrade the domain of precision either as this study had statistically and clinically significant results for patient reported outcomes and response. GRADE, the GRADE was only downgraded from high to moderate for study limitations for these 2 outcomes as the study was assessed as high risk of bias for the randomization domain and the baseline differences

in disease severity which may bias the results. So I think there were, there was more severe lesions in the microfracture group compared to the Agili-C group. There was one trial for AMIC in which a collagen membrane covers the microfracture site to promote new cartilage growth. This is another RCT that was industry funded and enrolled 47 patients. The patient reported outcome was more improved, for the AMIC group compared to microfracture with low certainty of evidence. Re-operations between groups was similar, with very low certainty of evidence and we were unable to determine the direction of effects for harms or so adverse events or serious adverse events, because the harms were reported for the total study sample, and not by group.

Discussion. We would like to note the limitations of comparative effectiveness research in evaluating these procedures. Head to head trials are not set up to study procedures under their optimal conditions, or specifically the size and depth of that defect that guides clinical decision making. And additionally, few studies reported on subgroup analysis. For example, most studies had a wide range of defect size in the inclusion criteria for both procedures so anywhere from one to 12 centimeters squared. Even if the defect was less appropriate for one of the procedures so, as we mentioned before, most of the data regarding defect size, and better outcomes is comes from single arms studies that we're not eligible. So there hasn't been a systematic comparative study of which defect sizes are optimal for each procedure. In in the absence of this data you know, we've, the field has used single arm studies and expert opinion to make clinical practice decisions. So comparative effectiveness research provides some information about which procedures have greater or comparative effectiveness though it doesn't provide all the data needed to make these comprehensive recommendations. And is with most medical care, clinicians and patients use evidence to tailor decision making to the clinical context as we do with most evidence based medicine and recommendations. So, for example, a patient may have a larger defect, but not be able to invest the time needed for the longer rehab period for MACI. So microfracture may be a better fit, even though there's evidence of greater effectiveness of MACI with patient reported outcomes and response for patients with larger defects. And another example is that if the defect involves subchondral bone, the surgeon would probably look at OATS or OCA, because you could replace the damaged subchondral bone as well as the cartilage, while MACI and microfracture would not. Knee replacement is likely the most relevant comparator for chondral defect repair, though we did not find any studies of this comparison. One reason for that is that the patients that present for cartilage repair surgery are generally younger, and knee replacement is usually reserved for patients over 50. We also did not find any comparisons of chondral defect repair to conservative therapy. These patients are likely to have already undergone therapy like PT and joint injections prior to presenting to the evaluation, for evaluation for these procedures. In terms of limitations of the evidence. Many of the included studies have high risk of bias. This is of particular concern for the NRSIs, because of confounding. As discussed above, procedure is often based on clinical or defect characteristics, and these were often not controlled for in the analysis. For RCTs with high risk of bias, here was often poor reporting of the randomization process. How missing data was handled, if at all, and whether statistical approaches were used to reduce bias. Only one study reported time

to return to work or rehabilitation time, which would be very helpful for a more general population behind, beyond high level athletes. There were a variety of patient reported outcomes used which made it difficult access across studies. And often there wasn't data to calculate a standardized mean difference, so that was that would have been helpful that was not something that was available to us. There was also a wide range of follow-up times across these studies, which makes it difficult to compare the short term results versus long term follow up, which informs the difference in longevity of these procedures. So for studies that reported outcomes at 6 or 12 months as well as longer term follow-up, those additional time points from 2 to 15 years. And, and these were for 2MACI studies, these were for MACI and OATS that have to go back and check how many. In general, patient reported outcomes for MACI or OATs were maintained at the second follow up time point.

Here we review some of the limitations of the HTA. We did not include validated measures for general quality of life choosing to focus on patient reported outcomes related to knee symptoms and function only. We thought this would be more useful for the committee. We also did not include studies of 1st or second generation procedures though there is a body of evidence on them. And as a reminder, 1st generation has been phased out, and second generation does not have a FDA approved product in the United States. But of note, we did screen the full text of all studies that included ACI in the title or abstract, because the terms ACI and MACI are often used interchangeably by surgeons, so we ensure that the procedure was an older one in the methods before excluding it. We only included comparative study designs which increases our ability in infer causal inference but may miss longer assessments of harms, as well as procedures that are difficult to include in a trial context such as OCA. We did review the MAUDE database and identified 3 records for MACI. All 3 records reported that technicians noted that the sterol culture dish was leaking and surgery did not move forward for any of these patients.

So in this section we review other policies. The checkmark indicates a cover, a coverage policy was identified, and a dash indicates that we did not find a coverage policy for that procedure. So there is no Medicare NCD and 2 insurers have no policies on, for any procedure, though I believe one of our public commenters said it wasn't needed. I'm sorry I can't remember which insurer that was. So the 3 insurance insurances that have explicit coverage policies cover OATS and OCA. And 4 cover ACI, MACI and health, United health is the only company with a specific policy for microfracture. Common clinical requirements in these policies, or a patient too young for a knee replacement, only one policy gave a definitive age less than 55, and the other suggested it. Premera, Regence, United all required closed growth plates for OATS, OCA, and MACI. And the defect size ranged from greater than 1.5 cm to 2 cm for MACI. That's across 3 insurers and one insurer included a size criteria for OATS, and that was greater than 1 cm squared. So this is a review of our top line summary. MACI may be more effective than microfracture with moderate to low certainty of evidence. OATS is possibly more effective than, or of comparable effectiveness, as microfracture with low certainty of evidence. 1st line MACI or OCA may be more effective than performing these procedures as second line procedures after a failed bone marrow

stimulation procedure with low certainty of evidence. And then harms for all comparisons are probably comparable, but few events, many studies, there are few events in many studies are not reported, so low to very low certainty of evidence. So that's the end of the presentation, and I'm happy to take questions.

Sheila Rege — Thank you. Open for questions.

Clint Daniels — I'll go ahead Dr. Reddy. Great presentation. I, I was curious on the subgroups that we're comparing to microfracture, so like MACI and OATS can you clarify? Were those all 1st line or was that a mix of 1st line and second line being compared to the microfracture?

Shivani Reddy — The only 1st versus second line procedures for the 4 that I presented.

Clint Daniels — Okay. Thank you.

Tony Yen — Dr. Reddy, I have a question for you about your presentation about the cell-free implants, I think it's on page 58 of your presentation. I was a bit surprised to see how PROs and response was color coded green in terms of certainty of evidence. Can you tell me more about that?

Shivani Reddy — Sure would it be helpful if I share this slide again?

Tony Yen — Yeah, because and the reason is it seemed like the baseline for the 2 comparison groups are quite different.

Shivani Reddy — So that is something that was that we did know that the comparison group included microfracture and chondroplasty. So chondroplasty is just debridement of the cartilage and then microfracture continues that with drilling holes. We did decide to include this study because it is a FDA breakthrough device. And it did show, so I mean that was the main reason that we included it though we did recognize that the comparator group, is the procedures are similar, but one is more you know, one is just for symptoms, and the other one is really trying to repair the cartilage.

Sheila Rege — I have a question. Can you again let us know about the contraindications for MACI and the studies?

Shivani Reddy — So I think one of the some of the common things were around osteoarthritis, comorbidities, age I'd have to go back to the primary studies, but that was often one of them, those were often the most common exclusion criteria. That's something I can look up and get you some more information about.

Leila Kahwati — I think valgus and varus deformities were a common exclusion criteria, as well.

Shivani Reddy — Yes, they were. So you're right malignant of the join, and.

Leila Kahwati	Yeah.
Shivani Reddy	They kind of There was a bit of a range somewhere around 15 to 30 degrees of misalignment.
Sheila Rege	There was something else you had said in one of the slides, I should have written it down. So yeah, if you don't mind. And that was just a surprise to me. So, if you don't mind looking at you had presented it.
Shivani Reddy	Okay.
Sheila Rege	It. It just wasn't on the slide. Thank you.
Shivani Reddy	Okay. It'll take me a few minutes to pull up, but I can take additional questions while I'm doing that.
Sheila Rege	Well, it's during the break. We could do it during the break. Any other questions?
Conor Kleweno	Yeah, I had a I had a question on the risks. Yeah, although our arthroscopy is sort of a more probably newer strategy for the MACI. I know, traditionally, a lot of these were done with an open arthrotomy with the version of the patella. And I was surprised that there wasn't a lot of reporting on knee stiffness as a potential risk. And I don't know if some of the studies reported on their technique of arthroscopic versus open procedures. And if there was any reporting that you saw I didn't see in in what was reported for knee stiffness or range of motion.
Shivani Reddy	So I don't recall knee stiffness or range of motion. We can do a double check of that, but we did abstract, we did pull out open versus arthroscopic and that's something else I can look up for you on the break. So we can see whether the evidence for MACI is mostly based on open versus closed procedures.
Sheila Rege	Dr. Franklin had had his hand raised.
Gary Franklin	Yeah. Hi, thank you. I had a question on MACI versus microfracture. Is there anything on the measure of clinically meaningful improvement and function between those 2 procedures?
Shivani Reddy	Yeah. So for the patient reported outcomes for, they weren't always the same across procedures, but we do have a chart of The MCIDs in the report and the change in patient reported outcomes was clinically significant as well as statistically significant.
Gary Franklin	Thank you.
Sheila Rege	You know, I forgot if there was any more people for public comment at the top of the hour.

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Sheila Rege	Should we ask now, or Josh, Melanie, Val?
Josh Morse	Val, have you seen any additional.
Val Hamann	No, I haven't seen anybody else, but if there are any just last minute individuals who were looking to speak for during the public comment, if you could please raise your hand, and then we can get to you in a little bit. Which I'm not seeing anybody else.
Sheila Rege	Okay, good. Thank you. Sorry about that.
Josh Morse	Thank you. Val.
Conor Kleweno	Dr. Oakes has a question.
Evan Oakes	Thank you, Dr. Reddy. Can you comment a little bit more? I thought I heard a public commenter say something about the MACI procedure in terms of time out of work and stuff, and seemed to describe that as a two-stage process, in that it was actually better in that sense, then microfracture which required more but then I heard you say something slightly different. Any, can you clarify that for me a little bit in terms of time out of work with these 2 procedures comparatively, and how that all works you said something about the, the rehab for MACI? Thanks.
Shivani Reddy	So. Yes, from our literature review, and speaking with our clinical, our clinical consult our internal clinical consultant this does require the, the time to you there is the time to culture the cells but then there's a certain amount of time afterwards where rehab protocols might be changing, but that you know, there's concern about dislodging the graph, so it's a slower ramp up to movement. I mean, one of the things we did look at was the rehab protocols for each group. In these studies and it basically seems same. So I wasn't sure about that. It was, this is really based on you know what our clinical consultant said and it's, it's really like a, a longer 1st and also the literature review. So that, that kind of came up quite a bit there, and it is something that patients are gonna have to consider and then the other thing I think you asked about rehab time or time back to work. Yes, that was something that we specifically looked for in each study, and we really didn't find it. So that's you know, I think that's one of the evidence gaps.
Conor Kleweno	Dr. Reddy, I also just wanted to compliment you on your limitations commentary. I thought that was a very sort of accurate to what the topic, you know without getting into the granularity of the procedures. I think you captured a lot of the challenge of interpreting the data of this of these procedures.
Shivani Reddy	Thank you.
Sheila Rege	Yeah, that was an excellent summary. Both by Dr. Nam and Dr. Reddy. Thank you. If they're normal questions, I would suggest we actually go ahead and start the next phase.

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Tony Yen Hey, Sheila, I think John had his hand up.

Sheila Rege Oh, sorry! John!

John Bramhall Well it. It's a little tangential as often. So I, I repeat the price for the summary and the presentation Dr. Reddy, that's really good. What I want, what I wondered, and this may. it doesn't come from the data that you've looked at so it's a little again conversational. What, what proportion of the people that get, let's say, the microfracture you know, historically, as being the common one, what proportion of those patients do you think want to get a total knee replacement later in life. I, I, I again I understand it's not coming from these trials but when you were reading, did you get a feel for that?

Shivani Reddy You know, it's a really good question. I, you know I don't have an answer for that. I know that was actually one of the outcomes we were looking at as well time to knee replacement. But I don't. I don't think I have a good answer for that, either anecdotally or from the evidence. I don't, I don't know if our clinical consultant is still on, and whether that's something he could speak to.

Michael James Yeah, I think, microfracture, total knee replacement. Microfracture with MACI or OATS is a bit of an apples and oranges, because I think both of the procedures are somewhat temporizing in that MACI and OCA have outcomes that are more like 10 to 15 years of relief and restoration of cartilage, whereas microfracture is typically 2 years where it becomes fibro cartilage, and then it degenerates fairly rapidly after that. So my thought process is for the younger patients, who are, you know, 20 to 40 years old. This gives them a 10 to 15 year bridge before you know their cartilage ultimately starts to degenerate even with these restoration. So I think the ultimate end goal of total knee replacement would be similar for patients who have these large cartilage defects earlier in life, but the main difference would be there symptoms in that 20 year period between when they have the initial injury and when they need to go on to total knee replacement. So one of the main scenarios we see these cartilage defects is a patella dislocation. So traumatic patella dislocations often leads to patella defects and oftentimes lateral femoral chondral defects. And this happens in patients who are 12 years old up to 35 years old, and so if they have quite a big sometimes they'll shear off all of their patella, and if we can't give them an option such as MACI or OCA we're essentially just telling them that they're gonna have knee problems for the next 30 years until they are the earliest possible age for a total knee replacement. So I think comparing microfracture to OCA, I think they probably need a total knee replacement earlier, having only a microfracture. But I think, even if they get an OCA or MACI at the age of 25 probably by the age of 65 they would end up needing a total knee replacement regardless. So we're just essentially trying to delay the need for that. So.

John Bramhall That's very helpful. Thank you. So, so basically, what I get from what you just said is the microfracture approach, it's, it's not gonna give you 20 years of, of relief likely it's something that is a sort of a, a temporizing process, which short term helps symptomatically, but am I right it might be applied to someone who is, let's say 50 and

has a problem and you say, well, we can, we can get you over the hump and get you to a point where you could get an arthroplasty but the membrane based, the matrix it's actually quite a long term solution for these patients. Is that right?

Michael James

Yeah, I would, I would definitely say, that is what I counsel my patients. The reason I say that it's apples and oranges is because micro stimulating the formation of fibro cartilage which lasts for 2 years pretty much just as well as hyaline quite as well, but it rapidly degenerates after 2 years. So once you follow these patients up to 10 years they'll typically regress back to their pre microfracture state. Whereas with OCA, OATS, and MACI you're ultimately you're generating hyaline-like, well hyaline-like in the MACI setting and actual hyaline cartilage with OCA or OATS, and I tell patients that you know, I would expect 85% of them would get 10 years of relief. There are cases of failure prior to that and then some can get 15 to 20 years. So if I have a young patient, you know I've done about 10 OCA in the last year, and if I have a young patient who's, you know, 18 years old. I'll tell them that I'd likely be seeing them again for another procedure at 30 if everything goes well. But that's better than telling them oh your knees gonna hurt, you're gonna have to alter your activities because you're gonna have recurrent swelling. These defects tend to rub and cause a lot of inflammation so I did a lot of my training in Canada as well, and we didn't have these options and it was very difficult telling these patients that there was nothing we could do, especially when they were this young children if they're wanting to have a more active lifestyle so or not, children, but adolescents. So I would say that it's you know it historically microfracture has been the comparator but I don't perform a lot of microfracture just because I think it's just delaying their symptoms a couple of years, and it can burn the options of MACI and OCA by disrupting the subchondral, subchondral bone. So does that answer your question?

John Bramhall

Yeah, sure does. It, it sure does. I guess the that whole issue of, of the different subgroups of patients right in in a way that it's an extra confounder because the clinical decision that you've described and the Dr. Reddy describe those clinical decisions are, gonna take many times precedence over a sort of an aggregate randomized study that looks at 2 different treatments, one of which is not applicable to this subgroup of patients so. Well, I think, I think we have to take that into account.

Michael James

One of the scenarios you mentioned that I didn't comment on was the older patient, trying to delay the need for an arthroplasty. So by the time they're needing an arthroplasty a lot of the time they have you know, tricompartmental degeneration. But I've found that doing a chondroplasty, or you know, I don't really do microfracture older patients, but because the bone is different quality as the age if you if you do, too aggressive at a con of a chondroplasty or microfracture, you could induce something called subchondral collapse and I've seen it in a patient where you're like trying to clean up the cartilage and make it feel better, but because the bone is already degenerative and weakened it can, it can cause a worsening of their symptoms. So I'm, I'm pretty hesitant older patients to do an aggressive chondroplasty or microfractures. So I've kind of because I have these options available to me now I, I rarely perform microfracture, so.

Shivani Reddy	And I just want to say that's also something we found in literature reviews and some of the pathology results is that you have this increased inflammation of the subchondral bone with a microfracture in that. That really reduces your success with one of these other procedures like MACI or OATS.
Sheila Rege	If there's any more questions. That was very helpful, Dr. James. If not, how about we take a 5 min break, and then come back and start the committee discussion and this decision. And in anticipation of that, if the staff would just put up where the agency medical director had the recommendations as a starting point.
Josh Morse	I can do that, Dr. Rege, I do you want this? It's on a couple of slides. So I put it on a word document for our usual conversation.
Sheila Rege	That would be awesome if you could.
Josh Morse	Okay. Thank you.
Sheila Rege	So a 5 min. break. And we'll reconvene when all the committee members are back.
Josh Morse	Do actually do we want to start with the decision aid?
Sheila Rege	No, we, we I think we'll start with the Agency Medical Director and see how we feel about it, and then go to the decision.
Josh Morse	Okay. Thank you.
Sheila Rege	5 min break. Did I time that right with 5 min? How was everybody doing. Okay. So let's do the easy one 1st, the recommendation of not cover was cell-free implants and AMIC. How do you say that? I don't even know. I'd have to actually use the actual words. Any of the committee members have issues with that? And we'll go through the efficacy and stuff but is this, we should probably spell that out.
Josh Morse	Yeah, I'll spell that out.
Sheila Rege	If everybody's okay, we can next take on MACI and other FDA approved 3rd generation strategies, and now we could move to, keeping this in mind, move to what Josh was suggesting where we look at our evidence kind of template. Any discussion on this? Conor, Tony, you guys are helping me help me out here.
Conor Kleweno	No, I think it's appropriate to move on. If there's no concerns about the non-coverage for cell-free.
Evan Oakes	Yeah? Had a.

Sheila Rege And we can. We'll only take them.

Conor Kleweno Dr. Oakes is. Dr. Oakes is raising his hand there.

Sheila Rege Okay, thank you for that. Dr. Oakes.

Evan Oakes Yeah, thank you. I was just looking for and wondering about the osteoarthritis comment that the public person, public commenter about defining that and kind of looking for that, and wondered if others were wondering about that too, and how we can make sure that's incorporated into our decision.

Conor Kleweno Here it has outer bridge 3 or 4 on both of those things that are displayed.

Sheila Rege I.

Evan Oakes Thanks. I'm outer bridge. Okay, thank you. Yeah, thanks for pointing that out. Conor.

Conor Kleweno Yeah, I mean, obviously, we can discuss whether that's the one we all want to use. But.

Shivani Reddy I can. Sorry.

Conor Kleweno That that is one of the classifications.

Sheila Rege And doesn't excluding degenerative arthritis cover that too?

Evan Oakes Thanks.

Conor Kleweno No, I think the comment was the severity of degenerative arthritis. And so, when you know, instead of just saying arthritis, you say, what does that mean? And there are some.

Sheila Rege Okay.

Conor Kleweno Classifications, the intern observer reliability of which are variable. The 2 most common are the KL and the outer bridge, and I think both of those the public commenter had cited in other payers coverage decisions.

Clint Daniels Conor, and, and maybe Dr. James, would it make sense to cut the word degenerative then is it? Is it redundant with outer bridge classification 3 and 4 already listed?

Conor Kleweno Where do you see the.

Clint Daniels Are we looking at the MACI and OATS definitions? So the, the MACI, it said the 1st bullet says average 3 or 4 and the last bullet says malignancy, degenerative, and.

Conor Kleweno — Oh, sorry. Yeah. So there, that's my error there. We do need a classification for the overall joint.

Evan Oakes — Yeah, thank you. That's what I, I just realized. That's what I was referring to, not the, the indications for when it you know the cartilage, but to the osteoarthritis definition.

Conor Kleweno — Yeah. Yeah. And I think that we've, we've definitely gone in circles with determination and wording where we kinda have to remind ourselves to go back to what the evidence has supported in this, and maybe Dr. Reddy can help us with, with some of what we can base this on.

Shivani Reddy — So there were 3, there were 3 severity measures that were used. So it was Outer Bridge, Kellgren, and then the ICRS. You can correct me if I don't have this right but outer bridge is based on arthroscopy tolerance, Kellgren based on. X-ray, and then ICRS is MRI or arthroscopy. And all of these studies included the inclusion criteria was either 3 or 4 of any of all of those measures. And what I, what I, what I found was that 3 was generally like a, a full thickness defect. They do, they do change a little bit so there's like for Kellgren there's some joint space narrowing which can indicate some mild OA, but that's by X-ray.

Michael James — Just to clarify about the indication for the procedure or the contraindication, because the indication I think they'd be referencing the outer bridge classification for the defect itself.

Shivani Reddy — And then.

Michael James — But I think for indications they're talking about the status potentially the entire compartment or the, the joint itself. So I'm just wondering in the studies, the previous public commenter was saying that they were recommending contraindications for Kellgren-Lawrence grade 1 and 2 of the of the entire joint. I'm sorry I'm just, I'm wondering if we're talking about the same thing here.

Conor Kleweno — Dr. Nam has a comment.

Shivani Reddy — E, at.

Ji Young Nam — So when we are developing this recommended conditions. In terms of the excluding degenerative arthritis, we also thought that it's a little bit vague, however, based on our evidence, some studies excluded osteoarthritis evident on X-ray, and, like the Summit trial says that Callahan, the KA criteria more than 3 or 4 are excluded, and the other study, one of the RCTs comparing microfracture to MACI, which is Neil Cart study, was saying, ICRS 3 to 4 kissing lesions are excluded. So all the studies have so much different criteria for osteoarthritic reason for the knee. So that's the reason why it was a little bit vague in terms of degenerative arthritis in the joints. Thank you.

Shivani Reddy — And as to what Dr. James was saying, some of them are specific about which compartment has these changes and others are not.

Sheila Rege — I think we that is something we're gonna as we, as we, you know look at the safety, efficacy, we're gonna have to look at how to define osteoarthritis as an exclusion. So thank you, Dr. Oakes for pointing that out. So just, just to refresh our memories this is kind of where the agency medical director had come in after spending a lot of time looking at all this data on MACI. And is everybody okay the committee keeping. MACI is, you know, one category, and then looking at OATS and OCA as another category, and lumping those together. Any discussion on the classification? Doesn't sound like it. Then. Go ahead if somebody raised the hand. Sorry.

Clint Daniels — I, I just said seems reasonable.

Sheila Rege — In that case, then, Josh, we can go to our planning aid.

Val Hamann — I did just want to before we get started so I can have all of the correct voting for you guys here. Would you like the cell-free and AMIC added together in there, so you can vote on safety cost effectiveness for each of these procedures.

Sheila Rege — Yeah, let's, let's keep. Since the committee is decided that they're okay with the way.

Val Hamann — Okay.

Sheila Rege — Dr. Nam, thank you very much had classified it. Let's do our grouping in that same manner.

Val Hamann — Okay, can you? I will just need just a couple of minutes. So I don't know, Josh, if you wanted to kind of pull up.

Sheila Rege — But, but what we could do while you're doing that I'm not looking at voting yet, Josh, if you could just do our aid, so we can, especially with your committee members. Go over. This is kind of like us in in person we used to do a straw poll. Is it safe? Is it effective? And does it provide value, improve health outcome. In terms of this let's go with the easy ones which is which is where we said we're not going to be covering it, we'll go through that, and we'll go through. Is it safe, effective. And does it improve value? And then we'll get an explanation of how we're gonna vote on that. Any before we start, is there anything that the committee feels is not as oh, wait! Before we go there, I think, Tony it was you and Conor who had come up with the how we, how we classify that I'm gonna have you during a strategic year or, or Josh kind of explain how we, how we vote on that.

Tony Yen — I'm sorry. I don't quite remember what I said during the retreat.

Sheila Rege — It was more well, it'll come up we'll, we'll go through it when we go through the voting.

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Josh Morse Yeah, and.

Sheila Rege So just for the new committee members, we have a choice of not covering, covering unconditionally or covering with conditions. And so that's, that's what we're going to be voting on in the straw poll on each of those I call it the buckets.

Josh Morse Right, so. So working backwards, this will be your, you'll get to this vote. This will at a final vote you'll make a decision about these coverage outcomes which are outlined in the States the creation of the program. In the decision aid we have prefilled for discussion the outcomes that were describing the report and in the slide presentation for safety, efficacy, cost and, and special populations. And then your straw poll voting to get a sense of the groups interpretation of the evidence. You then have what Val is preparing is the, the voting through this process on how confident are you in the evidence for safety, efficacy, cost effectiveness, etc. And in the past few meetings we've moved this document into a PowerPoint presentation that integrates these things. So we're gonna transition to that when you're ready for that.

Sheila Rege And we'll, we'll explain it, Dr. Oakes, while we're going through the voting. So your full understanding of where we're going. So this is just a straw poll. It lets us know if most of our committee members are pretty comfortable. That and, and we will you know that we're either not gonna cover or cover unconditionally, and if we're covering with conditions. Then we're thinking about what conditions and exactly what you brought up that the procedures not being done for treatment of degenerative arthritis, osteoarthritis. So we'll, we'll then refine that later. So let's.

Tony Yen Hey, Sheila.

Sheila Rege Do, do you want to go through this straw poll first or do you want to go through the safety, efficacy, and what's the last criteria? Tony, help me out there.

Tony Yen Yeah, Sheila, I just wanted I apologize for interrupting. I just don't see the session. It says, like what I'm trying to log into that polling sort of thing the software session does not exist.

Val Hamann Yes. Yes, I so we ran into issues during that we figured out after the 1st meeting, and so I have to close that.

Tony Yen Okay.

Val Hamann Or other people have to sign. You have to sign in again. And so then it looks like another seat is added. So that's why I have to end the session and so I did just start that and I believe I have all of the questions now prepared how you've discussed today. So we can definitely jump into that PowerPoint which will then take us through voting on safety, efficacy, cost effectiveness, and then that straw poll vote on coverage. So if that sounds good, I can definitely start that if. Or how would you like it?

Sheila Rege That would be helpful. Because we've, we've, yeah, we've gone that to where it guides us through this process.

Val Hamann Perfect, and I will share that, Josh, if that sounds okay, and then you can tell me next slide and we can go that way so everybody can see.

Josh Morse Sounds good.

Val Hamann Okay, and you're able to see that.

Josh Morse Yes.

Sheila Rege Yes.

Val Hamann So Josh feel free to take over.

Josh Morse So here's the overview of the process that we're going through today. You've seen the presentation from the State Agency Medical Directors. We've had this scheduled public comment periods. You've had the evidence report presentation. And there's been questions and answers which can continue throughout this meeting. And then we're in the discussion and development of, of a draft determination phase moving towards some final votes. Yeah. So This is, we've got the overview built into here. So the goal here is achieve better health outcomes by paying for what works and asking questions about safety, efficacy, and improvement in health outcomes. Can move ahead. So coverage determine principles that there'd be evidence based, and we hope results in a net health benefit from this process. We want to know if there's evidence available so we've seen what evidence is available. We will assess here in the next part, how confident we are in the evidence and how applicable that is to the question for policy at hand here, how generalizable it is to what we're what we're asking, and then into the next slide please. So the design of this program is meant to give the greatest weight to the best available evidence. The evidence that's most valid and reliable. Considerations as you go through this should include the sources of the evidence, the steady characteristics that you've heard about from Dr. Reddy, how consistent the information is across the available studies, how current and relevant they are and any issues around bias built into the studies potentially, and then any special impacts based on sex, age, ethnicity, race, or disability. These are questions that are built into the program by law. Next slide, please.

And again from our evidence tool, is there sufficient evidence, yes or no? To determine safety, effectiveness, and cost effectiveness. If there is evidence, is it indicated for all conditions? And if not, then we're likely moving to coverage with conditions. And here you can see kind of an overview of safety, efficacy, and cost, and what goes into assessing those and, as I said preloaded in the pre-published decision aid the outcomes that were addressed in RTIs presentation from the evidence findings. Okay. So The evidence considers alternatives and the comparisons to those alternatives. And we're looking for evidence that confirms improvements in health outcomes versus not

	covering these technologies and management with other potential technologies or alternatives. Next slide. Okay. So here we go the part that I'm most familiar with. For safety like I showed on the other screen we have included from the evidence, safety concerns related to infections, joint fusion, knee joint crepitation, and pain. And at this point in the you know, we've traditionally stopped and asked are there other outcomes you're concerned with that you want to discuss.
Sheila Rege	Conor, you had brought up any stiffness, but I there wasn't anything in the evidence. I just look back. Are you comfortable with this?
Conor Kleweno	Yeah, yeah, I think what we've done in the past is, put it there. But just say that there's no insufficient evidence.
Sheila Rege	So would you like to put any stiffness there, and sufficient evidence.
Conor Kleweno	Yes.
Sheila Rege	Josh, can you make that happen?
Josh Morse	I'm not editing those slides, but I'm I am taking notes in the other document, and I looked like Val took it down so that it can be editable.
Sheila Rege	Okay. Anybody else?
Josh Morse	There we go. Thank you. Val.
Sheila Rege	I remember. And, and I don't, I didn't see that as a safety thing, but I remember there was a lot of discussion about aligned knee and, and I don't know how to say that an orthopedic terms, that there was not a misalignment. I don't know why there was misalignment whether there was more complications. Is that a.
Conor Kleweno	I, I think it's if you, if the anatomical axis of, of the joint and mechanical accesses off that that would be a contraindication. So I think those people were excluded. Is that what you're referring to.
Sheila Rege	That is what I was referring to. So I, I don't think that's.
Conor Kleweno	Yeah. So I think this think that was an exclusion criteria for the studies.
Sheila Rege	Okay. So we'll just put that as exclusion criteria.
Conor Kleweno	Yeah, it's, it's not part of the safety of the procedure.
Sheila Rege	If we're good with this we can move on.
Evan Oakes	There was one comment. Thank you, Dr. James, about the and I don't know if it applies here or not but the degeneration of the bone with the microfracture at a certain age.

That's not what these procedures per se. I'm just, I just wanted to make sure I brought that up there was something, if you did it, in people that were older, and the bone health wasn't very good. But that may or may not apply to this grid, but I thought I'd mention it in case that applied here as a safety concern for any of these.

Michael James Yeah, I think.

Sheila Rege Dr. Oakes, we should make notes of those because we're gonna have to put that in the exclusion criteria. But Dr. James.

Michael James Yeah. The subchondral collapse one issue with the OCA one of the reason it's it's nice to have both MACI and OCA available is that MACI doesn't compromise the subchondral bone. So if you do, MACI, first, you can do OCA down the road but one. I'm not sure how you would express this as a complication. But if you do an OCA first, you have to dig out a certain amount of bone, typically, it's about 7 And so that makes any subsequent difficult and if the OCA goes on to failure, then you have a larger defect than you started with typically, but that's not necessarily a complication that would just more be related to failure of the osteochondral allograft after failure of integration. So there's not typically like a graph versus host response in this, but oftentimes, not oftentimes, but sometimes the graph won't take maybe 10% of the time so that is a complication, and it just results in failure of the graph or the generation of the cartilage. So.

Evan Oakes Thanks for the explanation. I wasn't sure if this cap, this grid was for complications, or for or if that's the same as safety and I was just kind of wanted to bring the couples up for consideration. But, thank you. I, it sounds like it's hard for us to figure out a way to put it into safety, so I'm happy to move on.

Sheila Rege Thank you. Thank you for bringing that up, and any other safety issues. And, and help me understand this this is for all the procedures. We've lumped everything together? Or are we specifically talking about one or one of the buckets.

Val Hamann No, I. They were previously altogether, but I have broken them out now by procedure, so you will vote on. Let's see. You'll vote 3 separate times on safety, efficacy, and cost effectiveness.

Sheila Rege So is this safety that we are discussing for?

Josh Morse This is overall. This is not for all 3 categories?

Josh Morse Broken out by procedure.

Sheila Rege And is everybody okay with that? I think I am okay moving on.

Josh Morse But when, yeah, like, Val said, when you get to vote, it's definitely it's broken out the way you've chunked it per Dr. Nam's recommendations.

Sheila Rege	Good. We'll move to efficacy. Oh, do you wanna vote?
Val Hamann	Did, did you want to to vote, or would you like to go through all the grids first.
Sheila Rege	No, we can vote if you have it out here.
Val Hamann	Sure. Yeah. So if right now, I have 3 connections. So we'll just wait on the 4 others again. If you can go back into ttpolls and utilize that same information you did earlier.
Josh Morse	Oh, so are we not voting by the procedure grouping for safety.
Sheila Rege	We are. Right?
Val Hamann	Yes, so I can give a preview of like, we'll do MACI. Then we'll do yeah.
Josh Morse	Okay. I see. Thank you. Okay. I caught up.
Val Hamann	And we're just waiting on one more connection.
Josh Morse	Thanks.
Val Hamann	Okay. And so we have 7. So we'll go into the voting now.
Sheila Rege	Wait before we go to the voting. Can you go back? Sorry. This is where Tony, was it you, Dr. Yen, that at a strategic retreat came up with this? If we could have an explanation for our new members on what low medium and high risk means in each of those categories, if you go back. Oh. What happened?
Conor Kleweno	Tony can comment as well, but I think I think what this was, we in the past had struggled with all the committee members being on the same page for safety and what that means, and what you are comparing it to, and what the data showed. So we, we tried to reclassify it, so that there would be more consistency, and, and everybody feeling comfortable that they were on the same page. Not perfect but that was our newest iteration of categorizing these. So you know, for example, and what we had, you know, I, I brought up knee stiffness, there's, there's no, there's no studies on that, or you know there's or, excuse me, there'd be no studies that report anything about safety. For these procedures, we could say it's low risk, in your opinion moderate risk or high risk and low risk and high risk are safe and unsafe respectively. But then we had along that line of reasoning how confident you were in your evaluation of that based on the evidence.
Tony Yen	Thank you for explaining that, Conor. You did better than I could never do.
Conor Kleweno	Try, try my best.

Sheila Rege	Dr. Oakes when they in the strategic retreat we just discuss ways of making things more efficient, and each committee member kind of thinks about how to make things improve things, and this process is so much better than it was couple of years ago. Let's move on to voting, Dr. Oakes any questions?
Evan Oakes	No, thank you.
Val Hamann	And then, when this poll should launch automatically. And we have 7. Then we'll move on. We'll move on.
Conor Kleweno	Now for this, I thought we were. Okay, we're still doing all the categories for this one as well.
Sheila Rege	Yeah, even though.
Conor Kleweno	Okay.
Sheila Rege	We didn't find evidence that would be in the efficacy criteria, not the safety. Unless we say we have low confidence, and we don't know. You okay with that?
Conor Kleweno	Yep.
Val Hamann	And waiting on. That concluded the safety portion.
Sheila Rege	And now in this one. I wonder if we should I think we should do the easiest if it's not too difficult. Val, for doing this? Let's just do the, the autologous matrix induce chondral genesis the AMIC, and the one that most of us felt not to cover. Let's just do that first. We'll do the efficacy and cost of that, and then we'll come to the efficacy and cost of MACI, and then OATS and OCA, I think that's gonna help us and you can take some time, too.
Val Hamann	Okay. I, I have them ready to go. So.
Sheila Rege	Okay, perfect.
Val Hamann	Okay, so we'll do the efficacy first.
Sheila Rege	Which one do you want to do first?
Val Hamann	So this one is efficacy for the AM.
Sheila Rege	Perfect.
Val Hamann	And then I can have us jump out to the cost effectiveness for this.

Sheila Rege	And so, Dr. Oakes, is this pretty clear? If you say equivocal, you mean you don't know but oh, the data didn't suggest it. And if you, if we vote more then it means that there's sufficient evidence that these modalities have a meaningful impact on patients and patient care. That pretty clear?
Val Hamann	Let's run that again. We.
Josh Morse	I think, I think equivocal in this case means equal. So we may need to change our terminology here. But I just think, if the evidence showed that they're, they're equally effective, that that would be what that's meaning here.
Conor Kleweno	Yeah, exactly. So let's say, there was a number of studies that showed their equal and then that's what your opinion was. And then, based on the quality of evidence, you would say low, medium, or high versus you, just there wasn't that much data, or there wasn't data, you would say, no relevant studies is that. An accurate way to describe that.
Sheila Rege	Correct. And if if you say equivocal that means you feel it's equally impactful or works as other therapies which then later may mean that you think it should be covered, which is fine, but that's just explaining. So let's take that vote with that explanation to see if. That's something that the committee members meant.
Val Hamann	That polls open again.
Sheila Rege	Okay.
Val Hamann	And then we will jump down to.
Evan Oakes	I would, I would point out one thing we might want to say equal, then, not equivocal by definition, is kind of an ambiguous term it means ambiguous. So just to. If that's what.
Sheila Rege	Right. I, I like that, and I think at the strategic retreat, I think or is that something we can change.
Conor Kleweno	I think we I think we defer that to our next retreat. If that's all right.
Sheila Rege	Next meeting. Yeah.
Val Hamann	Okay, so we'll jump over to cost effectiveness for these procedures. And that poll is open.
Sheila Rege	Conor, since you're on a roll, would you like to explain what this would mean.

Conor Kleweno	The think this is the same idea, and the, the cost effective is category is where mostly, where the no relevant studies came from, because in a lot of topics there was not specific cost evaluations done so.
Sheila Rege	But if I decided to check more, what, what are your thoughts on what this is saying? If I checked H, I, or J.
Conor Kleweno	Yeah.
Sheila Rege	Does that mean that this procedure is cost effective? Or is this procedure.
Conor Kleweno	Yes, it would be. It would be more.
Sheila Rege	Or are the evidence based alternatives cost.
Conor Kleweno	It would be more cost effective if that was your opinion.
Sheila Rege	Okay. Does that help Dr. Oakes?
Val Hamann	We're waiting on one more response. Sheila, would you like to go back up for the others or move on to a straw.
Sheila Rege	No, I'd like to now just have a summary of the cell-free implants and autologous matrix in induced chondral genesis.
Val Hamann	Okay, so this is looking at the safety for those and then we have the efficacy. And then we have our cost effectiveness.
Sheila Rege	Given this, I like a discussion from the committee members about whether, remember, if we pull up the agency medical director where there was a recommendation of no coverage. If we took a straw poll today right now, would that be something we would be comfortable with?
Clint Daniels	This is Clint. I, I wanna comment, so I voted cause there was one study that seemed to be supportive of the technology. However, it was high risk of bias. So I that's why I downgrade it to equivocal. I would be comfortable with not covering, though I think this is something that it's too new, there's not enough evidence, and probably makes sense to re review in the future when the studies that I think one of the public commenter talked about a study that's going to come out but it's we don't have the data now. So that that's where I'm at on that.
John Bramhall	Yeah, I agree. Well, so I agree Clint. As I recall this.
Sheila Rege	Anybody else? Go ahead.

John Bramhall: There's a study that's not being published yet, that's 4 year data. And then there was an assertion from one of the representatives that there was 5 year data available and being processed so. But we don't have that. And I agree with you, Clint. I think it that if you were gonna prognosticate this may be something we'll be looking at in 2, 3, 4 years down the line, because there are sort of structural advantages to the idea of, of using cell-free extract that are attractive. And the study, I think we only know one study that was graded as, as moderate. It's not a bad study, but it's a single study. So. So I agree with you, Clint.

Sheila Rege: Sorry I'm speaking with it, muted just based on past experience, because it's hard to keep the buckets straight. Is there a way we can do a straw poll vote on cover unconditionally, cover with conditions and not covered just for those 2. Is that something we can do a straw now? Thank you very much.

Val Hamann: Yes. Yes. And that poll is open. So we have 7 for not covered.

Sheila Rege: Okay. And that's a straw poll.

Val Hamann: Yes.

Sheila Rege: We can always change our mind and then now, if we'll move on to the, the next was MACI, right?

Val Hamann: Yes, and you have currently voted for safety on MACI. So are we, you're feeling comfortable to move into efficacy.

Sheila Rege: Correct. Is everybody okay, with that. Okay, let's move on, then to efficacy.

Val Hamann: Okay, that poll is open. And then would you like to move on to cost effectiveness for this?

Sheila Rege: Yes, please.

Val Hamann: Okay. That poll is open. And would you like to move on to a straw poll?

Sheila Rege: I'd like to move to a summary if we can first.

Val Hamann: Okay. Yeah. Okay. So this is safety. This is efficacy. And cost effectiveness.

Sheila Rege: Any, any discussion before we move on to a straw poll. So when we'll just straw poll of cover unconditionally, cover with conditions, or not covered.

Val Hamann: So we have 7 for covered with conditions.

Sheila Rege	Okay, any discussion before we move on to the next category. Which was the osteochondral restoration techniques. Okay, we will move on to that. We've already done safety. So now we need to do great. Thank you.
Val Hamann	That's open. We'll go down to cost effectiveness. That's open. So we'll do a summary now. So here's safety. Efficacy. And cost effectiveness.
Sheila Rege	Any discussion? Or can we move on to straw poll of on not cover, cover with conditions, cover unconditionally? Okay, we're moving on.
Val Hamann	7 for cover with conditions.
Sheila Rege	Okay. And now we'll have to go back and look again at the Agency Medical Director recommendations. And figure out conditions. So we'll close the poll.
Tony Yen	Hey, Sheila, can I propose applying those same conditions for MACI as well as for OATS and never say this correctly, and OCA.
Sheila Rege	We can talk about it right? I remember there was a difference that was presented in terms of the yeah the size.
Tony Yen	Okay, I apologize. Maybe we can lump the rest of that stuff together. Seems like everything else is actually really similar. And to be frank with you, I don't know enough about either of these procedures to limit them by size.
Sheila Rege	Any discussion from Dr. James or orthopedic colleagues on the Committee?
Michael James	I think osteochondral autographs or OATS, that's typically limited to 2 to 4 cm squared just based on the fact the size of the plugs is limited and the donor site because you're looking for donor sites that are non-articular, and oftentimes there's not a big enough plug greater than 4 cm squared. So we do a snowman technique sometimes a mosaicplasty where you use 2 different plugs, but that somewhat limited. I think, in lesions less than 2 cm squared you could still do a notes procedure, but it, it would depend, I would say, on the indication and the location. In the patella, as Dr. Clinton mentioned in the public forum, OATS is very difficult because of the morphology of the patella, so I tend to shy away from using OATS on the patella, so I use MACI or OCA for all sizes, OCA obviously not for lesions smaller than 2 cm squared, and I think the other main distinguishing factor between the 2 would be subchondral bone. There is a newer technique for MACI called a sandwich technique where you bone graph but I don't think there's as much evidence for the sandwich technique as for using OCA when there's subchondral involvement.
Sheila Rege	So what I'm hearing is maybe we should keep it separate, Tony, if that's okay, just to get the nuances that hopefully will be guided through. And most of, I think I agree with you most of it will be the same.

Tony Yen	Sounds reasonable.
John Bramhall	And.
Sheila Rege	I, I do have another question, and it wasn't in the data. But I'm pulling up like Aetna's coverage, and as I'm kind of questioning why they say it has to be age 15 and older with documented growth plate closure. Is that something we have. And is that important?
Clint Daniels	Looks like we have the growth plate closure. It's the second sub bullet. But not an age.
Sheila Rege	Is that enough? Is the question, I don't remember it in studies of any age mentioned.
Conor Kleweno	I, I'd be okay with the growth plate closures cause there is sort of a trend of differing ages at which people are having their growth plates closed the bell, the bell curve is changing to some degree, so.
Sheila Rege	Okay, and I know we had an assumption in the studies that there was physical therapy. I, I like to keep it up to the doctor. But is that something the committee wants to consider.
Conor Kleweno	I, I would recommend against that just because we're dealing with something structural. And so.
Sheila Rege	Okay.
Conor Kleweno	Therapy something structural that you're trying to change as opposed to like a total knee replacement where you're just getting rid of all the structure. And so in that case there can help either whether or not you're gonna get your knee replacement. In this case you probably know some conditions you're just gonna aggravate it. I think so.
Sheila Rege	Okay. And then how about what you had said about the, the stable and alignment. Is that something assumed.
Conor Kleweno	We can. I mean. Michael, you could comment. I would, I would find it unusual if somebody would indicate somebody with a malignment, you know, tibia vara or something, you know it would it would definitely be out of.
Sheila Rege	Okay.
Conor Kleweno	Standard of care to do that. So.
Michael James	Yeah, I would, I would agree. I think the one danger is that if it's becoming, you know, more used by generalists, they may not treat all the associated pathology. But most of the indications and contraindications for OATS or MACI include a contradiction be uncorrected, malignant. So that's typically in the coronal plane. So like greater than 10

degrees varis valgus, I would shy away from giving an actual degree. Just because it, it's can be somewhat case specific, and then the other a contraindication, I would say, is uncorrected ligamentous deficiencies. So if you have a deficient ACL or deficient collateral ligaments and you don't correct that and you just replace the cartilage, you're gonna overload that cartilage again. And then one that's often in the literature for ephemeral sided lesions is a meniscal deficiency greater than 50 % that's uncorrected. So oftentimes these cartilage are in the setting of a full knee reconstruction so that'll include an osteotomy potential ligamentous reconstruction and then the cartilage procedure and sometimes a meniscal allograph. So. I would include the uncorrected malignant as a contraindication.

Sheila Rege For I for the OATS and OCA for?

Michael James Yeah, for both the MACI and the OATS. And it also pertains to the patella dislocation because if you're just replacing the cartilage or restoring the cartilage, and you're not correcting the propensity of the patella to continue to dislocate with a ligament, reconstruction, or a tibia tubercle osteotomy to correct their alignment, then they're likely to just wear out that cartilage reconstruction without malignant, so I think ligamentous laxity would pertain to the patella and collaterals and cruciate ligaments so uncorrected ligamentous deficiency and uncorrected malignant.

Conor Kleweno Do, do you see some people do that because that you know we do have to balance here what is indicated and contraindicated versus what is just sort of malpractice or not, you know, like at some point you know, like, don't do this if the person has a fused joint, you know what I mean. So there's.

Michael James For sure.

Conor Kleweno I agree with everything you're saying. I don't have the experience in. Are you seeing people doing these that are like I can't believe they didn't you know address the tibia Vara, or they this, the patient has complete cruciate ligament deficiency, and they still did this. So if, if there is some of that. Then I, I would agree we should put some of these stipulations.

Michael James I think some of it's nuanced like some people say. Oh, they're in a little bit too much, valugus, to do an OCA without a distal femoral osteotomy. I rarely see someone who's got a horrifically maligned knee and they just try a cartilage procedure in isolation, but I would say it probably falls into the realm of more malpractice. And this would be, you know, it would be a little bit getting into the weeds in terms of what constitutes malignant and what constitutes, I mean ligamentous deficiency, you know, typically, that's pretty straightforward. But I think if we can just keep it in the scope of you know what's standard of care, I think we can probably avoid putting these just to overcome or avoid over complicating.

Sheila Rege — Is this mostly done by orthopedic? I'm hearing. Was there one common made that some of this is doesn't require. I mean, do other people other than orthopedic surgeons do this? The OCA or OATS procedure.

Michael James — Podiatrists may do it for the talus, but I don't think anybody beyond an orthopedic surgeon would do it in the knee. I hope not so.

Sheila Rege — Okay. So as long as it's, it's something I, I don't know enough about this, so I rely, Conor, you tell us.

Conor Kleweno — Yeah, this is tough cause I think Michael brings up some really good points. I. I just don't know where to stop with some of it. And you know it, it's almost like a global question like you know. Let's say we're talking about some other topic, and you know, where do you draw the line of telling somebody like don't do something that's ridiculous.

Sheila Rege — And I only used.

Conor Kleweno — And it's, it's, it's tough. It's tough, because there's you know, are we adjudicating people to actually do standard of care or we trying to just try to exclude some certain things based on data. That I think that's a tough line. Looks like Dr. Oakes has his hand up. I'm sorry.

Evan Oakes — No, that's perfect, Conor, thank you. I my comment actually was very related what you just said. And my, I wanted to just touch on the bullet about. I'd rather us remove the body mass index to your point, and let that be between the physician and the patient. I think we're learning more and more about the limitations of that metric and I just wanna make sure we're not excluding. It's pretty definitive, if we put that in there as a exclusion criteria. So I wanted to have a conversation about that, and maybe suggest we take that one out. Unless there's really strong evidence that it's very, you know, linked to that body mass index being a failure point for these procedures.

Conor Kleweno — Is, is there maybe that's a good question for Dr. Reddy. Is there any studies, or even the Health Care Authority on that we can just sort of mimic some of the exclusion criteria from the studies and say, hey, we're just basing this on the, the data that we're. Utilizing.

Shivani Reddy — Well, there was no studies that did a subgroup analysis by BMI category, and you can say there were only 3. There were a handful of studies that required the BMI to be less than 30 or 35, or on the flip side the exclusion criteria also arranged from BMI greater than 30 or 35. You know, looking at the mean BMI across the studies, that was in the overweight range 25 to 27. But you know we don't really no one has really done a subgroup analysis, for obese versus not obese.

Sheila Rege — So, Dr. Oakes, we, we generally, and I agree with you BMI is such it has its fault. But when we make these recommendations, we're held to either keeping it with what the

study, enrollment criteria were. And then later you'll see we also look at other coverage from other insurances. So we're not out of line and most of the others do have BMI in there.

Conor Kleweno — And a question for Michael on the malignant. Would you ever do a concomitant like distal femoral osteotomy, or tibial osteotomy and the MACI, and the same procedures where this not coverage would not make sense? Or would you always stage that?

Michael James — I think it depends on the comfort of the surgeon. So, some people will do it all in one procedure. If it's just an osteotomy and a cartilage restoration, most people try that at the same time, because it's just you go through your arthrotomy. And the MACI procedure itself is not overly you know it's not time consuming but if you're doing a minuscule transplant and ACL and an osteotomy and a cartilage restoration procedure, some people do it all in one, but that'd be an 8 hour procedure, but a lot of people would stage it. I would tend to stage it. You know do the osteotomy first and then, you know, come back and do the other procedures, because osteotomy is a pretty intensive recovery and whatnot.

Sheila Rege — Dr. Reddy did any of the studies have anything mentioned about this, the aligned knee, or the aligned.

Josh Morse — I think you're muted.

Conor Kleweno — Think I think you're muted there, Dr. Reddy.

Shivani Reddy — Okay. Can you hear me now?

Sheila Rege — Yeah.

Shivani Reddy — Okay, there were some that did, and I focused on the RCTs. But in terms of sometimes a lot of times, they did not give a specific degree, and when they did, it ranged from 5 to 20.

Sheila Rege — But there, there was mention of it in the study that, that was a criteria. And so what do we keep it very generic. Do you, I mean just stable and aligned joint or is that too much?

Conor Kleweno — I think stable and aligned is too vague to mean anything and, and sort of day to day, practice.

Sheila Rege — So you you like. I'm just worried that not covered with you're okay with the way it is now.

Conor Kleweno — Well, my only question was that that question to Michael. You know, if you say it's not covered with uncorrected malignant and then you say, well, I'm gonna do that

procedure at the time. Does that create sort of a circular argument with the with the provider and the and the payer here.

Michael James — I think as long as they, because I think it's pretty well understood that if you're gonna be doing me to correct it, I don't think people would do the cartilage and then do the osteotomy later, I think, doing it at the same time as long as you say you know I'm planning to correct the mal alignment at the same time as the cartilage procedure. I think that would be reasonable to cover that. Most of the studies as the contraindications they just, you know, say that if you're not gonna address the alignment because the, the, what the things I have seen is that you know, if you do OCA in an you know a medial femoral condyle but you're still embarrassed then it'll just go on to fail, and I think if there are some providers who are not as well trained in in knee reconstruction it's easy to put in an OCA, it's just easy to put in a plug, but it's harder to do the osteotomy, so the, the concern would be if they just do an OCA thinking that it's dealing with the problem when really it's overload plus the cartilage. So. And I don't think that helps with the potential over complication of things. But it's just a really, it's tricky because I think there would be outliers who would try this procedure in isolation, but uncorrected malignant, becomes very subjective and you can't get an agreement on a, a degree where it requires definitely higher than us the osteotomy. So.

Sheila Rege — Conor, could you? I mean we could either remove it all, or we could say uncorrected, malignant, with a parentheses, saying covered if a corrective procedure is done in combination with or prior to.

Conor Kleweno — Yeah, I think incorrect in malignant is, is reasonable because it at least draws people's attention to that and, and because it, it is standard of care. For myself and Michael it would be ridiculous for somebody to, to do it, but we do want to avoid somebody doing a MACI or without correcting that and so, perhaps a slight amount of check range, I think, putting on there as a you know, sort of uncorrected malignant, unless done concomitantly the same procedure, or something like that.

Sheila Rege — Unless a corrective procedure is done.

Conor Kleweno — I would. Concomitantly.

Sheila Rege — Yeah. And it'll make the English better unless a correct procedure is done. You okay with that? Anybody else from the committee?

Conor Kleweno — Dr. Oakes got his hand up.

Evan Oakes — New topic. But so finish this one first, if it's, it's fine.

Conor Kleweno — Okay. And

Sheila Rege — Anybody else have a problem with those not coverage?

Conor Kleweno	I would, I would say the same question to Michael on the ligamentous deficiency.
Michael James	I think the same word. Yeah.
Conor Kleweno	You know. I think. Yeah, maybe unless stabilization.
Michael James	Yeah.
Conor Kleweno	Procedure done concomitantly
Michael James	Yeah, I recently had an ACL, an ACL you get, you can get really bad cartilage defects. And so he blew his ACL and he had this big cartilage defect so I did an OCA an off the shelf, OCA and ACL at the same time. So if you just say, on either uncorrected or unaddressed ligament, ligamentous deficiency. And just saying, unless a corrective procedure is done concomitantly so.
Sheila Rege	Prior to all concomitantly, I think would be better.
Michael James	Yeah.
Josh Morse	You're gonna have to help me with that.
Sheila Rege	Go ahead and just do it the way, unless, uncorrected. Unless a corrective procedure is done concomitantly
Michael James	Yeah, just the same.
Sheila Rege	Concomitantly.
Michael James	Same as the malignant one. Yeah.
Sheila Rege	Yeah, is done. So prior to all concomitantly so just add.
Michael James	Yeah.
Josh Morse	I tell me again.
Sheila Rege	Josh, you can just add, after done. Prior to, or. Those 3 words prior to, or. And the same for the top. Sorry about that.
Josh Morse	Okay. Gotcha. No worries.
Sheila Rege	Any more discussion on this?
John Bramhall Evan Oakes	I'm just wondering. Oh, I'm sorry, Dr. Oakes, got your hand up. When you said this, Dr. Did you mean that particular topic?

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Sheila Rege	Does this just these 2 sentences.
Evan Oakes	Or. Okay, yeah, no, not for me.
Sheila Rege	Dr. Bramhall.
John Bramhall	Yeah. A question for Dr. James, or Dr. Kleweno, the, the Mackey, as I understand it, the Mackey is not an appropriate therapy for patients who have actually a, a bony defect, a subchondral defect. That's, that's my understanding.
Sheila Rege	Oh, I would. No, no, you can't go, Dr. Bramhall. Stop. Dr. Oakes is ahead of you.
John Bramhall	Yeah.
Sheila Rege	You're not just talking about this not coverage. These 2 sentences correct.
John Bramhall	I'm talking about the language of the non-coverage.
Evan Oakes	In general.
Sheila Rege	Okay, we're gonna go to Dr. Oakes just because he.
Evan Oakes	Oh, sorry!
Sheila Rege	He, he was 1st sorry. And then Bramhall. Go ahead.
Evan Oakes	I had to understand one. I'm, I'm sorry I'm not gonna let the BMI thing drop yet. I noticed that we have a contingency or a statement in the age one that says that there's discretion of the agency and I just wanna, I kind of wanted to get comment from our Ortho people on this because I just if we put their BMI less than 35, I'm just worried that it's just gonna be an a definitive statement, right? And there are people that are healthy, and probably very amenable to surgery, that are, have BMIs older that you know I mean, this excludes muscular people, for example, right? And so kind of wanna just argue once again, for just at least a some sort of a modifying statement for this.

Michael James Yeah, I talked to my patients about. The one concern is just the overload of the, the MACI or the OCA. But I tried to talk to my patients about getting under 40, but closer to 35, and just see if they can, if they're making strides, and they're getting closer to 36 or something like that. It's still not ideal. But I, I understand it's definitely a tricky topic, but I think greater than 40, for sure there would be a higher likelihood of failure of the MACI and failure of the osteochondral allograph and autographed. So we could, I mean, you could say 40, but I think that there is a legitimate physiologic concern beyond 40, just of the cost effectiveness of putting something in that's at a much higher likelihood of failure. It's safe thought process of the uncorrected malignant because the.

Evan Oakes Okay.

Michael James The malignant contributes to an overload of a specific compartment. So if you're in varus you're gonna have so varus is like being bow legged, so you're gonna have 60% or more of your load going through the affected medial compartment, and so adding more BMI on top of that will just overload it so that's why we try and correct it to neutral. So you're putting equal loads. So that that would be my, I think we could go to 40, but.

Evan Oakes Or Dr. James the, the only I just wanted to make sure I'm vocalizing this. I'm worried about inherent sort of discrimination of people.

Michael James Yeah. Sure

Evan Oakes Above certain with the different body sizes. So I just want to be particularly mindful about the statement and the bullet we put in here, and how definitive it is. And that's all I'm speaking up to and so if there's a very distinct reason, I'm totally okay with it. But I just wanna make sure I'm not letting that go lightly.

Michael James Yeah, I understand. I think that, I think most reasonable clinicians would know would probably not offer it if they felt that the BMI was going to be you know, causing your jeopardizing the procedure. So unless the patient finds out about it from somewhere else, and brings it as an option, then it becomes more of a an issue, and those are always, you know, tough conversations to have, so we don't necessarily have to put it in there as long as we know we expect that the clinicians will, you know, be indicating this reasonably so.

Evan Oakes Well, and the other thing and just to kind of pursue that one little is that this sounds like it's distinctly different from age is what I'm hearing you say, like that's why we can put that line in there about discretion of the agency for age. But maybe not for BMI. And I'm just, that's what I'm trying to understand.

Michael James Okay. I think. Yeah, I, I think it can be discretionary by the clinician, and if we need to, if they're wanting to indicate a patient who's BMI is greater than 40 that would be a

discussion about, you know their practice in general age is another. Age is also difficult, because some people have knees that look 30 and they're age 60. And I tell people sometimes you've got an old knee but a, a young heart, and sometimes it's a reverse, you know some people ha are 50, and their knee looks pristine. But I don't typically offer these procedures to anybody greater than 45 or 50. So. Yeah.

Conor Kleweno — I just, I just wanna comment on the, the BMI and discrimination. You know there is also a limit of prudence. And you know there is a history in orthopedics of procedures done that weren't a good idea and a procedure that went poorly is a bigger disaster than what you started with, and sometimes that is dependent on variables that are sometimes uncomfortable to talk about with patients, and one of those can be BMI. And, and then, where that soft tissue envelope is on that patient, whether it's their hips, or their abdomen, or their neck, or their back or their knee, it does definitely change the parameters of the risk stratification. So there are reasons for some of these to make sure we do things with prudence. So.

Evan Oakes — Conor, that's I mean, it's Dr. Kleweno, and that's totally, it's just, it's we seem to be sort of bridging this gap between the Agency Medicaid making that decision for the doctor versus the doctor being responsible themselves for making those correct decisions. And I'm just, that's why I'm, I'm just trying to make sure we're walking that line the right way, you know, between an agency, saying, no, you can't. When, in fact, there may be situations where that's why I'm appreciating the input from both you and Dr. James on this. But that's what I'm listening for is what I'm trying to get at.

Sheila Rege — Dr. Oakes, are you comfortable then given that it's, it's more a wait on a joint mechanical issue?

Evan Oakes — A bit. I did hear Dr. James comment that there is some. I'm looking at that at the discretion of the agency, and wondering if there's language that we might put in there above, you know, between 35 and 40 at the discretions of the provider, or something to that effect of the surgeon. That's what I'm looking for. And wanting to make sure that we're just not we, the Medicaid Agency, and Land I, and so forth, are not the ones that are limiting and diving into these individual decisions that we do want to allow for decision making. And so that's what I'm trying to be mindful of. So I would.

Sheila Rege — Dr. Nam, would you like to comment because we don't wanna burden you? But we don't want to deny care. So.

Ji Young Nam — So definitely I can kind of provide the reasoning behind those recommendations. So, 1st of all behind this age as well as BMI, what we considered mostly was the evidence base. So based on our evidence review the inclusion and exclusion criteria, and the actual study population included were important because the included studies, the population was the one who could went through the surgery, and where the evidence suggests. So, for example, for BMI less than 35, the reason why we put it there was because most of the studies had the BMI limit either 30 or 35, as Dr. Reddy mentioned. So we thought that the evidence exists for those studied population who met the

includes and exclusion criteria, and that is the reason why we put it there, because we did not feel that the evidence exists for like people who are not actually included in the studies. And in terms of the age less than 50 older at the discretion of the agency it was also the same. There was a discussion about whether we put it like younger than 50, or like 55. However, based on our evidence review the most study populations. Age was between 8, 18 to 50, so that is the reason why we came up with the age younger than 50 and also the reason why we put the at the discretion of agency was that, as Dr. Oakes and other committee members mentioned, there are variations, individual variations, the activity levels, as well as Dr. James mentioned the knee joint, the aging of the knee joint might be quite different individually so we wanted to put some cushions on there to make sure that it's not strict younger than 50, but also we want it to be following the evidence base. So it was more about our reading of the evidence, and what the evidence are giving us in terms of the age inclusion criteria, exclusion criteria. So that was where we kind of came a bit.

Evan Oakes

I appreciate that. That's why I'm thinking of. So maybe I'm, I'm missing you, Dr. Nam, but that sounds to me like we're applying a different sort of decision point to the age than we are to the BMI. The evidence was as it was for the age but yet we put in a discretion of the agency statement. It doesn't sound like the age was any different in those studies than what the BMI criteria were and yet we're not putting a discretion of agency in the BMI line. So that's what I'm trying to point out and understand.

Ji Young Nam

So in terms of the BMI it was generally in terms of the exclusion criteria was BMI more than 30 or BMI more than 35. For the age, there are some variation, so most of the studies younger than 50, but the Summit trial was the age 18 to 50. So there are some variation, but most of the included study population, or age between 18 and 50 was our understanding based on the evidence review. Thank you.

Evan Oakes

Well, I don't wanna hang up the group for sure. I'm fine with it the way I can live with it. I just wanna make sure I was not letting that go too easily on that, and really diving into this as best we could. So I appreciate the conversation. Thank you, everybody.

Sheila Rege

Thank you. Then Dr. Bramhall, we're gonna, you had a question.

John Bramhall

Yeah, thank you. I just wanted guidance from our experts. Is it necessary to have an exclusion comment for the MACI that suggests that if there's subchondral, a bony involvement that is not appropriate, and it's an open question, but is that necessary to have language of that type?

Michael James

So classically, the indication for MACI was a minimal subchondral bone involvement but the Vericel people are reporting a new technique called a sandwich technique where you bone graft the subchondral bone and then put MACI on top of that. I don't know if there's long term data supporting that at this point, so you could either leave out the subchondral bony involvement or just state that you know, I, I don't know if in the next 5 years there's gonna be long term data that shows that the sandwich is a viable option when there's subchondral bone involvement, I don't really consider MACI

at this point, I just go straight to an OCA or OATS. But there is this new technique that they're thinking so I don't wanna limit it if it shows that that is a very viable option. But it is currently my indications are minimal subchondral bone involvement when it comes to MACI.

John Bramhall Okay. Thank you.

Sheila Rege So Dr. Bramhall. Are you okay with it, as is?

John Bramhall Yeah, I mean, yes, it's it falls into a similar category as Dr. Oakes is pursuing. It's, it's this you know a wiggle room, I suppose one way of saying, but allowing the practitioner some discretion. And, and, and following their own standards of care and the professional standards of care. Yeah, I'm okay with it.

Sheila Rege Okay. You know, this, this falls in very well, because we usually break after we kind of have a tentative document. That we, we don't nobody has heartache on or.

Conor Kleweno That sorry Sheila. Interrupt you, that alright?

Sheila Rege Yeah.

Conor Kleweno The one thing we hadn't there was sort of we tabled, but needed to come back to was the degenerative arthritis whether we needed a carifying

Sheila Rege That's true.

Conor Kleweno Reference to the. You know, Kale, and I think we could probably do that pretty, pretty, straightforward,

Sheila Rege Do you wanna do it? It's, it's coming on noon we were supposed to break 11:40. I took the chairs.

Conor Kleweno Happy to happy to do it after the break, but and I don't think that will take.

Sheila Rege And you'll think about. And you'll think of something that we can kind of agree on is that good?

Conor Kleweno Yep.

Sheila Rege How long a break do we want in the past we've had a 20 min break. Is that enough? Or does people. Okay, I'm gonna go for a 20 min break. We will come back. And 20 min at 12:20.

Josh Morse Sounds good. Thank you.

Sheila Rege One more minute, I think. Shall we get started, Josh, I think, would begin by projecting what we have so far.

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Josh Morse	Is it showing on the screen?
Sheila Rege	Hang on just a minute. Yes.
Josh Morse	Great.
Sheila Rege	We have stopped with a reminder that we had not talked about osteoarthritis or degenerative arthritis. We do have the statement excluding malignancy degenerate and inflammatory arthritis in the joint. Any discussion on that?
Conor Kleweno	Yeah, I mean, I guess I'd propose something real simple. Just put Kelgren's grade 3 or 4. After the degenerative like in parentheses.
Josh Morse	Can you spell that, Conor?
Conor Kleweno	Yeah. It's K ELLG REN dash Lawrence.
Josh Morse	And you had a grade.
Conor Kleweno	3 and 4.
Josh Morse	Is that numeric, roman numerals?
Conor Kleweno	Yeah, I don't know what the original, but it should be, you can just do regular numbers, I think 3 and 4.
Josh Morse	Okay. Yeah, I'll look it up, too.
Sheila Rege	I'm looking it up. It just has number 3 and 4, moderate and severe. I would like a discussion and Dr. Nam, any, any thoughts on that, since you have guided us with the literature.
Ji Young Nam	So in terms of the Summit trial, which is the largest RCT comparing MACI to microfracture, their language of the exclusion criteria was KL osteoarthritis grade 3 or 4, and for the other 2 RCTs, one had exclusion criteria, but just mentioning osteoarthritis and the other was mentioning osteoarthritis in the images. So I think that it just like variation of the language in terms of defining the osteoarthritis in those, in those studies.
Sheila Rege	So it sounds like it was mentioned, it was consistent with what's what the intent was in in all the studies that it either had to be documented, but they were excluding it and this just makes it even better by saying, only moderate or severe is that, is that what I'm getting, Dr. Kleweno? Is that what you're proposing?

Conor Kleweno — Yeah, I mean, I think as, as it turns out, I think most people would probably ignore the terminology for arthritis for the Kellgren stage one and 2. So. I, I don't know if it's necessary, but we did comment on it, and I and I don't think it's unreasonable to have some specificity here.

Sheila Rege — Any discussion, any heartache over that? I'd like to go back to Dr. Reddy with the evidence report. Is there anything in terms of exclusion criteria that we are missing or that we are too stringent on?

Shivani Reddy — Well, I think the one thing that I saw was whether concomitant cartilage surgeries, like other meniscus or, or one of the other ligaments. There were some studies that would exclude people who had an injury other than the articular cartilage defect. But that was that wasn't all of them. And then one study people with prior surgeries on the same knee and one excluded people with Injuries to the contralateral knee. So I, I can't speak to why those decisions were made, and maybe our, our experts can talk about that. But the main things were the osteoarthritis grade, malignant, some of them had a weight or BMI threshold and then I think the one thing is the presence of another cartilage defect was sometimes part of the inclusion or exclusion criteria.

Conor Kleweno — I think the contralateral knee is probably I'm not sure but you know it's hard to rehab if you have injured side maybe I don't know if there's another reason they had it, but.

Michael James — Yeah, I'm not sure why they would include the contralateral knee. But I think in regards to the other cartilage defects, there is some discussion, rather bipolar defects are contraindication. But I think it's, it's somewhat context dependent and in the case of a patella dislocation oftentimes you sheared off the patella and the lateral ephemeral condyle and an otherwise pristine me so it would make sense to do both lesions. I think the only the slippery slope of that is, you know, I've heard of some people doing it in like a 55 year old with, you know, tricompartmental MACI, and I don't think that that is something that most reasonable clinicians would attempt, so I don't think it's necessary to include that, and I think, excluding bipolar lesions, I think that would limit some procedures where I think it would be clinically indicated to do more than one. But it's just, you know, if you're doing it for pure arthritis obviously, that's essentially malpractice, that's not standard of care so I don't know if we need to address that.

Sheila Rege — So given now that this is kind of what we're building for coverage with conditions. Just going around, we used to do this when we were in person with the committee members going around the table, and I'm going to have Val call on us. Any you know any concerns about this it's kind of like a straw poll about this language. Val, I'll have you just go around the room please.

Val Hamann — Sure. John Bramhall

John Bramhall — No, and Sheila, just to be clear you're, you're looking at this, we're looking at this slide with MACI and the OATS and the not covered. That's the slide we're looking at. Yeah.

Sheila Rege	Correct.
John Bramhall	With that information. I don't have any concerns about that. It seems, it seems appropriate. You covered the arthritis issue, covered the degeneration, yeah, you covered malignancies. We've got this size issue I'm not competent to judge where the 3 cm or 4 centimetres that's not something I can interpret, I accept it. And we have a classification scheme. So the requests from the agency was a degree of precision about the pathological underlying for the need for the treatment and I think we've got the language that would help them in that way. Bottom line. I'm happy with this. Thank you.
Sheila Rege	Going on.
Val Hamann	Clint Daniels.
Clint Daniels	Hi yeah, no concerns either. My main question had been on the degenerative piece, and I, I like Conor solution for that. So I'm, I'm happy with how it is.
Val Hamann	Chris Hearne.
Chris Hearne	I don't have any big concerns. I think that the decision we're looking at here the language we're looking at here pretty well reflects the data we were presented. And I like the specificity again in the grading, the degenerative changes. I think that's, that's useful. I'll just give my 2 cents because there's a discussion earlier about BMI. This is a little bit of an aside, but I, I understand Dr. Oakes concern about that, because it seems like that's not you know, firmly rooted in the evidence we were given. It seems, like most lower or a higher BMIs rather, were excluded in these studies and so who's to say on the other hand, you know I can't remember a time when this committee has bucked those, those recommendations about BMI, and it comes up fairly frequently with different orthopedic technologies. And so you know there's an argument to me that we should be consistent either way. So anyway, that's just my thoughts on the matter. I don't have any big concerns.
Val Hamann	Conor Kleweno.
Conor Kleweno	No, I feel like I've spoken too much here. But hopefully helpful to get this in an acceptable state.
Val Hamann	Evan Oakes.
Evan Oakes	Oh, we've had a great discussion. I'm fine with it. Really good. Thanks, everybody.
Val Hamann	Sheila Rege.
Sheila Rege	No, I'm, I'm very comfortable with it. I would ask, though, given that BMI and there may be other measures that are you know we all, as clinicians know as accurate to put

that as a topic for the strategic retreat on, on kind of a discussion on measurements like any, any measurement that we, as clinicians feel is not the most robust kind of ways around that.

Val Hamann — Tony Yen.

Tony Yen — I don't have any concerns about what's written so far. Did want to appreciate Dr. Oakes' comments about BMI. And I do really wanna appreciate his, I think his efforts really making sure that we're not excluding people who may also benefit. My interpretation of the literature is that the literature unfortunately, exclude that population and I think one of our charges over here is actually to try to use the literature as much as possible as a guide towards evaluating these technologies.

Val Hamann — And that's everyone for today, Sheila.

Sheila Rege — Dr. James, I'd like to invite you to make any comments given that you have clinical expertise in this.

Michael James — I think we've addressed things pretty thoroughly. Yeah, overall, I just you know my concern is that the what Dr. Kleweno was chatting about in regards to the malignant and the ligamentous insufficiency, I'm just wondering how those will be handled on a case by case basis. If there's gonna be like you know, sports medicine who will look at it and see, you know as a gestalt what is uncorrected malignant, and uncorrected ligamentous deficiency I just don't want those to be too much of a barrier going forward just because there is a level of nuance associated with those.

Sheila Rege — I'll let Dr. Nam, and Dr. Nam, I'd be curious about your, your thoughts about how we were things, and then maybe you could answer Dr. James.

Ji Young Nam — So in terms of the wording, I thought, it's really thorough, and thank you so much for such robust discussion, because I learned a lot listening to you because in terms of the malignant and ligament issues, I noticed that there are lots of exclusion, specifically mentioning model alignment as well as ligament insufficiency and is the committee members discussed, I was not so sure how specific the recommendation should go or not, so I was benefited by listening to you. Thank you.

Michael James — I think one of the sorry.

Sheila Rege — I think Dr. James.

Michael James — Go ahead.

Sheila Rege — Just to answer you. I think it is going to be left up to the clinician. It's just kind of a you know, and Dr. Franklin, who's got more expertise for this or Dr. Zerzan-Thul can answer this, but it's just a reminder to the clinician that, you know, just to make sure that, that's checked.

Michael James	Okay, thank you so much.
Sheila Rege	If, if everybody's comfortable with this, I, I will tell you we are how many hours ahead. I, we've always said we would take a break of 5 min break, but since we just came off I would ask the indulgence on this committee to not have another break given that we just added the Kellgren-Lawrence grade 3 or 4. And go on to, we'll 1st do us, should we just do the final vote? Is that okay with everybody? Or do you want to do a straw poll? I'll take a motion for either.
Conor Kleweno	I saw Tony motion for final vote, and I'll second it.
Sheila Rege	Okay. Any, any objections to going to a final vote? Perfect. Then we'll have to do that via the polling correct?
Val Hamann	Yes, and I just started that session again so you may have to log in once more. And how we've done this in the past is Josh, if you want to display this, so members can read the conditions as you answer this vote, and then I can display those answers after you have voted. I'm just waiting on one more connection before I launch the poll. That poll is open for MACI.
Sheila Rege	And so just to let everybody know if you vote yes, you are voting it to be covered with conditions and the conditions are the ones we just discussed. That's on the screen.
Val Hamann	Okay. And we have. 7 to confirm or approve conditions as written for MACI. The next question goes into OATS and OCA. And again 7 to the coverage conditions as written for OATS and OCA. And then, Sheila, we do have, I do have another question for the cell-free and AMIC.
Sheila Rege	Correct because we just did a straw poll on that so we need to do a final vote.
Val Hamann	And then this one would be as a not covered.
Sheila Rege	So if you vote yes, here we are going with what we agreed on the straw poll which is not to cover. So A means not to cover.
Val Hamann	Yes.
Conor Kleweno	Yes means no here on this one. Okay.
Sheila Rege	Yeah, unfortunately, that's, that's why I was making sure we should have said.
Val Hamann	Yeah, yeah.
Sheila Rege	And not to cover. And if we come up with a confusion or difference from the straw, we'll go back.
Val Hamann	Which we have 7 for yes, so, Josh, would you like me to display these now?

Josh Morse Yes, please.

Val Hamann Okay.

Sheila Rege So. That is covered with conditions and the conditions for what was outlined that we just discussed.

Val Hamann Yep. And then this one is for OATS and OCA.

Sheila Rege And that's also covered with conditions. And this was not to cover and now we have to go on to the rest of our process about whether we're consistent. Any, any discussion, any heartache, thoughts from the committee members before we move on? Okay, we're gonna move on then.

Josh Morse So I'll share my screen here briefly. So back to the decision aid. You've just completed the vote on the covered with conditions for MACI, and then for OATS and OCA, and then voting to not cover the cell-free, and the autologous matrix induced technologies, Thank you very much. And so the next item that needs to be completed before we can, can stop here is are these determinations consistent with any identified Medicare decisions and by that we mean a national coverage decision from Medicare. Not local coverage decisions, but just the national NCD coverage decision. And is it consistent with expert guidelines? And if not the committee is asked to just for the record note why, the committee's decision might be different or not consistent, please. And then in your decision, we've documented that there was no national coverage determination. We also documented that apparently there are no local coverage determinations for these procedures, as well. And then we have taken from the report the guideline information that RTI put together. And that is available to you to consider in light of the decisions that you've just made.

Sheila Rege So this is the, these are recommendations from the American Physical Therapy Association, the Society of Pain and Neuromuscular and the European, the National Institute for Health and Care Excellence. And we have to just make sure that we are not completely an outlier in in terms of this in these recommendations. I don't think we are, I know we've discussed and rejected the, the, the no, this is just I think we're consistent with this. Any, any discussion about this? We did not, we did not put anything in there about physical therapy or rehab therapy, but that would be covered by the agency, correct? Josh?

Josh Morse Yeah. Physical therapy is covered by the agencies.

Sheila Reg Okay. I don't, I don't see any that we are inconsistent with any of this. The only thing we're inconsistent is we, e did not go into conservative therapy, we discussed it, and we rejected.

Josh Morse Okay.

Sheila Rege — Having people try you know the one or 2 months of conservative therapy. If nobody has any thoughts, objections, were, we do need somebody other than me to opine that we are consistent.

Conor Kleweno — I I can do that, Sheila, representative orthopedic surgeon. I think we are consistent, for you know what limited things are out there. I would also just like to comment once this is public record and as an orthopedic surgeon, I think that we did review the evidence. I thought the evidence base did make, Dr. Reddy made a great comment about the difficulty of determining all of this given the variation in lesions and size and techniques utilized. It is a procedure done commonly in practice so we do wanna make sure that we are not limiting access to patients by withholding covering, or recommending no coverage. But I would advocate to my colleagues in orthopedic surgery that they continue to use this procedure for very well indicated patients select patients where this can be used to improve their outcomes and the mobility and pain.

Sheila Rege — Thank you. Any anybody else want to comment on this? The, the only discrepancies I see are, there is something here for less than 2 cm squared but we we've looked at the data that we were presented. There is an age, and we discussed that and rejected an age lower age of 15 or 18. And we also rejected requirement for conservative therapy prior to the procedure being done tried and failed therapy. So I think, Josh, we have addressed everything.

Josh Morse — You have. Thank you. Dr. Rege. That concludes our agenda for today.

Sheila Rege — Great. Can you tell us kind of and this is just because we have some new members. So the next, the process for our decision now it will go, you know kind of the next steps for what we came up with today.

Josh Morse — Certainly. So after today's meeting we will take what you've written, and we have a template that we publish these determinations in will spell out some of, the all of the acronyms that aren't currently spelled out on the document will spell those out. And within a week or 2 we'll put this document out online as a draft and send a notice out via our GovDelivery system for public comment, and that'll be available for 14 days for public comment that'll happen between now and the November 15th meeting at that next meeting we'll bring that information back to you it'll be part of the previous meeting business where anybody who's commented you know, on language, or any intent and then in the decision aid which I'll go back to the, the next steps in this. Well, hopefully, it's in this document. Yeah, here we go. So this is what happens at the next meeting. At the next public meeting the committee will review the proposed findings and decisions, and consider any public comments that we receive prior to a vote for a final adoption of this decision. So in the 2 questions that you're asked at that about this draft are based on the public comment, was the evidence was the was evidence overlooked in the process that should have been considered so. If you know, a, a relevant study was, was somehow missed in this process, which has been going on for probably a year that's important for us to know and that's a you know, something that the committee should consider. And then the other question is, does the proposed,

does the proposed findings and decision document clearly convey the intended coverage determination based on review and consideration of the evidence so your decision today if you know sometimes the intent is not perfectly clear, or, as you had a great public comment today, asking for clarity around definition, for a condition. It's that kind of thing that we hope to catch between now and making this final. And that's what number 2 here is. So we, we hope that at the next meeting there's not a reconsideration of the evidence, we technically aren't prepared for that. We don't usually have our evidence reviewers at the next meeting this is a very focused question about with something major missed that should have been included, and then we can decide what to do if we need to at the next meeting. And then number 2 are there is there anything not clear about what you intended, based on your vote today in the decision that should be edited. And then, once that final vote occurs in in November the agencies will, that decision will be is published it's final, and the agencies will do as they can to implement that their programs.

Sheila Rege — Perfect, and our next November meeting, which I hope everybody will attend, is what date?

Josh Morse — It's the 15th

Sheila Rege — November 15th. Very good. Dr. Reddy, Dr. Nam, you did an incredible job. Thanks to your hard work and preparation ahead of time. We are finishing early and we had consensus, which in our committees sometimes doesn't happen because we're you give us yeah, you give us very tough questions to, to debate. So thank you. Any other discussion? If not, I will take.

John Bramhall — I'll just answer that I thought that those presentations by Dr. Reddy, Dr. Nam were very well paced. Very well organized, and I think it was a big help, certainly, to me, potentially complicated topic, pretty detailed lot of moving parts. And I felt subjectively that we reached our decisions much more easily than we have for some topics in the past, so congratulate. Thank you.

Shivani Reddy — Thanks.

Josh Morse — Yeah, and I'd like to say, you know. Val has done a tremendous job with that PowerPoint presentation which I'm not yet fully accustomed to but Val is sourced that technology for the past 2 years to make that voting easier along with Melanie, who you haven't heard much from Melanie today since cochlear implants, but tremendous amount of work from our team. So thank you.

Sheila Rege — I think all that hard work you've done ahead of time and in all honesty, what the decisions or the fine-tuning we did of the process during the retreat has helped tremendously.

Josh Morse — Completely agree.

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Sheila Rege	Well, thank you, and I will take a motion for adjournment.
Clint Daniels	So moved.
Sheila Rege	I don't think we need a second on that.
Tony Yen	Okay.
John Bramhall	Second. Got it.
Sheila Rege	Take take care, guys bye.
Josh Morse	Thank you. Have a good weekend.
John Bramhall	Thank you.
Ji Young Nam	Thank you.
Tony Yen	Thank you.
Judy Zerzan-Thul	Thank you everyone. Bye.
Sheila Rege	Thank you very much. Bye.
Tony Yen	Bye.