Washington State Health Care Authority

Washington State Health Technology Clinical Committee Meeting

Whole Genome Sequencing

June 14, 2024

DISCLAIMER

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Josh Morse	It's 8 o'clock. Dr. Rege. Let's see
Sheila Rege	Yeah. Thank you very much. Welcome everybody and as we know, we are here to, as part of HTCC, the panelists especially are here to make recommendations based on review of the scientific evidence we will start with HTA program updates Josh.
Josh Morse	I think we may want to start with a roll call. I think we have I'm seeing 8, but let's confirm that we have, if we, if you don't mind doing that first. Val, can you lead us through role call and then we'll do this.
Sheila Rege	That would be great. Thank you. Let's do that.
Val Hamann	Yeah, just one second. I believe we had one more come in. Okay, great. Okay. John Bramhall
John Bramhall	I'm here finding my, finding my way. Good morning. Thanks, Sheila.
Val Hamann	Clint Daniels
Clint Daniels	I'm here. Good morning.
Val Hamann	Janna Friedly.
Janna Friedly	Good morning. I'm here.
Val Hamann	Chris Herne.
Chris Hearne	I'm here.
Val Hamann	Conor Kleweno.

Conor Kleweno	Here.
Val Hamann	Christoph Lee.
Christoph Lee	Here.
Val Hamann	Laurie Mischley.
Laurie Mischley	Present.
Val Hamann	Sheila Rege.
Sheila Rege	Here.
Val Hamann	Jonathan Sham.
Jonathan Sham	Here.
Val Hamann	Tony Yen.
Tony Yen	Here.
Val Hamann	And that's all we have. So everybody that. Everybody's here.
Josh Morse	Okay, how many is that? Is that 9?
Val Hamann	10.

Josh Morse

10, great. Thank you. Excellent. Okay, I'll go through our updates here from the program or background. So this is our June 14th Health Technology Clinical Committee meeting. I'm Josh Morse, I'm the program director for the HTA program here at the Health Care Authority. Some meeting reminders, there'll be a transcript, we are recording this meeting and we do publish the transcripts. They're available in the meetings and materials after the meetings are concluded. We aren't using chat for this meeting. It may be, we try to disable it. It may not be disabled, but we ask that you please don't use it. It's not effective in these virtual meetings for what we're doing today. We will, we may ask you to use the raise hand feature for public comments when we get to that part.

So some background on the HTA program, the health technology assessment program is administered by the Health Care Authority. This program brings evidence reports to this committee, the Health Technology Clinical Committee, to make coverage decisions for selected medical procedures and tests based on evidence for safety, efficacy, and cost effectiveness. Multiple state agencies are participating in this process and to identify topics and ultimately to implement the policy work of this committee. This includes the Health Care Authority, running the programs, the Uniform Medical Program and Apple

Health Medicaid, the Department of Labor and Industries, the Department of Corrections is also implementing these determinations. State agencies put these policies in place they implement the determinations from the HTCC within their existing statutory frameworks. So the purpose of this process is to ensure that medical treatments, devices and services paid for with state health care dollars are safe and proven to work. The program provides resources for state agencies that are purchasing health care. Through this process, we develop scientific evidence-based reports on the medical devices that are selected and bring that to the health technology clinical committee. The program supports the HTCC to make determinations for the selected technologies based on the available evidence.

There are multiple ways for anyone to participate in this process. We have a website that contains all of the publications from the program and information about the meetings and path of the current meetings and past meetings. Anyone is invited to sign up for program notifications and receive those by email. Anyone may comment at various times throughout the course of a topic review on proposed topics on key questions on draft and final reports and on draft decisions. Anyone's invited to attend these public meetings and present comments to the committee on the topics as they're reviewed and anyone may nominate a health technology for review or for rereview. So today's agenda, will have previous meeting business to start with, which includes the minutes from the last meeting on May 17th. We will review comments received for the bariatric surgery draft findings and decision that draft was created at the last meeting. We will do the same for the spinal cord stimulation, draft findings and decision there are comments there as well. We will then, the committee will consider a petition asking for tumor treating fields to be rereviewed and we will have information for you on that and you have that in your meeting information. And then we will review a new topic and that is whole genome sequencing. During the whole genome sequencing review, there will be a public comment period. Time is limited during that period, we do have a number of people signed up, but we will be asking for individuals who may wish to comment during that time. And, Val will manage that when we get there. During the public comment period will ask you to clearly state your name declare any conflicts of interest. This is the public comment portion of the meeting when we get there. You'll see this slide and we will ask that you limit your comments to be allowed of time.

After today's meeting. The program will publish the minutes and transcripts from this meeting and any final determinations that are made today as well as any draft determinations. Draft determinations after this will be open for public comment for 2 weeks. Future HTCC meeting. So right now for September we have treatments for chondral defects of the knee scheduled. The final key questions are out for that topic in the draft report is in process with the contractor. Same is true for vertebroplasty. I believe it's actually final key, key questions at this point and they're working on the draft report and then in January, we have a retreat of the committee. We're currently working on additional schedule for 2025 with new topics. This is contact information for our program and the address for our program website. If there are any questions, I'm happy to address them now. Okay, thank you.

Sheila Rege Thank you. Do we want to discuss the petition review next? Josh?

Josh Morse	Well, the agenda order is we'll do the previous meeting business and then go to the petition. If that's okay.
Sheila Rege	Okay. That's good. So I will take a motion for the previous meeting minutes and approval.
Josh Morse	I can project those.
Janna Friedly	So moved.
Christoph Lee	I second.
Sheila Rege	Anybody all in favor say aye. Go ahead.
Laurie Mischley	I.
John Bramhall	I.
Jonathan Sham	I.
Clint Daniels	I.
Tony Yen	I.
Conor Kleweno	I.
Chris Hearne	I.
Sheila Rege	Okay. Anybody else opposed? Anybody abstaining? Okay. We're going to the bariatric surgery draft findings and decision.
Josh Morse	Okay, I'll be right there. Okay, I'm gonna share my screen.
Val Hamann	We're not Josh, we're not seeing anything.
Josh Morse	Okay, so here's the timeline, the overview and the comments for. Oh, one more click. Thank you. Appreciate that. Here's the timeline for the periodic surgery review. The, topic selection started last July. We find ourselves here at the end of the comment period in June. And the numbers over here on the right indicate the number of days that these were out for public comment. We did receive comments. There are 6 comments. They are supportive of your determination. And I'll turn it back to you, Sheila.
Sheila Rege	Great. And off I should have seen this in our packets. Is there any discussion? Do you need a motion from us Josh or just that we have reviewed this?
Josh Morse	This is your opportunity to consider and in the comments, I don't believe there were any suggestions to change language around intent. This, We did. And Melanie, if you can

confirm that the version that we're looking at here is the updated version in the packet based on agency feedback?

Melanie Golob No, that so the draft updates there and track changes in a different document just because that was the draft findings from the last meeting and then.

Josh Morse Gotcha. Okay.

Melanie Golob We mocked up the changes, based on I think a couple internal concerns about clarification of BMI in the different criteria.

Sheila Rege Do you want to project that, for us or would that be?

Josh Morse Is this the version, Melanie?

Melanie Golob Oh yeah, yeah, that's it. Perfect. Thank you.

Josh Morse Yeah, here we go. So, these did not change the intent, they just clarified, you can see here.

Melanie Golob Yeah, and I, I can describe what happened here if you'd like, but essentially it just clarified, the BMIs that were associated with the thresholds that were associated with non-Asian descent what BMI which was greater than equal to 35. And then with Asian descent, the greater than equal to 32.5 because that was what was in the literature and what the committee decided on, but it wasn't entirely clear when people were going back through and reviewing these. And with that second bullet under adults, the type 2 diabetes, again, clarification that the greater than or equal to 30 referred to BMI for non-Asian descent and then BMI greater than equal to 27.5 for Asian descent and then that was it for the adults and then for adolescents down below just clarification that the BMI was greater than equal to 35 for an obesity related complication in adolescence.

Sheila Rege That was our intent. So that makes. Total sense.

Melanie Golob Yeah.

Sheila Rege Any other insights from committee members? And you do not need a motion from us, Josh, because nothing's changed, correct?

Josh Morse We do need a final vote, so we need a motion and I think a second to, to do a final vote on this to approve this as written as you see it.

Sheila Rege Okay, and then this was the one that people that I try the new voting process, correct?

Josh Morse Val are we using the, okay, great.

Val Hamann	Yeah. Yes. So if. You were all sent an email last night, so if you could log in to ttpoll and put in your code that you were given again please don't share that and once I see all 10 connections in there, we can launch that poll.
Sheila Rege	Who would that email come from? It'll come from you.
Val Hamann	Yes.
Janna Friedly	And, Val sorry, I must have missed this, but once we're in the, in the polling it will pop up?
Val Hamann	You haven't launched it yet. I have not launched it. No, I'm still, I'm only seeing 8 connections right now, so waiting for 2 more.
Janna Friedly	Okay.
Sheila Rege	I'm having trouble, Val. There we go. Just came. Okay.
Val Hamann	Okay, just waiting on one more.
Sheila Rege	Probably me, I mean.
Val Hamann	There we go. Okay.
John Bramhall	Val, will it be, could it be launched in the screen of the Zoom Meeting? Would it be launched in, in the website?
Val Hamann	It will in the website. So. Nope, we're good now, so I'm about to launch it.
John Bramhall	Are you waiting? Is it me that you're waiting for? I can't tell. Oh, okay.
Val Hamann	Okay, yep, here we go.
John Bramhall	Alright, okay.
Sheila Rege	Val we don't have to hit send or anything, correct?
Val Hamann	Nope, I have everything. So. We have 10 that have approved those findings and decision.
Josh Morse	Great. Do you want to show that result or?
Val Hamann	Yes, I can.
Josh Morse	Wonderful. Thank you.
Sheila Rege	Now we will look to the spinal cord stimulation draft findings and decision.

Josh Morse

Okay. Here is the timeline and the history for spinal cord stimulation. We received 3 comments that did cite evidence, commenters, the folks who've submitted these are listed here. These comments were shared with you. This is the draft as it was published. As you know, Dr. Rege, Dr. Friedly, we went over these comments with you. And we have a draft prepared for you to start from based on your feedback for the committee. And if you'd like me to project that, I can start from there or I'll turn it back to you, Sheila and Janna.

Sheila Rege

Yeah, so committee members, this is these are these for comments and based on that Josh met with Janna and me about, how to, how to kind of expedite the meeting to try and incorporate some of these and if we can project those, there were some comments that, for example, 2 studies for patients workers comp with failed back surgery syndrome was included, they, one of the commenters felt that was flawed, patients are not randomized and Janna, help me out. I have a little bit of a cold, so I'm having, I've got the head thing going.

Janna Friedly

Sure. I mean, so I can just say from a high level, there were a number of requested changes the criteria in, in general. I, I think just from a high level, the requested changes were to loosen the restrictions on and, and the criteria for spinal cord stimulators. And they, I went through myself, carefully each one of those requested changes and I helped to make these, the suggested changes here based on looking at the evidence and weighing that with, you know, making sure that there's clarity and, and that there's also enough rigor and safeguards around this procedure and I think from my perspective I'll just say that you know, this is a this is a procedure that has, mixed evidence, as we saw, limited evidence. It has a very high risk and it's one of the most it has the most, complications of one of them the highest rates of complications of procedures and it's, it's very expensive so in my thinking about this I, I feel that we should, should put a significant guardrails around this and that it's reasonable to think about making sure that this is limited to people that it that have really for an extended period of time have tried many different options, other options to manage their chronic pain and that we also have some rigor around the how we are choosing the patients in terms of the diagnosis and what it's being used for and, you know, I just want to emphasize that this is a chronic condition. And so I think some of the comments about shortening the timeframe to 6 months of, of treatment and that sort of thing. I, in my mind, you really need an extended period of time, with, multiple different, other treatments. So that, that's from a high level, my, my thoughts about this and, and how I frame these changes.

Sheila Rege

So Josh, could you summarize kind of the significant changes while you're projecting it so we could look at it?

Josh Morse

Yeah, I'll scroll through here. So, these changes are put in via track changes on the document that was published during the draft period. So, the first change is to add based on the comments another pain scale here, change complaint to symptoms, change compliance to adherence, add an equivalent psychological counseling to the to the requirement that was originally cognitive behavioral therapy alone. That is under the

failed back surgery syndrome area that much of this repeats for the non-surgical refractory back pain. Again, with the pain scale change adherence versus compliance adding, you know, an equivalent psychological counseling intervention and then under painful diabetic neuropathy, I think there's a little bit of difference here, which is again, the pain scale, languages is expanded and then some clarity added around symptoms consistent with diabetic peripheral neuropathy, including bilateral stocking glove distribution pain. I don't, Dr. Friedly may want to comment on that and then the same here with vibratory sensation testing with a tuning fork plus sensory testing with the I don't 10 G is that gram, same as weinstein mono filament a little bit out of my area of expertise here. So, and then adherence. So some greater specificity and, addition of the pain scale based on the comment. What isn't changed as was already stated was the 3 commentators I think all asked for less than 12 months and you can see this in the submitted comments, right? So, There's a nice table that Dr. Singh provided which inventory their recommendations and the other 2 commenters. They weren't the same, but they were very similar as far as what they were asking for in addition of asking for coverage of CRPS, I believe. So. But. Janna.

Janna Friedly

Yeah, I'll make a couple of other comments. The one about the psychological counseling, the one thing I wanted to, you know, some of the other changes were around loosening the requirements for psychological evaluation, to essentially a screening tool in the clinic and if that's if there is no significant mental health condition that the requirement be changed and I just want to point out that cognitive behavioral therapy is one of the most well-studied interventions for chronic pain in the absence of depression, anxiety or other significant mental health conditions. It is really a cornerstone treatment for chronic pain. And so I think in that spirit, you know, and there are other treatments like mindfulness and other psychological interventions that have been shown to be effective and are covered. So I think that's that that was the change recommended there. And then with the diabetic neuropathy, I think there were comments that we should not rely on sensory loss as, as a, criteria for diagnosing diabetic neuropathy. And just some context around that. I think the real, you know, standard for determining that someone has peripheral neuropathy it is mostly a clinical diagnosis and you do, have to demonstrate some, impairment in, in sensation, using a monofilament and vibratory sensation testing, so those are the 2 easy ways in clinic to determine sensory loss, it's something that can be done and should be done by any primary care physician or any, any pain physician could do this as well and you only use a nerve conduction study really for complicated cases where there's questionable diagnosis, it's not clear or there potentially is some other condition going on, which is important to rule out. So, I think that this wording captures, captures that.

Sheila Rege

Committee members discussion?

Laurie Mischley

This is Laurie. I don't have a discussion about the cognitive piece, but in one of the letters they talked about using the ODI that we had required it for something and then it hadn't been validated in the way that we were using it and they just suggested loosening the language and to an, a validated measure not specifying ODI in particular. It is, I can't see what page that's on, but.

Sheila Rege I remember that.

Janna Friedly Yeah.

Laurie Mischley Yeah, I just it was the only one I they seemed very well justified in their ask and to require it be a validated measure made sense, especially when they told us that it wasn't validated in this context. So I would be in favor of changing as they ask functional disability assessed using a functional, a validated functional measure. So.

Janna Fridley Yeah, I think that the challenge is that without a definition without, without a parameter for what, what is moderate to severe, you know, functional impairment, what's the threshold for, for impairment. So the ODI is a validated measure it is, it is used to classify you know functional disability it's one of the most common ones that that is that are used. I think if you if you just say functional disability assessed by a validated measure then there's no definition to that and that really is not a not something that could be operationalized or something that could be really, really used in any practical way. And it just, it, essentially opens it up to not having any kind of functional disability. So I think that's where there's a little bit of a struggle and the ODI is a validated measure, it's used very commonly and that cutoff is used not to determine. Okay. You know, I guess I grappled with this too and my feeling about it, my thoughts about it were that yes, it's one specific tool, but this is a, this is a. And invasive procedure, that is essentially a permanent invasive procedure to require one specific validated tool, that they, that they have to do is, is not an unreasonable, request in my, in my opinion, but.

Laurie Mischley Hey, I certainly wouldn't argue over. I just don't know if we're correct. I mean, they provide a reference when they say that ODI is only validated in the measurement of back pain and does not address neuropathic leg pain and they go on to provide a reference about if there is a validated measure for neuropathic leg pain, that might be more appropriate and I wouldn't argue with that. I don't know what they're saying is true. But they provided a reference and that. Made their ask same reasonable. So I just don't know if, if it hasn't been validated for what we're requiring it be used for, I want to make sure we're not doing something. I should, I should have looked up that reference. But if they are misleading and it has been validated in the purpose of using it.

Sheila Rege That's the one reference they have in a general of neurosurgery spine, 2019, that's the one you're talking about. That’s what I remember. Just looking at well let's let me have others comment first.

Jonathan Sham I guess my only question maybe to Sheila and Janna is, I guess did you guys have any kind of discussion about the CRPS coverage? It seems like that was a concern from multiple parties and several brought up that it was in our decision was contrary to coverage policy of all commercial payers and Medicare. And just kind of how you guys. If that was discussed at all. What your thoughts are on that. It seems like that's kind of the big, you know, there's some wordsmithing things which are fine, but that's the covers decision as a whole. That's kind of the big one that I think. Was different from previous.

Janna Friedly	I, I can weigh in with my thoughts, I did review this and, you know, obviously I, as, you know, I voted no coverage for all of the conditions, but, in particular for, CRPS, they didn't provide any new evidence and we, we did have a very thorough discussion about the evidence that was presented to us and voted based on that so there was nothing new in their in their arguments that that I, in my opinion changes are thought process around around CRPS. There was nothing new that we hadn't reviewed before.
Tony Yen	Janna, I just wanna. Oh, sorry, Jonathan. Go ahead.
Jonathan Sham	Yeah, I think some of the Oh god, that's alright.
Tony Yen	Yeah, Janna, I just wanna thank you for your really, I think, considerate comments and thoughtfulness about this topic. Really appreciate that.
Clint Daniels	I was gonna just comment on the ODI thing again a little bit. This is a really commonly used form for back pain and we use it for back pain both in our clinic and the threshold we have is actually pretty low. I think it's very reasonable and it's a very low burden thing for someone to do in the clinic, so I personally, no, no problem with keeping it. And I like, I like all the other edits. That they put together as well.
Sheila Rege	Any other comments? I applaud Janna for really taking a deep dive into this. If not, Josh, what do you need from us at this point?
Josh Morse	We need to move to a final vote as we did for bariatric, accepting these changes. And accepting this as the final determination for spinal cord stimulation. And, I think Val will get through the voting process.
Val Hamann	Correct.
Josh Morse	So if you're, if you. If everybody agrees with the changes as they are. There's a hand up it looks like.
Sheila Rege	We're just doing hand up?
Conor Kleweno	No, I was, had a question actually.
Sheila Rege	Oh, sorry, Conor.
Conor Kleweno	Okay, sorry, it's just, you know, we do this, you know, several times a year, not every week. So is our vote to sort of accept what is written to go along with moving the process forward or is our vote supposed to align with how we voted for coverage? Like for example, several of us voted no coverage, but now we are, you know, do you see my point here?
Josh Morse	Yeah.

Conor Kleweno Like, so previously we voted, you know, some people voted no and some people voted yes for a different version of this document. So are we supposed, I'm okay with the changes if that's what's happening, but am I supposed to vote along with what I previously voted or am I voting for acceptance of the edits here?

Josh Morse You're voting. Yeah, that's a good clarification. So the vote for cover versus not cover versus cover with conditions it was done at the last meeting.

Conor Kleweno Okay.

Josh Morse And you approved the draft as you see it without the edits. The edits are based on the public comment period and scrutiny of the draft. And, so your final vote here will be to approve it with, with the edits in there. Now if the committee is essentially if the chair has a consensus from the group that yes, you accept these edits or you could vote on the edits and then do a final vote on the draft as it's written. My sense is that you're all in agreement with the edits as you're seeing them and I think we can move to a final vote and that will make this decision final but the vote is not, the vote is to accept this draft as the final determination for spinal cord stimulation.

Conor Kleweno So it's different than in the original vote, basically.

Josh Morse Yeah, you're not voting cover, not cover with conditions. You're just voting to approve this as the final determination.

Conor Kleweno With the premise that the vote has occurred for what we're doing? Okay, thank you.

Josh Morse Correct.

Sheila Rege And for this, do you want to go back to the polling system? But for this, we had not used that. We had used that bariatric surgery. How would you like to proceed?

Josh Morse Yeah, Val, what's your plan for this one? Is that you gonna use?

Val Hamann I, yeah, I do have this in ttpolls so we can do the voting software if you are comfortable with that Sheila?

Sheila Rege I am.

Val Hamann Okay, so if you all wanna jump over, I'll give you just, a couple of seconds here to jump back over to ttpoll and then I will launch that polling question for you. And that poll is open. We're waiting on 2 more responses. One more. Okay. And we have 10 to accept the findings and decisions as written.

Josh Morse Great. Thank you, Val. Thank you, everyone. So that concludes the previous meeting business and now we are on to the conversation about a petition for whether to select tumor treating fields for rereview. And Melanie has some structure to discuss this.

Sheila Rege Before we go there, Josh, can you, because they are new committee members. Can you go through the process of, steps of somebody petitions the committee and then kind of the steps that happen along the way.

Josh Morse Yeah, great question. Thank you.

Melanie Golob We also have that in the slide deck as well. Right.

Josh Morse Yeah, Melanie's gonna do that. Thanks, Melanie.

Sheila Rege You're gonna cover that, that's good.

Melanie Golob Yeah, perfect. Perfect queue up.

Johs Morse Yeah, this is not something that happens too often. So yeah, I think. She's got it all in there.

Melanie Golob Yeah, let me, share my screen. Okay, hopefully you can all see that.

Josh Morse Yeah, we're seeing that. There we go.

Melanie Golob Great. Okay, so. Yeah, this is a unique situation that we're asking. The HTCC to review. And also just after these last 2 discussions, just want to say how much we appreciate the work that the HTCC does. I know this is not an easy task to go through all of this and make these decisions, but we appreciate the thoughtful review that goes into it. So petition, we typically get requests, petitions to review or rereview topics through the HTA program. And If they're selected by the director, they go on the regular schedule to review through the course of the year. If they're not selected, they go through again the kind of typical process of these were not selected, the petitioner can kind of go to an extra step and ask the HTCC to review the petition to see if it should be reviewed or rereviewed. So that was the case with tumor treating fields. So it was originally reviewed in 2016 and rereviewed in 2018 and most recently we had another petition submitted and it was declined to select for rereview in this most recent cycle. The current determination from the HTCC is it's not covered. So that's kind of a history of, of tumor treating fields so far. And so as I was saying previously, the, the petitioner has requested that the HTCC consider the topic for rereview. So what this group's task is is based on references provided in the petition, which the petition has already been sent out to this group and attached to meeting materials, could the evidence presented change the previous determination. So again, the previous determination is not covered. So if the committee decides that it should be selected, tumor treating fields will go through the regular process of rereviewed. So that'll be a separate meeting, it'll be voted on an evidence report will be created, go through the typical process. If not, that decision will stand to not be selected for rereview. And the petitioner has the option in subsequent years to also petition again. But for now the directive of the HTCC is to determine whether or not it should go through rereview.

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Sheila Rege — And the timeline if this committee votes and decides that this is topic because of the data. How does that work?

Melanie Golob — So that it'll go through just the typical timeline as well. So once it's selected, it'll be posted as a topic that's been selected. There is a public comment period for it'll go through kind of the typical just topic selection and key questions scoping and so it'll take probably about 9 months to go through that process and it will be slotted in to the 2025 meetings if it's selected, but it'll go through those typical, you know, public comment periods and, questions, draft evidence report, final evidence report and then committee meeting on the topic. So a typical timeline for a review or rereview. So any other questions though before we get started on looking at that.

Okay. So this petition again, you should all have it as well. This is something that we looked at internally and the director considered also in not selecting it. But so, 27 articles were cited in the petition. 23 of those have been published since 2018 which was the year of the previous report. And here's a breakdown of the different study or article types, they're not all studies. So just kind of want to draw your attention to 6 of those were guidelines and 5 of those were reviews. So again, not primary evidence. So that leads down to 16 of those could be considered primary research and 13 of those were published since that previous report. Looking at how many of those would meet the PICO or scope of those key questions of the previous review, 12 of those would not meet the PICO or inclusion criteria of the previous HTA review done on the topic. 4 of those, 4 those 16 we're non RCTs, meaning that there are no RCTs presented. And as we've discussed before, when topics are not covered to show that a topic should be covered you need to show effectiveness and again, that's typically done through RCTs. So here's a just kind of summary breakdown of all the, the studies that were presented in the petition and I think you all looked at it but just kind of some details about the 4 RCT or for non RCTs. that might meet the PICO or inclusion criteria. 3 of those were retrospective, one was an economic study. One of those retrospectives showed no new safety concerns. One only dealt with patients with ventricular peritoneal shunts and one was 18 years at a single center comparing clinical versus hospital data. And then the economic study that talked about cost-effectiveness was funded by Novocure and the authors and reviewers were also paid by Novocure. So that is a summary of the evidence presented in the petition. So the next thing that you would do is vote, but before we do that, are there any questions on any of that?

Sheila Rege — So. This is, this is just a clarification, this is prescribed by radiation oncologists and they, do have a tried and clinical trial where they are expecting results, I believe they announced in 2026. Kind of their definitive trial in a glioblastoma multi-formA. And this company also thinks that they could work in lung cancers and some other cancers. So would not just be brain tumors which is how they were initially advertised and introduced as. So when this comes up, I will probably abstain just because that's what we've done.

Melanie Golob — Okay.

Sheila Rege — In the past. But it's the Yeah.

Melanie Golob Okay.

Chris Hearne Just to make sure I understand this pyramid is showing us the new articles in the petition, is that right?

Melanie Golob These were the ones that were included in the petition. Not all of these, 23 of those 27 were new since the previous report and 13 were, 13 of those primary research ones were new since the previous report as well. But they were all included in the petition.

Chris Hearne So no new RCTs?

Melanie Golob No

Chris Hearne No, Gotcha. Okay.

Melanie Golob Okay. Any other questions? Josh do we need a motion to, I know this is kind of a unique situation with a review or re-review.

Sheila Rege Since we have the polling, you could just ask whether this committee wishes to have this added.

Melanie Golob Okay.

Sheila Rege To work for the committee or so yes would be yes please add it no would be no and Conor has a question.

Conor Kleweno More just a comment and I'm okay to move on to the voting. I just thought that you know, saying there's 4 studies, but they're not RCTs. You know, we do consider well done prospective cohort studies. So I think maybe a more, sort of unbiased or whatever way you wanna say it is just, you know, that as you draw down your pyramid, there are 4 studies remaining and then I think you did a nice job of describing those well, you know, 3 retrospective one economic and sort of going through that. So I'm pretty comfortable to move forward with the vote. Personally, I don't think that I was convinced by, anything that you said to, to rereview. Very encouraged to hear what Sheila said in terms of a glioblastoma, cause in my brief research about it, it seemed where that was the most commonly discuss topic for this treatment. So I look forward to seeing the results of that trial in a few in a couple of years, I guess.

Josh Morse Yeah, and, just for the record the petition did provide a couple links to some unpublished news releases about ongoing studies that were sent to you as well.

Jonathan Sham Yeah, also just throw out there basically that there's an ongoing study of tumor treating fields and pancreas cancer that's supposed to end this year. So a lot more data coming down the pipe.

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Sheila Rege	And kudos to the company for really you know, trying to, Get the, the correct data about whether it works or not. I applaud the company for that.
John Bramhall	And Melanie is it correct that, following whatever decision is made, the HCA reaches out to the petitioner directly with some comment about, you know, finger on pulse and What have you? Is that true? You write to them directly? Okay, thanks.
Melanie Golob	Yes, yes. Thanks for the clarification.
Josh Morse	And they are in attendance today. Just looking at who is logged in. So yeah, but we will communicate with them and we've, we've worked with them for a number of months now and it's been I think from my perspective very good communication around this. So yeah, I agree with Dr. Rege. I said really appreciate how they've worked this and submitted the petition and the information.
Melanie Golob	Okay, so it sounds like ready to move. And I, Val, I'll let you lead the voting, but it will be through, through the same polling that you've been using.
Val Hamann	Yep, so if you want to jump over to ttpolls and that poll is live now.
Melanie Golob	And Val I'll stop sharing so you can share the results.
Sheila Rege	Actually, we couldn't vote that I could see.
Val Hamann	We have 9 responses. I will share that.
Sheila Rege	Okay. Oh, you have to abstained me. Okay, I good, I get it.
Josh Morse	Great. Thank you, Val. Thank you, Melanie.
Melanie Golob	Thank you.
Sheila Rege	Next.
Josh Morse	So yeah, go ahead.
Sheila Rege	We're actually about 8 min before so we can do a break if we're actually ahead of time. We have a break schedule before we discuss whole genome sequencing. Do we have our expert here, Dr. Amy Yuen already on?
Val Hamann	Yes, and Amy, if you could accept that promotion to panelists, that'd be great. There we go.
Sheila Rege	Amy, before we, go on break, would you, might, how do you stay, help me pronounce your last name? Is it Yuen?

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Amy Yuen — Yes. Yes, it's Yuen.

Sheila Rege — Yuen. Yeah, I know we've seen you before if you could, just introduce yourself briefly to us.

Amy Yuen — Yes, I'm Dr. Amy Yuen and I am a clinical geneticist. I am currently working at Kaiser Permanente. Previously I worked at Mary Bridge Children's Hospital and prior to that Wood Creek healthcare, working in the field of genetics and pediatrics. I did my training in Boston at the Harvard Combined Genetics training program and prior to the pediatrics residency at Massachusetts General Hospital and my medical school at Medical College of Virginia.

Sheila Rege — Thank you and welcome. We are going to take a break before we dive into the new topic. We will schedule for a 10 min break. Is everybody okay coming in at 9:05? Great. We'll see you back at 9:05 then.

Welcome back everybody. Thank you, Josh. Great, if everybody is good, we can start with the. Agency, the Medical Director presentation. Thank you.

Heather Schultz — Hello, everyone. I'm Heather Schultz. I am the Associate Medical Director for the PEBB and SEBB plans at the Health Care Authority and I will be providing the Agency Medical Director Group presentation for whole genome sequencing. Next slide. The evidence report is going to do a deeper dive into the technology of whole genome sequencing so I thought I would just provide a high level overview and reminder that whole genome sequencing is a laboratory procedure that is used sequencing the entire genome and it can be used at multiple different levels, the individual level, tumor tissue level or microorganism. For this assessment we are looking at whole genome sequencing in the context of the individual. Next slide, please. When you compare whole genome sequencing to other types of genetic testing, the big takeaways are that whole genome sequencing has the potential to expand the range of genetic variants that can be identified. A prespecified set of genes does not need to be targeted with whole genome sequencing, once the results are known in the future they can be reanalyzed when they're a new gene disease associations that have been discovered and there are different types of structural variants that whole genome sequencing can detect that other gene testing cannot. As a reminder of the scope of this review, we did not look at testing that was done in inpatient hospital settings or in research settings, both children and adults were looked at and the comparator care was any type of lab imaging, other genetic testing. A number of different outcomes were looked for in the literature, but primarily what was found was clinical utility. This list shows the different phenotypes that were included in

the studies in the evidence report and you can see moving from top to bottom that some of the studies looked at really broad clinical categories and then as you move down they funneled into more specific and then there were even a few studies that looked at specific individual diseases. Next slide.

After reviewing the evidence report, the agency medical director concerns were medium for efficacy, low for safety, and medium for cost. As a reminder, these are the evidence report key questions. There was limited evidence for safety and cost effectiveness. So a primary focus was on the efficacy of whole genome sequencing for this review. With that in mind, there are 2 questions that can arise to the top for efficacy considerations for whole genome sequencing. And the first is what are the potential benefits for using whole genome sequencing as testing and all of those benefits really derived from the potential for an increased diagnostic yield. The diagnostic Odyssey burden for rare genetic diseases can be large. For some patients and their families, they have months to years of lab testing, subspecialty referral without a clear diagnosis so if there is the ability to increase diagnosis for these diseases that would reduce the time and source burden for patients and families. There is the goal of, with increased diagnosis, being able to actually alter the treatment for those individuals as well as surveillance or monitoring plans for associated conditions associated with the diagnosis that are found. And then although the evidence report did not address the qualitative benefits, I do think that that's an important consideration for using whole genome sequencing. I mentioned the time and resource associated with the diagnostic odyssey burden, but there's also the psychosocial element of that burden as well. Having a diagnosis for rare genetic diseases also allows for additional family planning for future children and whether other family members should be tested. And it also provides an opportunity for those individuals and their families to be connected with support groups once they have that known diagnosis. So the other important question when considering efficacy for whole genome sequencing is what alternatives exist for testing. And I think that really depends on which patient population you're talking about. So for some genetic diseases, there are other workups that can be done and targeted gene testing that work as well as whole genome sequencing and coming to an answer. But I think the evidence suggests that there is a subset population of patients with genetic diseases in which there is not a good alternative for whole genome sequencing. Next slide.

Okay, this slide is pulled from the evidence report and shows the diagnostic yield evidence that was included in the evidence report and there are 2 important takeaways on this slide. One is that if you look at where the studies are falling the overall pattern you'll see that in most of the studies, they favored whole genome sequencing for increased incremental yield when compared to other forms of testing. The other important thing to note though is that second group of studies that were classified as separate cohort studies in the evidence report. You will see that there are a number of those triangles that are falling in the area of the graph that favors the comparator, but I think it's important to remember that these were not apples to apples cohort comparisons. So these are not studies that looked at a rare genetic disease, use the standard of care testing and then compared the same rare genetic disease and used whole genome sequencing and found an increased diagnostic yield with the standard of

care. A lot of these studies were, they were, most of them were not randomized. There was not a protocol for which patients got which type of testing. So there's a high risk of bias in some of these studies in which the more diagnostically challenging individuals had whole genome sequencing done and patients who had clinical phenotypes that were more suggestive of a disease that would benefit from targeted testing had different type of testing done. Next slide.

The 2 randomized controlled trials that were included in the evidence report are interesting. And I think shows some important evidence in that they were looking at similar types of patients and embedded in the study design was a single cohort type of design. So in these studies, not only did they compare 2 different groups, but they compared individuals and used them as their own control and those are the studies that have the greatest ability to show increased diagnostic yield. And both of those studies did show increased diagnostic yield for whole genome sequencing when compared to other methods. Next slide. So the first study was the Brockman study and that looked at both adult and children. They, these were patients who were seen in a variety of different genetic clinics and worked up as an outpatient. The largest patient populations came from the cardiovascular and the medical genetic clinics. The cohort sizes were similar and the initial takeaway makes it look as if there were similar efficacy in diagnosis between the 2 cohorts, the standard of care cohort and the cohort that got standard of care and whole genome sequencing. So, 19 diagnosis in the standard of care group and 24 diagnoses in the whole genome sequencing group. Next slide. But I think a very important additional takeaway is when they looked at the whole genome sequencing cohort those group of patients also got standard of care testing and they found that there were 9 additional diagnoses that were made with whole genome sequencing that would not have been made in that same group of patients had they just done standard of care testing. Digging into that a little bit deeper, we see that about half of those diagnoses are related to the primary phenotype that was the reason for doing the testing and the other half was related to other clinical phenotype findings and family history. And I think what is additionally important in this trial and the other randomized control trial is that there was the qualitative description that the clinicians reported an actual change in management or additional workup that will be done with that whole genome sequencing information. Next slide.

The second study was a study that focused on pediatric patients only. So these were patients who had leukoencephalopathy diagnosis. 2 patients ended up being diagnosed prior to randomization so the study ended up looking at 32 patients total. And this study also had patients serving as their own control so some, the first group of the first cohort had standard of care testing and whole genome sequencing done immediately. And the second group had standard care testing done for the first 4 months and if no diagnosis had been made at that point then those patients had whole genome sequencing done. And this study demonstrated much more diagnostic efficacy for that whole genome sequencing group compared to just using standard of care. Next slide. Of note also in this study the investigators found when they did the interim analysis of the first 32 patients that the benefit of treatment for the patients in that immediate whole genome sequencing group who didn't have to wait the 4 months was so beneficial that they

changed the study design so that they removed the cohort that had the delayed whole genome sequencing and are just doing an observational study moving forward. And that was because there were no individuals who were in that immediate cohort who received a diagnosis with the standard of care testing, which was primarily targeted gene testing and although there were 5 individuals who over the course of 4 months were able to find they were able to find a diagnosis that was smaller than the 14 individuals that were able to be additional, the additional individuals that were able to be diagnosed by whole genome sequencing. This study also called out again that there were changes to clinical management that were coming from those whole genome sequencing diagnoses. So referral to warranted some specialty follow-up initiation of specific disease therapy or prognostic counseling. Next slide.

So for safety and harm considerations for whole genome sequencing, the safety and harm considerations are pretty low since it is a procedure and the procedure itself does not have safety or harm considerations and the considerations are primarily related to what to do with the results. So there are variance of unknown significance in which it's not clear if those variants are related to the patient's clinical phenotype. There are secondary findings which are findings that are unrelated to the patients reason for having the testing done. So as an example, a patient could have congenital anomalies and be worked up for that and then have a finding of BRCA gene mutation. And that's typically addressed by genetic counseling that's done primary to the testing to have patients and families make informed decisions around what secondary findings they want reported. And then there is the possibility of rescinded diagnosis or essentially false positives where a variant is initially felt to be responsible for the patients clinical phenotype. But with additional testing or workup is found not to be the case. Next slide. So as stated, there was fairly limited evidence regarding safety and harm, there were 2 trials that were included in the evidence report. One just looked at variance of unknown significance frequency in whole genome sequencing and then compared that to other types of genetic testing and found a lower rate in whole genome sequencing and whole exome sequencing. And the second study looked at rescinded diagnosis after either type of next generation sequencing testing and found a fairly low rate. But again, neither of these studies, I think, add much in terms of helping to figure out whether safety concerns are considerable for this type of testing. Next slide.

For cost considerations for whole genome sequencing, the important things to think about are that the cost of performing the test has continued to decline over time. It was very difficult to get a firm handle on what the specific cost of testing is currently in 2024. There is still a difference between whole genome sequencing and other genetic testing. But exactly what that difference was, was hard to, hard to quantify. Another consideration to think about is that diagnostic yield is increased when dual or trio testing is done and that's when either a sibling is tested along with the patient or both parents so obviously sending out multiple tests increases the cost of the testing. But on the other side of the equation, whole genome sequencing could be used to replace or reduce testing that's currently being done so those costs would need to be considered as well. And this is an area where downstream savings are pretty difficult to estimate because of the rare and heterogeneous nature of genetic diseases and the different types of

treatment. Next slide. So with that mind, there were 2 trials that were included in the evidence report. Both of them were just, decision analysis models so these weren't looking at real patients but trying to model out comparing costs of whole genome sequencing to standard of care and as you can imagine from doing those sort of decision analysis models is easy to reach different conclusions, which is what happened in this case where one study did report that whole genome sequencing was more cost effective, less expensive and identified more diagnoses and the other said it was more expensive. Next slide.

An important HTCC decision that was made in the past that is relevant to the whole genome sequencing discussion is whole exome sequencing that was reviewed in 2020 and is currently a covered benefit with conditions. Next slide. And the reason that it's important to think about these 2 testings together is because they are both next generation sequencing technology. They're both using the same clinical scenarios where either a targeted gene is not known or the targeted testing that's been done has been unrevealing. Whole genome sequencing sequences as discussed the entire genome. So there are noncoding portions of the genome that can provide some additional information that whole exome sequencing is unable to identify. As mentioned before, whole genome sequencing also can detect some structural variance that other genetic testing cannot. And there was a similar PICO that was used in both these health technology assessments so whole exome sequencing also looked at children and adults looking for a genetic diagnosis. Next slide. This is also pulled from the evidence report and compares the diagnostic yield to whole genome sequencing and whole exome sequencing. Again, you see in the pattern on this graph that whole genome sequencing is favored when compared to whole exome sequencing, again, with the caveat of the separate cohort studies, you do see some again, but these are not ones, I want to remind folks that are comparing same diagnosis, same diagnosis, whole exome and whole genome, but comparing sometimes 2 different types of genetic diseases and there's that risk again of a skew of more diagnostically challenging patients ending up getting whole genome sequencing. Next slide. So this shows current utilization of whole exome sequencing, which we thought would be useful to use as a proxy for whole genome sequencing since in some of the same clinical situations it would be used. You can see that the volume is pretty small overall and you'll also note that there are more claims for the test then unique clients or patients and that's because of the duo or trio testing that was mentioned earlier. Next slide.

So the current state of coverage from state agencies is it's considered investigational for the PEBB and SEBB UMP plans. It's reviewed for medical necessity on a case by case basis for Medicaid and it's not covered for L and I because it's not relevant to a job related illness or injury. This slide I won't spend much time on. It is a, a slide this is the current utilization of whole genome sequencing which as noted because of the non-coverage is pretty small. As you can see with the cost information the payment that information also was a little bit conflicting because it looks like lower cost in 2022 than 2023. So I think the main takeaway this slide is that there's not currently large utilization of whole genome sequencing. Next slide. There are certain large payers that are currently covering whole

genome sequencing with criteria and there are others that have not yet moved toward doing that. Next slide.

There are a number of clinical practice guidelines that recommend the use of whole genome sequencing and there's a broad range of how specific those guidelines are so some talk just about specific diseases. The one guideline that we believe offers the most detailed recommendations with the best evidence base is the 2021 American College of Medical Genetics and Genomics guidelines. And those guidelines strongly recommend they look at both exome sequencing and genome sequencing as first or second tier testing in a targeted patient population. Next slide. This slide just demonstrates some of the efforts that went into that guideline. They did a review of 167 studies. They noted that there was emerging evidence that there's therapeutic benefit. And as we discussed, limited concern for negative outcomes because of the nature of the test itself. And then also advised in that last bullet point that it really is for a targeted set of patients and wouldn't be recommended for just first line testing for a large group of any patient. Next slide.

So to summarize what our considerations. We're, when making our recommendation. I went to start by just saying that genetic diseases are rare, they're heterogeneous and it makes the evidence base a bit challenging. So the diseases themselves do not lend themselves to large randomized controlled trials. So I think the evidence that is most useful for determining efficacy for whole genome sequencing is really looking at is this the test that can increase diagnostic yield, alter treatment plans and maintenance for patients with rare genetic diseases. And I think the answer to that question is yes, looking at the higher incremental diagnostic yields that we're seen across all study groups. Again, with that caveat that for some of the separate cohort design studies, which we're not comparing apples to apples, there's a skew there that makes whole genome sequencing look like it's performing worse and I don't believe that it actually is. But if you look at the studies that are using individuals as their own controls, those clearly support the use of whole genome sequencing. And another thing to take into consideration is that we are currently covering whole exome sequencing with criteria and whole genome sequencing has been demonstrated to provide increased diagnostic yield over whole exome sequencing. So our recommendation is coverage of whole genome sequencing with criteria that aligns with whole exome sequencing. So that would be limiting that this type of testing to individuals with congenital anomalies or moderate to severe intellectual disability or developmental delay. It would be in the context of being ordered by a geneticist with genetic counseling being done. Of course, we would want alternative non-genetic causes to be rolled out first and then again, this is really for not just any clinical situation in which there is a genetic ideology that's suspected, but one in which it's felt that targeted genetic testing is not going to yield a diagnosis. Next slide. And that concludes my presentation.

Janna Friedly Looks like, Connor, you have a question?

Conor Kleweno Yeah, could you go to the previous slide just with your recommendations and thank you for that presentation very concise and a great review.

	I was, had a question on your 4th bullet. Do you think that would need to be specified, beyond what the, sort of recommendation of a genetics would already have sort of decided. Because I agree with the second bullet point for sure. I just wonder if, that's needed if we are going to assume that this is going to be regulated by a by a you know formal geneticist managing this and I wonder if that would be under their medical clinical decision making.
Heather Schultz	Yeah.
Conor Kleweno	But I am not an expert in this field. So if that question is, is not a good one, I apologize.
Heather Schultz	I think that's that's an excellent question and one that might be good to punt to Dr. Yuen as well. I don't know if there would be situations in which a geneticist would skip pass a targeted test and do whole genome sequencing instead. But it does seem. I think it's an important guardrail to add in. I agree with you that it would probably be few scenarios in which a geneticist would think that there was a targeted test that's going to give them the answer and they would skip to something that much broader.
Conor Kleweno	Yeah.
Heather Schultz	But I don't see it. I don't see it as a barrier. That would interfere with the geneticist ability to select the test that they thought was most appropriate.
Conor Kleweno	Okay, now obviously we'll have time to discuss our thoughts as a group. I just wanted to know if there was a specific reason that you had based on your review to separate those 2 and that was my question. So thank you very much.
Sheila Rege	Anything else? Any other discover? Dr. Schultz, that was an excellent presentation. Thank you so much. Any other question?
Heather Schultz	My pleasure.
Sheila Rege	Let's go on then. I think we're too early for public comments, correct? Josh?
Josh Morse	Yeah, we're about 20 min ahead of the scheduled public comment time. We do have a number of people that are signed up in advance. Val do we know if those.
Val Hamann	We have all 4 of those representatives right here right now. So.
Josh Morse	Okay. So I think we could do public. Comment now, yeah.
Sheila Rege	Would you like to open it up? Okay, then let's go ahead and do that.
Val Hamann	Okay, our first group today, I will promote to panelists and there we had a number of sign ups for the Seattle Children's Hospital. And they will have 8 min to speak. You just wanna

make sure Dr. Dipple is looks like everything's working well. So just as a heads up I will give a couple of reminders as your time is getting closer to concluding. And then once it has concluded, I will let you know. Okay, so feel free to start when you're ready.

Katrina Dipple

Great. Good morning, everyone. Thank you for the opportunity to speak with you today about whole genome sequencing. It is exciting that the state of Washington Healthcare Authority has selected whole genome sequencing for this health technology review. Knowledge of the genetic basis of pediatric diseases has increased exponentially over the past decade, with genetics playing a role in virtually all pediatric conditions. We are now positioned to capitalize on this information and revolutionize pediatric health care. Specifically, use of whole genome sequencing increases diagnostic rates, enables faster diagnosis, reduces costs and increases access to life-saving precision therapies. But whole genome sequencing is not available to most children suspected of having a genetic condition, particularly children from underrepresented minorities. This creates a major health and equity and this disparity will grow in the state of Washington without a changing coverage policies. I am here today to offer our opinion as to why we think it is critical to make whole genome sequencing accessible to all children.

My name is Katrina Dipple and I have been a physician and clinical geneticist for over 20 years. I'm currently the medical director of genetic medicine at Seattle Children's Hospital. Today I'm speaking on behalf of myself, my colleagues, my patients, and Seattle Children's Hospital. Because my comments must be brief, I want to address some of the concerns raised in the health technology assessment and describe our experience with whole genome sequencing. The health technology assessment noted high concerns for safety, including potential to identify so-called variance of uncertain significance or VUS's. These variance of certain significance occur when there is a change in the DNA of the gene, but there's not enough evidence for the diagnostic lab to assert whether it is benign or disease-causing. The assessment noted correctly that the VUS or the VUSs are found less often in results from whole genome sequencing compared to testing using multi gene panels and virtually at the same rate as whole exome sequencing. But even when a variant of uncertain significance is reported, the concern for safety is no different than the uncertainty associated with use of many clinical tests. And indeed, up until the technology for exome sequencing was developed, my colleagues and I spent much of our time explaining the uncertainty of clinical diagnosis into families. So we are familiar with the anxiety by some families when a variant of uncertain significance is reported and how to interpret and frame the result to minimize potential harms. Indeed, there is considerable data that such anxiety is short lived and most potential harms are never realized by families. Moreover, the ability to adjudicate these variants and minimize the reporting of variance of uncertain significance or reclassifying a previously reported variant of uncertain significance to benign or disease causing is rapidly improving as testing by whole genomes sequencing scales. The health technology assessment noted the reported efficacy of whole genome sequencing varies widely. If used as a first line test. whole genome sequencing has an increased diagnostic yield compared to any other single test or combination of tests. In other words, it is the single most effective test for making a precise genetic diagnosis in a child. And whole genome sequencing is getting better every month.

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Indeed, my colleagues and I are currently studying not whether whole genome sequencing is the single best test to use, but what type of whole genome sequencing is the best test to use. As eventually virtually all genetic testing will be done by whole genome sequencing of one sort or another. This is partly due to the observation that the difference in diagnostic yield between offering whole genome sequencing at point of care versus the stepwise conventional testing. Again, in one of our ongoing studies, the diagnostic yield of whole genome sequencing and critically ill-born critically ill newborns is fivefold higher than conventional testing and in young children with developmental delay, it is threefold higher than conventional testing. Whole genome sequencing is an expensive laboratory test but cheaper than many types of testing commonly done to make a precise genetic diagnosis. Whole genome sequencing used as a first tier test is less expensive than the use of multiple genetic tests in succession. Moreover, the cost of whole genome sequencing continues to drop as testing is scaled because every step in processing and analysis can be automated. Use of whole genome sequencing as a first tier test also often shortens the diagnostic Odyssey considerably, typically from years to weeks. This gives care providers an unprecedented opportunity to intervene and prevent substantial morbidity and mortality, improve the quality of life with resultant reduction in health care costs. Finally, use of whole genome sequencing as a first tier test overcomes many structural barriers and biases that limit genetic testing and underserved populations and underrepresented minorities. This substantially improves access to a precession, precise genetic diagnosis and builds capacity for equitable precision genomic medicine. Since our time is brief, I would like to tell you about one patient that illustrates the potential benefit.

Val Hamann 2 min remaining.

Katrina Dipple For whole genome sequencing as a first tier test. His parents were eager to have his story shared with you today and gave permission for his name to be used. Evan is now 16. He was born full term after a normal pregnancy. He was born with club feet and was a little floppier than most babies, but it didn't impact him and he was sent home with his parents at the normal time. Over the years, it was evident that he had developmental delay despite extensive genetic testing and over 800 clinical visits over the course of his life, he remained without a precise genetic diagnosis. This past April, Evan collapsed in gym class at school due to cardiac arrest. Upon admission to our critical care unit, whole rapid whole genome sequencing was ordered. To everyone's surprise, whole genome sequencing revealed he had myotonic dystrophy. Myotonic dystrophy is due to a type of genetic variant that cannot be detected by whole exome sequencing or any of the tests Evan had over the first 16 years of his life. Moreover, his mother was tested and found to also have myotonic dystrophy and at risk for sudden cardiac deaths. Following Evans diagnosis, he had an implantable defibrillator placed. If Evan had access to whole genome sequencing earlier in his life as children today do, his cardiac arrest, hospitalizations, hundreds of hospital visits, tests, and the associated morbidity.

Val Hamann 30 seconds.

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Katrina Dipple — Would have been avoided. There are hundreds of kids like Evan with severe genetic conditions who lack a precise genetic diagnosis despite exhaustive testing and evaluation. Greater access to whole genome sequencing can change that. Thank you.

Val Hamann — Thank you for your comments today. Before we promote the next individuals, could anybody else that is not pre up today and wishes to speak today, please raise their hand. So we can make note of that. Okay, great. And we have our Next representative, you will have 4 min if you could once you get started again I will give you a heads up at 30 seconds so Ashley feel free to begin.

Josh Morse — Yeah, and before we get started, we just. Remind public commenters to please state if they have any conflicts or if anybody paid for them to be here today and just a reminder to committee members to. Just keep your cameras on as much as you can during these meetings. Thanks very much.

Ashley Arthur — Hi, good afternoon everyone. My name is Ashley Arthur. I'm the head of market access at GeneDx. We are a leading national genetic laboratory. We do focus on rare disease diagnostics. I'm here today to voice our strong support for Washington State Health Care Authority covering outpatient whole genome sequencing for the diagnosis of pediatric onset rare disease. Whole genome sequencing has revolutionized the field of genetics as we've heard already today, providing a comprehensive tool to identify the underlying cause of rare and often debilitating conditions. This powerful technology is becoming increasingly accessible to those with commercial insurance. This quickly expanding commercial coverage is enabling earlier and more accurate diagnoses for countless families. Currently, approximately 40% of commercially insured patients in the US, including those with UHC, Cigna, and Centen plans have access to genome in alignment with professional society guidelines. And I give that number, and want to say that some of these coverage policies have an effective date of July first and so I'm talking in the future a little bit but just a few days. However, as commercial insurance grows, there is a fast growing disparity in access for patients covered by Medicaid. Only 16% of Medicaid beneficiaries in the US today have coverage for a genome and without access to comprehensive genetic testing, patients face prolonged diagnostic journeys, this not only delays achieving the optimal treatment plan and avenues of support these children and their families desperately need, but it also results in higher overall health care costs. And we know the Medicaid population is enriched with medically complex patients who will likely be insured by Medicaid for years to come. In wonderful timing, there was an article published by the New England Journal of Medicine last week and it showed that 61 of the 218 families so about 29% of those receiving diagnosis from genome in the study had variants that required a genome for detection. No other test would have given these 61 families an answer. Obviously, all previous spin on diagnostic testing for these patients could have been saved, but avoiding the diagnostic Odyssey comes with many other benefits. And you can imagine some of those, but some that come to mind are less referrals to specialists these families have to navigate fewer trips to the emergency room, fewer nights spent in the hospital, less painful invasive tests, less ineffective treatments and the side effects that come with them, lower transportation costs, less time off work,

and often significantly improved outcomes thanks to early treatment and interventions for these families. As the pre meeting materials acknowledged and was mentioned earlier, there is limited published evidence about the clinical utility and health outcomes related to a genome diagnosis specifically. However, there is an abundance of published evidence and clinical experience that tells us about the power of achieving a genetic diagnosis by any means. So published studies have shown that greater than 70% of patients have a change in management following a genetic diagnosis. Whether a patient receives a diagnosis via a genome or another genetic test when they're able to stop intractable seizures with proper medication or have a dietary change that stops progression of the metabolic condition or take a growth hormone that lets them develop properly, the impact is just as powerful. So because there are greater than 10,000 genetic or greater than 10,000 rare diseases, 80% of which are genetic in nature.

Val Hamann 30 seconds remaining.

Ashley Arthur Genomic sequencing is often required to make these difficult diagnoses because I know it was talked about earlier, the targeted genetic testing that might be used, but, but it's hard to identify which targeted test to use for many of these patients. So by extending coverage to include whole genome sequencing, you can ensure that all children, regardless of their insurance status, have equal access to this life changing diagnostic tool and it also will bring health equity by making sure that that all these patients can achieve a diagnosis. So thank you for your thoughtful evidence review and the opportunity to share my comments with you today.

Val Hamann Thank you for your comments. We're promoting the next group and Max, you will have 4 min to present today, so feel free to start when you're ready.

Max Brown Alright, thanks so much for the time. So my name is Max Brown. I'm here on behalf of the Northwest Rare Disease Coalition. This is a statewide organization comprised of rare disease patients, caregivers, and family members who worked to advocate for policy change to improve healthcare outcomes for Washingtonians impacted by rare disease. I wanted to first start by thanking the Health Care Authority and HTCC for taking up consideration of expanding access for outpatient whole genome sequencing in Washington state. The fact that we're here today is part of a forward-looking conversation means that we're collectively making progress by considering a broader range of diagnostic options to help individuals with genetic disorders in Washington find appropriate treatment pathways more quickly and that's important to notable. Achieving a diagnosis can lead to better access to therapeutic interventions or initiate changes in clinical management, but just as often and equally important for families achieving diagnosis gives them the opportunity to engage in anticipatory planning, connect with complex care coordination services or become eligible for other social supports that can help take some burden off patients and caregivers. As you probably already know, where disease is classified as any disease that affects fear than 200,000 people in the US Although individual diseases might be rare, collectively rare diseases impact about one in 10 people in our country. About 30 million people nationally are about 750,000 people in Washington state alone.

And as other presenters have noted roughly half of rare disease patients are children. Now, 80% of rare diseases are genetic in origin, which is one important reason that I'm here today to encourage the adoption of a coverage policy that would broaden access to whole genome sequencing. Particularly for patients whose conditions are of an unknown origin. Now the first priority of the patients and families who participate in the Northwest Rare Disease Coalition is to work to end the common experience of what's called the diagnostic Odyssey. The diagnostic Odyssey is an average 5 to seven-year period of time when patients wanted the healthcare system seeking answers to explain the devastating impacts of debilitating illnesses affecting themselves or their loved ones. During this diagnostic Odyssey patients see an average of 8 separate physicians and typically experience misdiagnoses along the way. They're often subject to unnecessary testing or treatments that might address symptoms but not the root causes of their illness. And I'll also add that time is of the essence for our disease families given that half of rare disease patients are children, the diagnostic Odyssey also means that families often miss key developmental milestones along the way when an earlier diagnosis and access to more appropriate treatment pathways could have averted the needed for more invasive or costly or interventions later on. So as a coalition, our number one priority is addressing the diagnostic Odyssey because of the immense hardship and costs that families face during this difficult period of uncertainty. The emotional and psychological distress visited on families during the Odyssey is profound and so we look for moments when structural policy change becomes possible to create off-ramps for families out of the diagnostic Odyssey and towards achieving diagnosis. Whole genome sequencing coverage expansion through this process is one opportunity we think will have a meaningful impact on chronically undiagnosed patients in Washington state. There are over 7,000 known rare diseases and so it would be impossible to expect any individual clinician to know exactly what to look for when presented with a rare disease patient in the course of providing care in the communities that they serve. But what we can do and what I hope the HTCC will move forward with as it considers this expansion policy is give clinicians a more comprehensive diagnostic toolkit to deploy when more conventional sequential testing isn't yielding the answers they seek. Widing the guardrails of coverage to encompass whole genome sequencing, it's a meaningful step forward and averting the diagnostic Odyssey for more patients and will lead to better health care outcomes for patients while lowering costs for families in our health care system as a whole.

Val Hamann — 30 seconds.

Max Brown — Thanks so much for your time, consideration today.

Val Hamann — Thank you for your comments. Just want to send out another request as we are coming up on our last group that was signed up. So if there was others in attendance today that have not signed up but do wish to speak today please raise your hand so we can make note of that. That was my timer. Okay, Jesse, feel free to take it away.

Jessie Conta — Thank you, Val. Good morning, everyone. My name is Jesse Conta. I'm a genetic counselor by training and I've experienced in Pediatric genetics and laboratory stewardship and I'm here providing comments on behalf of PLUGS and I serve as a co-founder for that

organization and now in a consultant capacity. And just want to thank the director for agreeing to review whole genome sequencing as a topic today with you all. For brief background PLUGS is a national nonprofit laboratory storage of collaboration. We have over a hundred members across both the US and locally here in the Pacific Northwest and what's unique about the group is it represents labs, hospitals, patient advocacy groups, and now payers with the goal of ensuring that patients get access to medically appropriate testing at the right time and that we can balance avoidable financial liability not only for patients and families but also for the health care system so including payers. Insurance alignment is really critical to plugs missions, so really trying to connect the dots when something is new and research using the appropriate funding to cover that but as evidence evolves, ensuring that we get that into the hands of patients that can benefit from it is really important. And so the folks who've presented ahead of me have done a really nice job of highlighting the importance and power, I think that whole genome sequencing can have particularly in rare disease. In support of PLUGS mission one of the focuses we do is to create coverage policies I know I've shared feedback through this process with the committee about our approach to developing those which is when it the evidence meets that threshold to kind of provide an open doorway to get access. And so we worked closely with the community in 2019 for our whole exome sequencing coverage and we're just delighted to see that you're considering, you know, expanding on that to consider whole genome sequencing coverage as well. Ashley nicely pointed out that I think we're really right at a tipping point. We're seeing coverage from national payers and other smaller groups to be more favorable in offering this is coverage for this important tool for patients with rare disease but as Ashley pointed out coverage isn't universal yet. So I think this is a really important step for patients here locally to ensure that we don't have pockets of population that that aren't getting access this tool. We really don't want our patients with Medicaid to be left behind. So we encourage the adoption of this tool. We really think the time is right for it. But also while advocating for adoption, I just wanted to highlight the cost effectiveness concerns that were included in the report, which by the way was really thoughtful. One of the pieces I thought that was really helpful that was pulled out was the fact that finding evidence is this population of patients is really challenging and that the rubric for assessing that evidence should be, should be considered and so I just you know really commend the folks who put the report together for, for pulling that that piece out. So in terms of cost, I do think it's appropriate to consider what the clinical lab fee schedule says and how to perhaps suggest that similar to what you did for exome sequencing so that so that it's a responsible use of Medicaid resources but ensures access to this test and you know when it's used as a first line test, but ensures access to this test. And you know, when it's used as a first line test really is most cost-effective and shortens that diagnostic odyssey for patients and families. We submitted a copy of the PLUGS consensus policy that can be adopted for this process and would be delighted to serve as a resource to the Health Care Authority as you develop criteria. Hopefully that's the outcome from this. And so I just want to thank you again for reviewing this topic and for allowing us the opportunity to share our perspective and look forward to hearing your additional discussion today. Thanks, everyone.

Val Hamann — Thank you for your comments and I did not see any other raised hands for any other public comments today.

Washington State Health Care Authority

Sheila Rege We are in the timeframe for public comments, correct, right now?

Josh Morse We are. Yep.

Val Hamann Correct.

Sheila Rege Perfect. This is the time we, go on just a 5 min break. And we could do that and we're gonna come back. We could ask for public if there any public comments with that. Would that be okay with the committee? Hearing no objections, we're going on a 5 min break.

Josh Morse Thank you.

Sheila Rege I think it's been 5 min. I see. A lot of our committee members, we could go to beginning the, is there anybody, can we do a call out for any more public comments, please?

Josh Morse Val may still be away. We can.

Val Hamann I'm not seeing any hands raised.

Josh Morse Oh, thank you.

Sheila Rege Great. And we will go ahead with the evidence report, please.

Leila Kahwati Alright, thank you very much. I'm gonna share my screen. Can you all see the screen? The slides? Okay, great. Hi everybody.

Sheila Rege Yes, thank you.

Leila Kahwati Good morning for you all. I'm Leila Kahwati. I'm happy to present the evidence report for whole genome sequencing on behalf of our team who are listed on this slide, some of whom are on the call with me today. Here's brief organization of today's presentation. This slide includes many of the abbreviations that are used within the report and the presentation just for your reference. First a little background. I know you've already heard quite a bit about whole genome sequencing, so let me take you through a few of the key background points and then we'll dive into the evidence. So as you know, there are many rare disorders, some estimate over 7,000 that afflict between 6 to 8% of the US population and more than a 3rd of those are known to have a genetic origin but not all of those have treatment available. One thing to note though, however, and that's sort of represented by this tsunami wave on this slide is that nearly 250 disease gene relationships are being identified each year in the current era of genomic testing. So we may see many more diseases established as having a genetic origin in to the future. This slide is intended to put up the whole genome sequencing into the larger context of genetics testing. There's really 2 categories of genetic tests those that target the level of the let me turn my laser pointer on, here those that target the level of the chromosome which are those represented here at the top of the slide and then test the target sort of the DNA base pair level and those are here at the bottom of the slide. Historically, first-

tier genetic tests have included things targeted to the chromosome, including, including things like karyotype, fluorescent insight to hybridization in most recently chromosomal micro array testing. And then historically, Sanger sequencing has been used to interrogate the DNA base pairs associated with single genes or with multiple genes. Bu t the development of next generation sequencing platforms, also known as NGS, have largely replaced it. However. Sanger sequencing may still be used for confirmation of gene variants that are identified by NGS. Once important to note here is that the same NGS platforms can be used to evaluate for variance in a single gene or in multiple genes as part of a targeted gene panel. The entire exome, which refers to the protein coding regions of DNA that represent one to 2% of the whole genome or the entire genome also known as whole genome sequencing.

The next series of slides describes the whole genome process for some context. This is the simplified depiction, but I hope it illustrates the complexity involved in this testing. Relative to other lab tests. The first step is to cut genomic DNA into about 3 billion nucleotide base pairs and cut that into random small fragments. And then these fragments are passed to a sequencing machine that sequences the resulting fragments. Unlike Sanger sequencing, which is done sort of one gene at a time, the sequencing of these fragments occurs in what's called a massively parallel process. One thing to note is that sequencing the entire genome actually now takes less time than sequencing the exome because for whole exome sequencing and this is also true for multi gene panels there's a step in between DNA extraction and sequencing that gets rid of the non-exome regions of DNA before it goes on to sequencing and that additional step actually adds time for the process of sequencing, it adds a more complex workflow and that's 1 reason that whole genome sequencing is favored in acute settings for critically ill patients. And when experts talk about workflow efficiencies from whole genome sequencing, this is often what they're referring to. It's 1 less step then whole exome sequencing and multi gene panels which are typically based off of an exome backbone. In addition to sequencing being done in parallel, the use of bioinformatic algorithms and databases are what really characterized next generation sequencing from earlier sequencing methods. Once a patient's DNA is sequenced, the bioinformatics tools help to identify differences between the person's genome and a reference genome because of the volume of gene sequence that comparison cannot be done manually. It does require the use of computers and bioinformatics tools. What's key to appreciate here is that the same next generation sequencing platforms are used for whole genome, whole exome, and most of the multi gene panels. Identifying variants causally related to a person's phenotype is complex for a variety of reasons. The volume of variants that might be flagged by these bioinformatics tools could be in the hundreds to thousands or more. Information from parent or sibling genomes needs to be or can be incorporated into the interpretation that adds complexity. And then lastly, there's the knowledge on disease gene relationships associations is constantly evolving and being updated. As mentioned on the previous slide, the process of interpreting variance between somebody's DNA and a reference genome begins with automated variant filtering and prioritization using these bioinformatic databases and tools. In combination with detailed information about the patient's phenotype and this sort of filters things down to a smaller pool of genetic variance that a team of human scientists manually then review. This team uses genetic databases, the research literature,

statistical modeling, and additional clinical phenotype or epidemiologic data to make judgments about whether the variants that are identified from the comparison to a reference genome are causally related to the patient's phenotype.

After the variants are thoroughly reviewed and analyzed by the team of scientists, a clinical results report is generated. Variants that reside in genes associated with disorders that overlap the patient's phenotype or clinical condition and that are known to be pathogenic or likely pathogenic are included in the clinical report. In some cases, variance of uncertain significance or VUS may also be included in the report if there's some relationship with the phenotype or other supporting data that suggests the relationship. So patients for whom a pathogenic or a likely pathogenic variant is identified are usually considered as having a molecular diagnosis. And so when we talk about diagnostic yield as an outcome, we're really talking about a molecular diagnosis. If the patient has or the family has opted in, a variance in a defined set of genes not associated with the phenotype but which are considered medically actionable or that have reproductive consequences for example like a BRCA mutation, are also included in the clinical report. Again, if the patient and family have opted in.

The clinical report is then returned to the ordering clinician and to the patient and then clinicians compare the reported variance to the patient's phenotype to confer a clinical diagnosis if that's appropriate. Secondary findings may be shared at that time if the families opted in. Reanalysis can be offered to patients who do not receive a diagnosis at least, after a year or so or more. The DNA itself is not re-sequenced during reanalysis. Rather, the variants are just reinterpreted through the lens of updated bioinformatics tools and evolving databases of disease gene relationships. Relevant to the HTA that we conducted is that there's sort of 2 flavors of whole genome and they're whole genome that are conducted in a clinical laboratory ordered by clinician in the context of an existing patient-provider relationship. These are labs in the US that would be CLIA certified for high complexity testing and that routinely perform a variety of clinical diagnostics. They're either usually hospital-based or commercial labs. There's also research whole genome and these are tests conducted in an academic or research laboratories that are not necessarily CLIA certified. The results are not intended to be used specifically for diagnostic purposes and these results are supposed to be confirmed in a clinical ad prior to being used for diagnosis. Whole genome performed on the patient is referred to a single 10 whole genome and variant interpretation in patients is bolstered by the availability of sequence DNA from close relatives such as parents or siblings and this is referred to as trio or duo testing. In addition, there is a distinction between standard whole genome and rapid whole genome where the sequencing, whereas the sequencing steps are the same in both rapid whole genome takes some shortcuts during the analysis phase to be able to turn around the results in a matter of hours to days as opposed to weeks to months with the standard process.

In terms of regulatory status of these tests, the FDA has the authority to regulate the safety and effectiveness of in vitro diagnosis, which generally refers to test kits that are manufactured and sold. But that's not how a whole genome works. There's a bit of

debate over whether whole genome is a test or a clinical service. And clinical whole genome is performed as a laboratory developed test and up until very recently, the FDA has not regulated laboratory developed tests. Laboratory developed tests fall under the purview of the clinical, clinical laboratory improvement amendments or CLIA, which is governed by CMS. CLIA, you know, regulates the general laboratory procedures used by clinical labs, but CLIA does not regulate specific tests. And further CLIA generally only applies to procedures for ensuring analytic validity. The clinical validity and utility are not governed by CLIA. And one interesting development that occurred while we were conducting this review is that in April 2024, the FDA issued a final rule that clarifies its authority to regulate laboratory developed tests as medical devices and it's intention to phase out the enforcement discretion it had been using for many years to start regulating these tests as medical devices. So, laboratory developed tests except for those that were commercially available prior to the issue and so the final rule or those that are conducted in labs associated with a health care system to meet an unmet patient need or when there's no FDA authorized alternative available will still be able to be used as laboratory developed tests. So it's not really entirely clear what the effect of this new rule will have on the availability and access to whole genome in the future.

The rationale as you've heard from Dr. Schultz for the use of whole genome is very similar to the rationale for the use of whole exome sequencing. Experts claim it may avoid or significantly shorten the diagnostic Odyssey, speeding the time to an appropriate intervention and guide disease management and alleviate patient and family burden. In terms of selecting whole genome over whole exome, both have high accuracy for identifying single nucleotide variants. Experts claim the whole genome is more accurate for identifying insertions, deletions, copying number variance, structural variance, variants that are in the intronic regions and repeat expansions. And as the knowledge of disease gene associations have increased and next generation sequencing technology, including both the sequencing and the analytics have improved and dropped in price whole genome has become nearly as feasible as whole exome and proponents suggest again it offers a more efficient workflow than whole exome particularly when the phenotype does not point to a clear targeted gene panel for testing. So the policy context for this is that as you heard in 2019, or I guess the report was in 2019 the coverage decision was in 2020, approved whole exome as a covered benefit with conditions. At that time, whole genome was not in widespread clinical use and so it was not reviewed. So the state selected whole genome in this round for use in output to review its use in outpatient settings because of high concerns for safety and costs and medium concerns for efficacy. One thing to note is that whole genome sequencing used in critically ill patients in acute inpatient settings such as the NICU, PICU, is already a covered benefit under the inpatient prospective payment system so it was not addressed in the review that we conducted.

Briefly, our methods, here's the analytic framework for our reviews. You can see we had one efficacy question or eat what we call EQ, one safety question or SQ and then one cost question. Here are the key questions that correspond to that analytic framework. In addition to the key questions on efficacy safety and cost. We also included a contextual question related to the diagnostic yield of whole genome based on systematic reviews

from just the past 4 years. To provide additional data beyond the scope of the studies that were included in, in the HTA. This slide is a summary of our study inclusion and exclusion criteria. We focused on persons of any age with suspected genetic disorders. We included standard or rapid whole genome alone or in combination with other diagnostic tests. We also included whole genome reanalysis. For comparator tests, we included usual genetic or non-genetic diagnostic evaluations which included things like single gene testing, multi gene panels, chromosomal micro array testing, and whole exome sequencing. We looked for studies reporting clinical utility, which includes diagnostic yield, health outcomes, non-health outcomes, not health outcomes such as psychosocial outcomes or patient experience. Cost effectiveness measured using US space cost inputs. And then for study designs, this is the only real difference between this review and the whole exome review is that we required a comparator group or a comparator test for the efficacy outcomes, but we did allow single-arm studies for harm outcomes.

Here's a brief summary of our search strategy and our other review methods. Our search was from 2013 through last October. We qualitatively synthesized findings for each key question and we rated the certainty of evidence using the GRADE approach. For rating the certainty of evidence we rated the outcomes that are listed here at the top of the slide. The rest of the slide is really just a for how grade certainty ratings can be interpreted. As a reminder, certainty of evidence applies to the body of evidence for a given comparison in outcomes, it doesn't refer to an individual study or the risk of bias of an individual study. Although that's certainly a consideration that is incorporated into the certainty rating. Other considerations include consistency, cross studies, precision of estimates, publication or reporting bias, and the directness of the outcome being measured.

So moving on to the findings, this slide depicts our search yield. We identified 35 unique studies, 32 of them addressed the efficacy key question, two address the safety key question and two address cost-effectiveness. I'm gonna walk through the study in population characteristics of the included studies on the next few slides. There was only one study that was completely funded by industry. There were 8 studies that had partial industry funding. Most studies actually reported did not report any funding support. This is because they appear to be retrospective analyses of data collected through routine clinical care. Just under half of the studies were conducted exclusively or partly in the US, 3 in Canada, and then the rest were conducted in other countries in the world. In terms of age of participants, over half of the involved studies analyzed data from children and adults. Some were focused exclusively on just infants, just children or just adults. And then the proportion of females in these studies range from 13% to 64%. More than half of the studies did not report the race or ethnicity of analyzed patients. This graph here depicts the number of studies reporting each category of race, ethnicity, and the range across the top here is the percent of participants in that respective race category in the studies that reported that race category. So for example, in the 10 studies that reported an Asian race category, the proportion of Asian participants ranged from 3 to 92%. The phenotypes evaluated in the included studies are depicted here on the left of this panel of the slide. As you can see, the most, the most number of studies analyzed diverse sets of patients without regard to any specific phenotypes. So they just took basically anybody

with suspected genetic disease and that was 12 studies. The next most common were studies analyzing persons with neurodevelopmental disorders, specifically developmental delay in intellectual disability. Although some of those studies may have included other disorders including autism or epilepsy, there was only one study that analyzed people with autism exclusively. And then many of the other studies analyzed various types of neurologic conditions. On the right, side of the slide is the recruitment setting, which here is not mutually exclusive, so this will add to more than 35 studies if you were to do the math. But as you can see, most patients are being were recruited from genetics clinics or specially clinics, tertiary medical centers there were no patients that were actually identified from primary care settings. So these are people who are receiving this test or getting this test in largely referral settings.

Study designs, Dr. Schultz mentioned a little bit about this. This was very tricky to categories in this review because many studies were simply reporting analyses from routine practice. They weren't designed as a study or conducted prospectively with few exceptions. We ended up settling on 3 categories to categorize and organize our findings. First was a single cohort design. In this design, there's a single group of individuals who receive whole genome and then they also receive a concurrent or historical comparator test. And then diagnostic yield is reported for both of those. And then you do the math and you can get to an incremental diagnostic yield which is the additional yield gained or potentially lost from whole genome sequencing and there's 11 studies with that. Next was a separate cohort design. In this design whole genome is used with one cohort of patients and then a comparator test or strategy is used in a separate cohort of patients. So these are 2 separate groups of patients and they don't all necessarily have the same genome as you might expect. In some cases, the separate cohort receives a concurrent test, in other cases, it's historical data. And similar to the first design, we're able to cut this author's report a diagnostic yield for each of those cohorts and then we can calculate or the authors calculate an incremental diagnostic yield. And there was 11 studies that use that study design. Then lastly is a design that we refer to as the diagnostic Odyssey path. In this design, an initial cohort of patients receives a genetic test. And only those who remain undiagnosed after that test go on to receive a next test. And only those that remain under next on and on and ultimately, those remain undiagnosed at the end of the pathway then receive whole genome as the last test received. And the yield from this last line of whole genome testing represents the incremental yield over the test most immediately preceding it. And one thing that you'll notice with this pathway is that the sample size becomes increasingly small as you progress along the pathway. And there were 11 studies that used the study design. So, 33 studies showed had empiric data relating to efficacy and or safety. And then we had the 2 cost-effectiveness days, which is Dr. Schultz mentioned, were decision analyses.

Lastly, here are the risk of bias assessments. As you can see, we rated the majority of the clinical utility outcomes as high risk of bias and that includes diagnostic yield. A frequent reason for high risk of bias is it particularly in the separate cohort designs is related to confounding since test selection was not random in all but 2 of those studies, clinicians chose which test to use, likely based on phenotype and or likely of being able to determine the diagnosis with a specific test. And it may be that they selected whole

genome to use for more complex phenotypes or when prior testing had failed to reveal a diagnosis. Other common issues across nearly all the studies was the lack of pre-specified protocols or analysis plans, the lack of robust measures and outcome assessment methods and the lack of transparency with respect to missing data. We ended up rating the studies reporting the safety and health outcomes as high risk of bias and we rated the 2 cost-effectiveness studies as having some risk a bias. Before I present the outcome results, I'd like to briefly mention some of the other sources of variation across this body of evidence. This includes things like whether clinical or research whole genome was used, the year of testing, because again, this, these testing technologies are evolving so quickly, which reference genomes were used shifts over time, whether the whole genome was singleton, duo or trio, the definition of a positive test and whether American College of Medical Genetics and Genomics criteria were used for classifying variants, the extent of pre-whole genome testing and evaluation that occurred, for example, whether the whole genome was used as a first line test or a last line test, and particularly for the diagnostic Odyssey studies, the number of sort of incremental testing steps along the way.

So here are the findings from diagnostic yield. This is a slide that Dr. Schultz shared with you earlier. This is the summary slide for the 32 studies that are reporting 37 comparisons for diagnostic yield. To orient you, we have diagnostic yield for whole genome on the vertical access. The solid symbols here represent the incremental diagnostic yields. This means the yield of whole genome relative to a comparator test. So any of these solid symbols that are appearing above this 0 horizontal line means that whole genome identified more diagnoses than the comparator test that was used. And then sit those solid symbols that fall below the line means that the comparator test identified more diagnoses. The open symbols on this graph represent the absolute yield from whole genome so without respect to a comparator. Unfortunately, few studies reported any measures of variance around these point estimates, so we don't really know how big the error bars are on these point estimates. And then the studies are grouped by design. The single cohort studies are here on the left, the separate cohort studies are in the middle, the diagnostic Odyssey path studies are here on the right. And you can see that there's pretty wide variation across both the study design groupings but also even within each study design grouping and that's because of many of the factors I mentioned on the previous slide as being sources of variation. But if you take a step back and just think about like what the overall impression is from this data, it's that most studies are suggesting that there's more diagnoses from whole genome relative to the comparator test. On the next series of slides, I'm going to break this down a little bit by comparator test.

So this graph depicts whole genome versus whole exome, which we have 21 comparisons reported in 19 studies. The data is again organized by study design. There's a little less variability in this graph compared to the prior one, but they're still pretty meaningful variation even within the same study design groupings. Again, overall most but not all of the sites suggest more diagnoses with whole genome as compared to whole exome. This graph depicts the 3 comparisons from comparing whole genome to chromosomal microarray in all 3 studies whole genome resulted in more diagnosis compared to

microarray. However, you know, we only have these 3 comparisons so it's a little bit of a limited set of evidence. We have 6 studies reporting between whole genome and multi-gene panels. Except for the diagnostic yield pathway whole genome, you know seems the same or only marginally better than these panels though, then again the number of comparisons is pretty limited for each study design. And then in this last group are 5 studies that report 6 comparisons and the comparator here was referred to by study authors as standard of care testing and this may have included a range of things including karyotype, single gene, multiple gene, CMA testing, but generally not whole exome, so it's like everything else except whole exome. And this this also presents a little bit of a mixed picture with respect to whether there's any impact on diagnostic yield. Again, we have the issue with the separate cohort studies, again, not necessarily being an apples to apples comparison, as Dr. Schultz mentioned.

In addition to those studies I just presented, we also identified one study reporting on whole genome reanalysis that was conducted among 22 children and adults with suspected genetic disorders from a single clinic. The initial whole genome yielded 3 diagnoses for diagnostic yield of 14%. And then the cumulative number of diagnoses after reanalysis was 8 diagnoses for a yield of 36% total and that represents an incremental yield from reanalysis of 22%. The critical piece of information that we don't know because the authors did not report it is the time interval between initial and reanalysis. That was not reported, but from what we've read generally, reanalysis is not recommended before a year, at least after the initial analysis.

In addition to comparator tests, we evaluated whether diagnostic you varied by phenotype of the patient. And again, on this graph, the open symbols depict the absolute yield and the solid symbols represent the incremental yield. The largest grouping of studies were those that enrolled all comers with suspected genetic disorders so this non-specific category. Again, you see a wide variety of yields here representing the variation in phenotypes in that category of patients. Whereas some studies analyzed more narrow phenotypes, for example, autism spectrum disorder, ataxia, abnormal white matter brain disorders, we had a couple of days looking at specific vision disorders and cardiomyopathy. I think the even sometimes within these narrow phenotype categories we still see a bit of variation. Before we leave diagnostic yield outcomes, let me briefly summarize data from the contextual question. So again, we included this question, supplement the data from the systematically reviewed key questions. For this we relied on the most recent systemic reviews of whole genome from the previous 4 years. We did not require studies to have a comparator group. So the data reported here is absolute diagnostic yield. And many of these reviews also included critically ill patients in inpatient settings and some excluded adults, some reviews were focused on very specific phenotypes. So this is a broader, these reviews come from a broader set of evidence than what we included in the systematically reviewed portion of the HTA. Some of those, these reviews did report a pooled summary estimate and that's represented by the diamond on some of these estimates and they also reported 95% confidence intervals and those are the little tick marks and then the long line represents the range of diagnostic yields reported across these studies. So even in these reviews, you can see there's a pretty wide range of diagnostic yields that are being reported across the studies. On average though, I

think what you would conclude from this data is that these absolute diagnostic yields are running a little bit higher then what we reported for diagnose yield from the studies we included. Again, this is probably because it's including a lot of critically ill patients in inpatient settings. And a wider variety of states that otherwise didn't meet our criteria.

Moving along to other outcomes, we were quite disappointed to find limited data on clinical utility outcomes. Further, this data was extremely variable in terms of how it was ascertained and reported by study authors and very limited availability of data for comparator testing strategies which is really only relevant to the studies of separate cohort designs. Further many of these studies had high risk of bias. So across the studies that had just some risk of bias, so we took a more narrow perspective on just looking at those studies. The percent of patients or families with a change in treatment, evaluation, management, or surveillance, which could have also include a referral of an at risk relative, that range was from 12% to 65% of people tested. And then with respect to time to diagnosis, this was reported in one of the 2 trials that Dr. Schultz mentioned. These study authors reported that a hundred percent of participants in the group that received first line test whole genome testing received a diagnosis within 5 weeks compared with only 22.8% of those that receive standard of care testing plus delayed whole genome. So that was the only study that explicitly reported on time to diagnosis.

On this slide are examples from 2 studies that reported clinical utility outcomes other than diagnostic yield and I just showing them as examples of the type of data that's reported and I put little snowflakes on them to remind me to remind you that each of these studies is really quite unique with respect to what they ascertained and reported, which makes it really difficult to draw a generalizable conclusions across the body of evidence. So in this example, on the left, which evaluated whole genome plus standard of care testing versus standard care testing alone in children and adults, of suspected genetic conditions, 25% of participants with a diagnosis from whole genome required additional workup because of the uncertainty as to whether the molecular diagnosis from whole genome explained the clinical features. And then in the study on the right, which compared whole genome to standard of care testing in infants with new onset of epilepsy, 48% of those tested had results that were either positive or negative for a diagnosis that ended up influencing changes to medical care or further evaluation or referral of relatives. And this was 30% among those that had, that received a diagnosis from whole genome. And one reason I chose these 2 examples is to illustrate is that clinical utilities sometimes observe even among those who did not, do not receive a diagnosis from whole genome. So in addition to conferring a diagnosis, the lack of a diagnosis may rule out some conditions or and or lead to further evaluation along a different pathway.

Only one study reported health outcomes in our team kind of considered what they reported is even a bit of a stretch for being considered health outcome. This was a cohort study among 357 children and adults from the NIH undiagnosed diseases network. These are people who are undiagnosed after a thorough clinical evaluation in routine practice who are then accepted into the network for various studies. To understand this health outcome, I need to convey the entire diagnostic process. The analysis included separate

cohorts. One received whole genome and the other received whole axon and the diagnostic yields were 19% and 28% respectively. Of those who obtain a diagnosis through either test that's this gray box here in the middle, 32% had a recommended change in therapy, 56% had a change in care other than therapy and then 55% had genetic counseling but no specific change in care. And of those with a recommended change in therapy, 29% experienced positive treatment effects, that's how the authors described the result, 21% hit unclear or negative effects and 14% did not go through with the recommended change and then outcomes could not be determined for 36%. So that is sort of the extent of quote-unquote health outcomes that was reported in this body of literature. Secondary findings, which are medically actionable genetic variance in one or more genes not related to the primary indication for testing were reported by 9 studies. 5 of these studies were limited reporting, limited their reporting of secondary findings to genes from the ACMGs recommended list of secondary findings and the incidents of secondary findings amongst those studies ranged from 0 to 12.5% of participants. There were 5 studies that also reported on a broader set of secondary findings, including and beyond the ACMG list. One of these studies also reported on the narrower, narrower list. In 3 of these studies, the incidents of secondary findings ranged from 4 to 9%. One study reported it slightly differently, they reported a mean of 2.0 5 findings per person. And another study reported a mean of 1.86 fine, 1.86 findings per person.

Alright, moving on to safety outcomes. We only identify 2 studies reporting outcomes that we would categorize, we categorize the safety outcomes. So one study was conducted among 1.5 million tests across 19 different clinical labs in North America. They reported the frequency of variance of uncertain significance also known as VUS. The VUS represents, could represent a potential harm as they can result in patient and provider uncertainty and downstream costs due to additional surveillance and or testing. The it's important to note here that VUS are reported for all tests that are based on next generation sequencing platforms, not unique to whole genome. The multi gene panels in this study had a rate of VUS of 32.6% and in the rate for whole exome, whole genome was 22.5% collectively. And then when you compare trio whole exome or whole genome to non-trio the rate is lower for trio testing compared to non-trio testing and that was statistically significant. And then when you look at whole exome compared to whole genome, there was no really they're pretty similar, there's no statistical difference. And I think as one of the speakers said earlier, this higher rate of VUS in multi gene panels is not unexpected because typically all view VUS is reported in the genes tested on a multigene panel and there's sort of a limited pool of genes that are tested. Whereas for whole exome and whole genome, the VUS's are usually only reported in gene the genes possibly associated with phenotype but it's over like a much larger denominator of genes. Another safety outcome reported was from a single cohort study conducted among 500 people younger than age 19 with suspected genetic conditions. And they reported on the number of diagnoses made with either whole exome, whole genome then that were later rescinded. So the, in the study, initial analyses reported a diagnostic yield of 52% for whole genome, of the of the 261 people that received a diagnosis 4 of them had them rescinded or that's a incidence of 1.5%. 3 of those 4 what happened was follow-up exams and tests were not consistent with the molecular diagnosis and then in one of the 4, a

different variant was reinterpreted that ended up being a better fit with the patient's phenotype than the original diagnosis.

Cost-effectiveness. So this slide summarizes information from the 2 cost-effectiveness analyses that we that we identified. Both studies were decision analyses that modeled the use of whole genome among populations of non-critically ill children with suspected genetic conditions. The study in the top row by Incerti and others modeled standard of care testing, which included single gene, multiple gene and other tests, trio whole genome and then standard of care testing then followed by trio, whole genome so 3 strategies. They studied the bottom by Lavelle and authors modeled similar strategies, but they also included some additional strategies that included whole exome sequencing. Both studies took a payer perspective and used cost inputs from CMS. The Incerti study here at the top found that trio, a trio whole genome strategy, first line trio whole genome strategy cost less than standard of care testing and resulted in more diagnoses and they found a strategy of standard of care testing followed by whole genome costs $24,000 more per additional diagnosis as compared to standard of care testing alone. In contrast, the Lavelle study found that first line trio whole genome costs $27,000 more per additional diagnosis compared to standard of care testing. So that's the mix sort of mixed findings that I believe Dr. Schultz was alluding to earlier. There, they, with modeling studies is so dependent on the inputs that you use, the cost that you use so it's not entirely unexpected to find sort of different findings and the fact that we only have 2 stays to go on sort of leaves us like with a mixed picture in terms of the cost of effectiveness of these of this technology.

So wrapping up now with the discussion, I'll summarize the findings using some evidence maps on the next few slides. So here's a recap of the effectiveness outcomes. The symbols represent the evidence base. The circles with the number of studies, which is the K, and the number of participants, which is the N and the color of the circle represents our certainty of that evidence, which for all of these outcomes is very low. The location of the circle on the grid represents the direction of effect. For example, we had 32 studies. reporting on diagnostic yield and we rated our certainty as very low favoring whole genome sequencing, meaning if whole genome sequencing found more diagnoses than comparator tests. Our certainty of evidence was also very low for clinical utility, health outcomes, and secondary findings and because either limited number of studies or too much variation in how these outcomes are measured. We can't really even discern a direction of effect in terms of whether we favor whole genome or favor comparator testing methods. With respect to safety, we concluded with very low certainty that TRIO whole genome results in fewer variance of certain significance compared to Singleton whole genome. And we decided that the frequency of the VUS from whole genome is not directly compared to multi gene panels because of what we talked about earlier. We had limited studies to determine other safety outcomes and the data for cost effectiveness was limited to just cost per additional diagnosis and because it was mixed it limited from us precluding a definitive conclusion one way or another in terms of which test is favored.

Here are the main evidence limitations. Limited studies reporting clinical utility other than diagnostic yield or health outcomes. We found no studies reporting on psychosocial or

personal utility outcomes, particularly those related to patient and family experience with the diagnostic Odyssey. However, a lot of this evidence is likely included in qualitative research studies which were not in the scope for this review. The version of next generation sequencing based tests included that were included by the studies in this review s whole genome, whole exome, multi-gene panels are likely already obsolete because we're talking about studies from like the past decade and this technology is really evolving very rapidly. We already talked a lot about the clinical methodologic heterogeneity in this evidence base. This is likely going to be true for any genetic test that is implied to the entire exome or the entire genome because these tests are used in populations with suspected genetic diseases or rare conditions for which there are thousands of varieties and for which the diagnostic path for anyone given individual is highly individualized. So this is a good time to kind of remind you of something that the National Academy's acknowledged back in 2017 related to the challenges of making evidence-based decisions about the use of genetic tests and that the evidence base for the clinical value of genetic testing is generally based on lower quality evidence maybe compared to other decisions that you might have to make. This is partly because of the methodological limitations with trying to evaluate these sort of tests within our existing study frameworks, but it's also because of the accelerated pace of the technology development in this space.

On this slide and the next 2 slides are the relevant excerpts from the clinical practice guidelines from professional societies or consortiums. As you can see from the 2 examples on this slide, genome sequencing is recommended as a genetic test but with variation in how broad or narrow of a population it's recommended. For example, the consortium here at the top which is an academic industry consortium recommends it as first or second line test for essentially any suspected genetic condition. While the National Society for Genetic Counselors down below recommends it more narrowly as an option for unexplained epilepsy at any age. Similarly, NICE guidance from the UK suggests considering whole genome for unexplained epilepsy and kids younger than 2 or features of a genetic epilepsy syndrome or for older persons who's epilepsy started between age 2 and 3. And then there's a European Group that recommends it when it's relevant for improving quality efficiency or diagnostic yield. The ACMGs guideline is specifically focused on pediatric patients with congenital anomalies prior to age one or intellectual disability with before age 18 and they recommend exome or genome as first or second tier tests and then the Canadian guideline was a little bit older it's from 2015 recommends genome wide sequencing which again refers to exome or whole genome as second line tests for those with suspected genetic conditions. Here's a summary of payer coverage, both Cigna and United Health Care cover whole genome with conditions and the specific coverage criteria are detailed in the report, full report and they're also located at the back of the slide deck.

Future research, there's a number of future studies that are ongoing or completed but not yet published, registered in clinicaltrial.gov. Some of the challenges for doing future research include the genomic heterogeneity again amongst phenotypes that are typically tested. And for outcomes like diagnostic yield, patients really do need to serve as their own controls. This technology is evolving quickly. Yet there are no standardized

approaches to measuring reporting things like diagnostic gel, clinical utility, harms, and impact on the Odyssey. Longer term funding, larger studies would be needed to robustly assess meaningful health and cost outcomes. However, it's not clear that this is really feasible given the diversity of phenotypes and rare conditions, the sample sizes for any given phenotype will always be small for rare conditions and so if you pull lots of different people together to get a larger sample size, then you introduce a lot of heterogeneity and diversity, genomic diversity. Briefly some limitations of our review. We limited to English language only. We excluded studies from non-very highly developed countries. We required a comparator test except for harms and we excluded whole genome used in inpatient settings.

So this side summarizes our conclusion. So whole genome may increase the yield of molecular diagnosis in people with suspected genetic conditions as compared with alternative testing strategies. The evidence for changes in management and health outcomes resulting from whole genome is limited. The incidents of actionable secondary findings from whole genome ranges from 0 to 12.5%. And few studies report outcomes related to safety and limited data on cost effectiveness. I'm happy to take any questions on the evidence report.

Sheila Rege — Kudos for a really comprehensive review and explanation. Thank you. Questions?

Jonathan Sham — I guess I just have a general question maybe for the chairs or Josh. This is the first time in my experience on the committee we've encountered a diagnostic test that we're reviewing and so just to clarify when we're evaluating cost, safety and efficacy, what efficacy really means in the context of a diagnostic test? Is it that the test is able to find things and does what it says it does. Or is that the results of the tests affect clinical outcomes of based on results. Cause it seems like we talked a little bit about both. I just wanna be really clear when I'm we're thinking about this what efficacy really means in the context of the test.

Sheila Rege — I'll have a vendor kind of apply on how in the key questions, how that was interpreted first?

Leila Kahwati — Yeah, so for efficacy for around diagnostic testing, it's mainly clinical utility outcomes so that's going to be like diagnostic yield. You know, can it find more diagnosis than a comparator test? The time to diagnosis, did, you know, can it diagnose more quickly than a comparator test. Changes in care resulting from a diagnosis, so does it lead to actual, you know, it's 1 thing to just to find a diagnosis, but does it lead to subsequent changes in care or management, which again could occur include identification of relatives who may need reproductive counseling as a result of the variant. That's sort of, those are the more proximal outcomes to, you know, diagnosis. Ideally, we would love to see then that cascade into more downstream outcomes like mortality, survival, morbidity, but we just don't, it's really hard to get to those more distal outcomes, but we and then there's non-health outcomes like personal utility, psychosocial outcomes like feeling relief or you know having anxiety reduced as a result of having received a diagnosis, the whole patient experience of the diagnostic Odyssey, those would be the outcomes that we would like

kind of bucket into the like advocacy category. Although if you found that this testing worsened anxiety, then we would have called that more like a harm, so these are sort of loose categories, but they do go beyond just diagnosis.

Sheila Rege — Thank you. Dr. Bramhall.

John Bramhall — So just to follow up on that diagnostic yield, I had the same kind of question as Jonathan. The diagnostic yield doesn't simply mean the identification of a variant in your analysis. It has to be tied to a medical phenotype, disease by name.

Leila Kahwati — Yes, it's a identification of a variant that has been is known to be considered pathogenic or likely pathogenic for that phenotype. So it's not just any variant. It's after the whole analysis that them the team analyzing the data can say with some assurance that they think it's causally related to the person's phenotype.

John Bramhall — And, and just to follow that, that relationship is, I'm assuming that that relationship is constantly changing.

Leila Kahwati — Yes.

John Bramhall — And that that is a function of the databases that are accumulating and the, you know, the post test, analysis, correct.

Leila Kahwati — Correct. Correct. That's right.

John Bramhall — And, thank you. And can it just ask one more question. And this this doesn't come from, from your presentation which I was excellent, thank you. It comes from just a sort of general feeling, a WGS variant appears so whole genome is analyzed and a variant appears a variant being something that isn't present in the in the reference material. I can you can you sort of hypothesis, suggest how often a WGS variant would lead or does lead to a variant that would be seen in whole exome sequencing. And what I'm getting at is that there's probably a variation that you would identify in the whole genome. That's in a in an intron, it's in a regular tree area that then leads to a, an exon change and I'm sorry this is this is a little bit just sort of fundamental it's not stemming from the detailed analysis of the data that you presented. It's, I'm sort of asking for your gut feeling that you presented. It's I'm sort of asking for your gut feeling. How often does a variant that you would see in whole genome also then lead to a variant that you would have seen if you'd done a whole exome sequencing?

Leila Kahwati — So if the variant is in the protein coding regions, and actually Dr. Yuen and I might ask you to step in after I give my answer to correct me, if the very is in the protein coding regions, the whole genome most of the time is going, whole exome and whole genome will find the same variance although it's not a hundred percent because there might be different bioinformatics filtering and tools that are used so it's not 100% but if it's in the protein coding regions they will find, they will both typically find it. If it's in a non-coding region, non-protein coding region, exome won't find it because exome is not considering those

regions. So that's one of the you know, purported advantages of whole genome is it can identify variants in the non-protein coding regions. Now, how often somebody's phenotype is explained by a variant in non-coding regions versus coding regions, I think is heavily dependent on the phenotype and the, the patient's phenotype. I don't know that there's like a ballpark number. Dr. Yuen and do you have a sense of how often that is happening?

Amy Yuen — So a number that's evolving. Because as we're able to do more whole genome sequencing, we're realizing more and more of. Important for pathogenic variants that are in the non-coding regions. Earlier data is somewhat, limited because we were looking at panel that we had available. Exome as that became available and those were focused on coding regions. And now that we can test more non-coding regions, that number is appearing to be bigger than had originally been realized in some of the early days when exome was coming out, people were citing that 75 to 80% of pathogenic variants were in those coding regions. And that number was probably an overestimate as we learn more about the non-coding regions. Another important difference is that typically genome will include the mitochondrial genome and typical exome platforms will not look at the mitochondrial genome. There are also certain types of variants that are not picked up on exome that genome can pick up as genome is advancing, we're starting to get some of the repeat expansion variants the exome could not pick up and we're also seeing improvements and structural variants, so different types of deletions and they're also even being able to recognize in some cases on balance translocation was present, which you could not see on an exome.

Sheila Rege — Thank you. I think it was Tony Dr. Yen next.

Tony Yen — So question for our vendor. I had a question on your presentation on slide 32 over here. Can you tell me why is it is that the incremental yield is so much more positive than the diagnostic Odyssey path as compared to the single cohort or separate cohorts.

Leila Kahwati — We.

Tony Yen — And this is just me kind of picking through it is that the diagnostic obviously path would be like a lesser yield because they've gone through more sequential testing?

Leila Kahwati — Yeah, we we've really struggled to understand why that was and we the only, the only thing we could come up with is that a lot of those studies are were retrospective and so I don't know that we have complete reporting of all the data for everybody along the pathway. So it may be that if they just didn't have data on people for the next step, they just dropped them out of the analysis. So that that really was the only way we could like. Try to understand why that pathway seemed more optimistic than the other pathways is that there's something related to reporting bias. In those studies.

Tony Yen — Okay.

Leila Kahwati — The other thing to know is like I'll just pick on this data point here that shows a hundred percent diagnostic yield, that was a sample size of 3. Right, so by the end of the pathway,

you're getting to like really small numbers. So we, you know, it was sort of unsatisfying not to be able to completely explain this, but we decided like if we just take a step back and like what is the like general signal, you know, it's positive and it, this diagnostic Odyssey path is perhaps showing a more positive signal than the other study designs, but in general they're showing it's you know the testing with whole genome shows more diagnoses. Yep.

Tony Yen — Okay, thank you.

Sheila Rege — Sorry, couldn't get off mute fast enough. I think it was Dr. Friedly next and then Dr. Kleweno.

Janna Friedly — Yeah, thanks. This was a great, report very clear and, and very helpful, so I appreciate that. I just had a question, for you or maybe our clinical expert about the recommendations from society guidelines. And if there's any additional context around that to understand it's not uncommon that we see that but I'm just curious if there was any, any other context, like were they the ones that were only recommending for epilepsy, for example.

Leila Kahwati — Yeah.

Janna Friedly — Where they, were they only commenting on epilepsy, was that the, the, the scope of what they were looking at, or.

Leila Kahwati — Yeah, like I think that's right. I think some of the guidelines are coming from a more narrow like disease perspective. So, you know, it's about diagnosis and treatment of epilepsy and then within that, you know, there's a section around whole genome. So it's not coming from like a test perspective. So I think that's part of it the other the other thing I suspect is happening is because these technologies are evolving so rapidly, it's just really hard for these societies to stay on top of the them with like a guideline. You know, guideline processes are very intensive and require a lot of resources, so I don't know how they make their decisions about you know, when to update the guidelines. And I don't know, Dr. Yuen and if you have other thoughts about that, but that was one other thought I had is that the way things, the pace at which things are evolving is so rapid that they just, you know, some of them may just not be able to keep up with what's happening.

Amy Yuen — Exactly. I think you've hit upon some really good points here is that. We have to think about what year was the guideline made. Advances are moving so rapidly. Prices are changing so rapidly in those times. So when you're factoring in the diagnostic yield for the price that ratio is changing. The 3rd point is that some of these guidelines were looking at more specific condition, epilepsy versus all pediatric conditions. So I expect a lot of the variation we're seeing in the guidelines is because of that.

Sheila Rege — Thank you. Conor.

Conor Kleweno — Yeah, I was just gonna make a comment, from Jonathan's, question. I think it's on page 21 you had where you were discussing, the outcomes or efficacy, excuse me. And you know, clearly we don't wanna support something that just gives us a bunch of information that is useless, but I don't really think that's what going on here and I think that for me you know, we can measure and study that the test is providing a diagnostic yield, but to say that, well, there's not always changes in care I think for me, I would view that a little bit softer that the lack of change in care is not a problem with the test, but just, you know, we haven't advanced enough potentially to alter that care or something like that. And I just think that I just didn't think that they if there's a lack of change in care necessarily needs to be a negative sort of ding on the outcome of efficacy in this scenario. Obviously this is an unusual setting. But I just, in my mind, I would soften my interpretation of the efficacy for that. Because not only are they rare conditions, but they're often times where, you know, we're still challenged with providing changes in care potentially. So I still think there is value in providing that information that there's efficacy, there's positive outcome and provided that information.

Christoph Lee — I think I'm next. I'm just gonna speak up. So I guess a question a couple questions for Dr. Yuen, my first question is would you consider a whole genome sequencing a first tier first line test now compared to whole exome sequencing and multi-gene panels.

Amy Yuen — Yes, and I would say in my practice I consider it often is either first or second line test. If there is a panel or chromosome array that is logical to start with I might do that first and then move to the genome. Often there's discussion with the family. If we start with a first line test and it's negative, that's also adding to the cost as well. So I want to keep the number of initial tests actually at a relative minimum cause I'm factoring in what is the cost if I'm going through multiple tiers of tests and don't have a diagnosis and then we go to genome versus going to the genome at the first or second tier so that's been my clinical practice. And we've moved more to genome recently as the price has come down. Whereas previously it had been more of a decision of. The panel or chromosome array and exome, now genome is starting to replace that exome as that broader test.

Christoph Lee — Right. And then my second question was to follow to that the agency is recommending that we use sort of the language we use for exome sequencing in terms of conditional approval. I don't know if you've had a chance to look at those slides, but would you agree with that? And do you have any, any changes you would want to make in terms of inclusion exclusion for whole genome versus whole exome?

Amy Yuen — I would agree that it should be somewhat similar language. I'd have to look back at the exact wording to see if I would recommend any other changes. But as I think about how I work in clinic, my approach is very similar deciding exome, now deciding genome. So I think those criteria can be somewhat similar.

Christoph Lee — Thank you very much.

Sheila Rege — Sorry, getting off mute, Laurie.

Laurie Mischley Yeah, my question is just related to the curation of the information that is delivered after testing in regards to matching phenotype and VUS. I work in neurodegenerative disease where being told you have hemochromatosis or lark 2 or GBA or APOE is relevant. And a lot of people would make different decisions and change course based on all of that and so I assume when you have a child who is coming in for nothing related to that kind of stuff. They're being worked up for whatever they're presenting within clinic, but they're getting a ton of additional information that has the potential to influence a lifetime of decision making. And so I guess my question is in terms of matching phenotype to the results delivered, that makes sense, but can they go deeper? I mean somebody somewhere knows this kid already also has to APOE alleles and hemochromatosis. Is that information available? How is that information available? Who decides if, that they get that information? Does it become part of their permanent record for help, you know, moving forward for insurance companies now that they have to APOE 4 alleles on their record is an 18 month old could that someday negatively ding them against getting long term care insurance? I mean can you just talk to me about what gets excluded and what's available?

Amy Yuen Yes, so that's a great question. So when these results come back, the report has been carefully curated and there will be multiple sections to the report. There'll be the primary findings that's looking for are there any variants that they've detected that are pathogenic or likely pathogenic that fit with the phenotype, the reason that we've given for testing and most of the laboratories are very good about collecting very detailed data. They want as much of the phenotype data as we can get them. Often they would like our note, they would like photographs if we have them so they're considering a deep view at the phenotype. So that's the primary part. After that, there will be the secondary findings. And generally most labs will limit this to the ACMG list. American College of Medical Genetics has created a list of genes that are, could be secondary findings that are considered actionable. So for example, if they saw this child has a genotype that puts them at risk for hemochromatosis, they're going to report that if they see a BRCA1, a BRACA2 variant, they're gonna report that. If it's not something that's currently actionable, those things are left off. So let's say this child has APOE4 alleles and there's a possible increased risk of Alzheimer's but I don't have anything actionable that I can do about that. That's a variant that could indeed produce harm if that's on that child's information record later on people are thinking about life insurance long-term care types of insurance do not currently have regulatory regulations so gene and current federal regulations protect our medical insurance from genetic discrimination but nationally, there are no regulations protecting life insurance long term care disability. So those will not be placed on the report. Once that report is back, it is generally part of the child's medical record. So it's going to be. In the record for other providers to see and act upon as well.

Sheila Rege That was an excellent question. Anything, other questions?

John Bramhall Well, I agree, it's a super question, but it does lead and I don't have gone down a rabbit hole, but now you've got a sort of shadow chart for a given patient. You've got a vendor, A test vendor who has got information which is objective which is stored permanently.

And then you have a parallel medical record which includes a subset of that information. And again, I, we can see where this could go, but, but this is, this is in your thinking, Dr. Yuen and you know, you, you have test results, you have access to a report that relates to specific phenotypes perhaps, but you know at the back of your mind that there is a whole genome's worth of data for that given patient that since stored in some way that's effectively inaccessible to the patient and to you and you could imagine that from the hypothetical from, from the first principle point of view that that that's generating problems for the future that we are gonna have to deal with at some level, probably not this committee, right? What, just, just expand your your feelings on that if you wouldn't mind just to give me some color.

Amy Yuen — Well, I view it mainly in a beneficial way because when that data is stored, if we don't have a diagnosis, then we can go back and reanalyze that data and that is the practice with most of the genetic testing labs that they'll actually do that for free within one to 3 years from when the test is run you could go back and reanalyze you could also go back and reanalyze even further into the future and I've had some patients where we'd had initially negative findings on their first exome or genome and later we go back and re-analyze. It's also can be useful if that patient wants to participate in a more research setting or if they'd like to go to the undiagnosed disease network. So it was one of our public speakers, Dr. Dipple is involved in the UDN. They have an expert clinical group that can then review the data using different pipelines to see if they can find a diagnosis. I think in light of recent publicized hackings of various companies, there is a potential theoretical risk, if your data is stored. Hopefully they are taking great precautions to protect that from hackers or malicious groups that might try to hack in and get data. We've seen that happen with the commercial direct to consumer companies like 23 and me where they were malicious groups trained to hack in target certain ethnicities or people in general who have testing. So there is a theoretical but real possible risk that's way beyond our scope to solve, but we would hope that all the companies would take great care to protect that data.

Sheila Rege — Let's move on because I know people have indicated some time constraints to just kind of what our committee is charged with, you know, kind of using the evidence of is it safe? Is it effective? Does it provide value improve health outcomes? Let's kind of keep our discussion focused on those questions? Any other questions related to them? Any questions for our vendor about the presentation and the studies that were discussed? Josh, I'll have you lead us into our grid of how we usually put this together are you going to be projecting that for us?

Josh Morse — Yeah, I think Melanie will be sharing that through PowerPoint.

Sheila Rege — Val is?

Melanie Golob — Yeah, happy to do so if you'd like.

Sheila Rege — Yes, please. I'm not seeing anything yet.

Tony Yen — Hey Sheila, thank you for doing so well with time today.

Sheila Rege Well, I know a lot of people have, we've tried on a strategic retreat too. Streamline our process. So thank you.

Conor Kleweno Agreed.

Sheila Rege Who are going to be my 2 I had 2 people designated, correct?

Conor Kleweno That one of them was me and I was just about to compliment you as well.

Sheila Rege Good. And there was another, was it Tony, was it you?

Tony Yen Yeah, I'm the other guy.

Sheila Rege Perfect.

Melanie Golob Josh, did you want me to walk through this or are you planning on doing it?

Josh Morse Yeah. Let's just go right into it.

Melanie Golob Okay, great. Okay. So, as before we have put the decision aid into a PowerPoint slide presentation to kind of focus the key points of, for the committee on the task your charged with. So this is what has happened so far. There's been the state agency presentation. There's been the open public comments and the evidence report presentation. There's been the committee questions and answers and then the discussion. So again, the main, the main questions that are being asked are is it safe, is it effective and does it improve health outcomes? And for a more detailed overview of the exact steps that go under this evidence decision framework please reference the decision aid that was included in the meeting materials. So the 2 main cover determination principles are, you know, evidence-based and does it result in a health benefit. So looking at safety, effectiveness, and cost, determine whether one, evidence is available, the confidence in the evidence and then applicability to decision. And so that is reflected in the new voting that has happened in terms of Is it effective? You know, is it safe? Is it cost effective? And then your confidence in each of those, those metrics.

So the evidence review process. The plan is to give the greatest weight to the valid, the most valid and reliable evidence. And things to consider are not just the nature and source of the evidence, but also the characteristics of the study, the consistency across comparable studies, so comparing apples to apples, the recency relevance and bias and then the special considerations so sex, age, ethnicity, race, and disability. And the visual over on the right is just, is kind of to orient on what goes into the determination, so from the report, the safety, efficiency and cost-effectiveness and then also consider the other information that was provided. Anything from the Director or advisory groups or the public's or anything provided in public comment. That all goes into the determination. And this is just kind of a detailed pathway based on the WAC for the committee. So the main thing is, is there sufficient evidence, yes or no? If there's not sufficient evidence or the evidence that's provided is not a good evidence, then the path is to not cover. If there

	is enough evidence to determine that it's the topic is safe, efficacious and cost-effective. Is it that way for all indicated conditions, yes or no? If it's not, then that's where that coverage with conditions is allowed and if it is then in certain situations coverage without any special conditions. And then these are the considerations for each of the safety, efficacy, and cost. So for a efficacy typically morbidity, mortality, and any non-fatal outcomes, short versus long term complications. For efficacy, you wanna make sure that it's beneficial and important health outcomes. Those specific efficacy outcomes and then costs is pretty straightforward. In terms of overall considerations, what the alternatives are. So is the technology that we're looking at, is it better? Is it less costly than alternatives? And in terms of the evidence, is it better health outcomes versus without the technology or procedure or test in this case? So this these are the outcomes and Josh happy to keep going through this or if you'd like to take over. I know you usually do this part, but, these are the outcomes that we had pulled from the report for safety. Are there any other outcomes or? That should have been considered in terms of safety that like we're not seen in the studies, that's kind of the point of this table is to see. Are there other things that should have been considered or that important for looking at safety that are not reported in the outcomes and how important are these outcomes listed in terms of thinking of safety?
Sheila Rege	Laurie, do you wanna list what you were concerned about?
Laurie Mischley	Yeah, I was hemming and hawing. But yeah, I do think, you know, I do see people discriminated against based on genes that they were, cards they were dealt at birth. And so I both believe that knowledge is power and more data is generally going to be more useful, especially as time goes on, but I do want to acknowledge that with delivering people some information about genes they carry, the way this current system is set up is setting them up for potential discrimination. And that is a safety concern that I would somehow list there, but.
Melanie Golob	Okay, genetic discrimination?
Laurie Mischley	Yep.
Melanie Golob	Does that Laura, would you say that accurately captures that.
Laurie Mischley	Yeah, yeah.
Melanie Golob	Okay, great.
Sheila Rege	And that was not in any of our evidence. So that's just something you know that we as clinicians are just concerned about. It’s a theoretical.
Melanie Golob	Okay.
Sheila Rege	Anything else? Otherwise we can move on.

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Melanie Golob	Okay. So based on this, I believe the straw poll is typically next to see if there is sufficient evidence on safety.
Val Hamann	So if you all want to jump back into ttpoll and enter in your login information that would be great. And then I can launch that poll when I see the 10 connections.
Josh Morse	Is the question on the next slide, Melanie?
Melanie Golob	Yes, toggling between PowerPoint slide decks right now. There we go.
Val Hamann	And I'm waiting on 4 more connections. And 2 more. And just waiting on one more.
Sheila Rege	I am not, this is Sheila and I am not getting choices.
Val Hamann	I haven't launched the poll yet because we are waiting on one more person to jump in.
Sheila Rege	Okay.
Josh Morse	And I think Dr. Sham stepped away. Are you?
Val Hamann	Oh, okay. Then yeah we have 9 so we can get started.
Josh Morse	Okay.
Val Hamann	And that poll is open now for safety. Waiting. Oh, there we go. So we have 3 with low and low confidence and we have 6 or low, medium confidence.
Melanie Golob	Val, would it be easier if I let you share this so that you can share the results as soon as they're up, would that be easier?
Val Hamann	Sure. Yeah.
Melanie Golob	Okay. It is nice to have the visual.
Val Hamann	Okay, so you're able to see that.
Melanie Golob	Perfect, yeah.
Val Hamann	Okay, are we ready to go on to efficacy?
Sheila Rege	Yes, please.
Melanie Golob	Okay, and just like the safety one, these are the outcomes that were prepopulated from the report based on the available studies, but are there any other outcomes that were potentially not included in the studies you would have liked to seen to gauge efficacy for this topic?

Sheila Rege — If I could raise my hand, I've always wondered whether any of these could. Replace any of the single gene studies at some point in the future but that wasn't in the studies. So I don't know the vendor can comment on that? Was there any discussion of that?

Leila Kahwati — Yeah, so I mean, single gene comparators were not, well, no studies used single gene comparators because I think I think if you have a patient where they have something really specific and you can know you can do a single gene you just would do it. So the only comparators we had were the multi gene panels and chromosomal microarray and whole exome. But theoretically, you can do single gene testing with these NGS platforms. That is possible.

Sheila Rege — I don't think I would add anything. That was just a question. If there's no other discussion, we can go on to the straw poll.

Val Hamann — That poll is now open.

Melanie Golob — Okay, should we go on to cost effectiveness? Sheila, is that okay? Great. So costs, again, a little bit more straightforward. Were these, you know, reflected in the studies? I don't know if there's any other cost outcomes that should be considered. But sounds like we can go ahead and move on to the straw vote for cost.

Val Hamann — And waiting on one response.

Melanie Golob — Okay, great. So we can go on to the next slide. And then any special populations and this doesn't need to be a voting question this is more just a discussion question. If there were any studies or any, anything focused on those considerations of the age, sex, comorbidity, adolescence, or pregnant individuals. So not sure if you wanted to discuss any of that, Sheila.

Sheila Rege — I'm open for discussion. I mean, I guess we've looked at some of the things about epilepsy being one of them, but I don't know if anybody else has anything to add here.

Tony Yen — I do wonder about ethnicity. Think different ethnicities have different genetic risks. And that's something that just wasn't discussed in literature at all. It's not, I don't think we can do anything about it right now, but right now, I think most, most databases depending on which database you go to. Like say, if we're using data bases here in the US, we're looking at primarily a Caucasian population.

Sheila Rege — Very true. So we can just, keep an eye out as, new data comes up, whether that's addressed. Is that what you want, Dr. Yen?

Tony Yen — Yeah, it's just, just to be aware of it's like, it's just a limitation of the technology in here and now what data is available.

Conor Kleweno — Oh, I wonder if, the expert, could make a comment on that?

Tony Yen — Yeah, good idea.

Conor Kleweno — You know, is, is that true or how true is it or how, you know, what the current status of that concern is?

Amy Yuen — Yes, that's a good point that has been raised is that when we think about what do we compare, comparing our testing sample to many of those databases are skewed toward more people European ancestry, Caucasian. There's fewer people of African or, Asian continents represented in that data and there are steps being taken to improve that comparator groups. So that we do get hopefully more equivalent yields among people of different ancestries.

Sheila Rege — I think we'll help. Oh, John.

John Bramhall — Didn't see. No, I didn't see there wasn't a lot of information in the report about the relationship with pregnancy but here's a slide that sort of pulls out a subpopulation and I think that there are explicit carveouts, am I correct for prenatal decision making on the basis of this technology in terms of coverage?

Sheila Rege — What, what, carveouts are you saying, John? I didn't get that.

John Bramhall — Well, you see where I'm going if a so screening is applied to a pregnant woman and yields information that gives some concern for the outcome of the pregnancy or the of the child. Is that something that we're supposed to be considering as a in our coverage determination later on, it's not as I recall explicitly called out in the data. But it's embedded in there somewhere. A concern about the relationship of testing a pregnant woman for her whole genome.

Sheila Rege — Let's, let's hold that question till we get to deciding on coverage or cover with conditions or not cover. Is that okay, John? And you bring it up?

John Bramhall — Sure, you bet. You bet.

Sheila Rege — We'll bring it up because right now is theoretical. Anything else? I think we've done special populations.

Melanie Golob — Val, do you want to go to the next slide the next? Kind of step in the process is either a coverage vote or further discussion on the different aspects of the sufficiency of the evidence.

Sheila Rege — Okay, I'd like us to go back to our straw poll. We've done that a few times. Is there any way we can summarize, where we stood kind of. With the majority for safety, efficacy, and cost effectiveness. So on safety, what was the? Can you summarize for me? So we felt it was.

Melanie Golob Yeah, so it was low. It looks like pretty much everyone thought low that it was safe. More people gave that medium confidence, some gave it low confidence So that's the efficiency of the audience for safety.

Sheila Rege So we Right, so Janna or. Who was a group at a strategic meeting who came up with this grid? Can you help say that in a succinct way or what we came up with that we have no confidence that this is safe?

Conor Kleweno I, I would say that we have low concerns for it being an unsafe intervention or test in this. And there's mixed confidence of that.

Janna Friedly I agree. Thanks, Conor.

Sheila Rege I think it's a concern that. Yeah, so it we pretty much feel this is probably safe, but the low confidence.

Conor Kleweno Well, I mean, I would say more people actually thought it was medium or I would say moderate confidence.

Janna Friedly And Sheila, but I'll just add, with, my, vote, I weighed a little more heavily the, the, the privacy, discrimination concerns and lack of knowledge that we have about the true effect of that and uncertainty. So just for context, but otherwise outlet. That that the data was. Suggestive very safe overall.

Sheila Rege Any other discussion on this on the straw poll of where we were? Okay, let's move on to efficacy.

Melanie Golob Yeah, it looks like the majority said more efficacious.

Sheila Rege And medium confidence is one?

Melanie Golob Yeah.

Sheila Rege Everybody agree any discussion on this? And then going on to cost effectiveness.

Melanie Golob And this was strongly equivocal.

Sheila Rege Which means similar to. Other tests is my interpretation of that. Anybody else have any opinions on that? Any discussion?

John Bramhall Well, it's a tough one, right? I mean the confidence is the confidence that's generated by the data in the studies that the studies span a period of time over which the cost of the specific genomic test has dropped from a thousand to, means it'll be a hundred shortly right. I mean this is shifting ground so my feeling, I think under purple one of us revealing anything, my feeling is that this These this test is, is much cheaper i n terms of finance,

in terms of dollars than almost anything else. And that's likely to be a trend that's, you know, increasing fast over, over time. So that's the reason for, I'm the one that says it's cheaper. And that, I have a high confidence this cheaper.

Christoph Lee — John, shouldn't it be more than versus.

John Bramhall — Say again?

Christoph Lee — Yeah, less cost effective. I think you wanted to be more cost effective then.

Sheila Rege — That's what I would have thought. You just said it.

John Bramhall — Well, yes, I do. That's absolutely right. Less cost is what I have so in my mind.

Sheila Rege — But.

John Bramhall — Rather than more cost but more cost-effective. So absolutely good. I'm glad we have these straw votes.

Sheila Rege — You, more, you're gonna more and you would actually be though you'd be that 0 would change to one on the.

John Bramhall — Yeah, I would go to I would go to be more cost-effective. I'd probably be the J out there or AJ.

John Bramhall — Thank you.

Sheila Rege — Correct. And, Dr. Friedly was next, I believe.

Janna Friedly — Yeah, I just wanted to comment, equivocal to me means that it's confusing or that there's, evidence on both side, not that it's not that it's the same, but that it's that it's, basically on uncertainty. And so I just wanted to clarify that's my definition of equivocal. I think we've talked about this before.

Sheila Rege — Alright. Dr. Kleweno?

Conor Kleweno — Oh, It's, I, I can retract. I was just if there's this discussion section I was weighing the testing odyssey, you know, although there wasn't strong evidence, I thought this was a more cost effective because of the data on the process of testing odyssey that we are presented with.

Sheila Rege — I went for equivocal low confidence because you know, asking the question of the vendor of the clinical data when is it used the first time I sense people still use single tests and then eventually they run this. And so. It's more like this, this is an added cost looking for something, but maybe I'm wrong. That's how I looked at the data. Any other discussion

before we go on? I just wanted us to be aware of how we were voting and make sure we understood what we were saying.

Clint Daniels — I was gonna say, I thought I went with low confidence and the as well. I thought it just seemed highly situational to whether they would use it first line or later, which creates huge variability and whether it saves money or costs more.

Sheila Rege — Right. For me, I mean, the BRCA test is so expensive and I would not even think about this, I would just with the BRCA, which is thousands of dollars. So it's interesting that the discussion is that this may be just as good and I'd have to see the data.

Conor Kleweno — I guess the way I interpret that is if there is something clear from a phenotype or a disease specific test, I think our expert mentioned that, that they would start with that. But for the scenarios where it's unclear then we are more cost-effective. So as opposed to doing a series of tests, we're going straight to this. So to me it was 2 disparate clinical scenarios.

Sheila Rege — I think if nobody has any more discussion on this, we could move on to the next decision aid we have to work on. Oh, we were, we were trying to help the staff will come up with this PowerPoint to help guide us through. Go ahead.

Melanie Golob — So yeah, so the next item would be a coverage vote. So a straw vote on coverage on if it should be covered, covered with conditions or covered unconditionally.

Val Hamann — And that poll is open.

Melanie Golob — Thanks, Val.

Sheila Rege — Okay, thank you. Any discussion on this? This is so much different than the last meeting where we were really, really split. So, now that we've decided, straw poll wise cover with conditions. Do you have that in US? Are you going through PowerPoint to help us still or?

Melanie Golob — So I think Josh will bring up a word document to draft those coverage conditions if you'd like.

Josh Morse — Yeah, so it sounds like the committee is ready to talk about additional coverage. Thank you. So what I normally do and you can direct me to do this however you like, but I will take off from where the agency medical directors made you a recommendation and in this case, Dr. Schultz has said the recommendation from the agency medical directors was to align with whole exome sequencing. The details of that, there it's quite a detailed decision for whole exome sequencing. It was contained in the and some of the slides here. I have created a copy of the existing whole exome sequencing policy and I have replaced whole exome with whole genome as a starting place for your conversation if that's helpful, if not we can start with a blank sheet. It's up to you.

Sheila Rege — I would prefer to have this unless they are objections.

Christoph Lee — Yeah, I agree. And I think as you read through it you'll notice that a lot of the concerns that were brought up in discussion are already addressed here.

Sheila Rege — Right. I like this. Are we okay with point number one? Let's take it point by point. Are we okay with point number one? Seeing no objections, we would move on if you will scroll up point number 2. And remember this is all of the following. And this is where we come up with target testing is not available. I, I'm comfortable keeping it in given that's what happens today. Anything anybody would want to add or refine.

Conor Kleweno — I guess I would query the expert as well since, you know, this is not, I'm not familiar with this as part of a daily practice, so I'd be interested in any comes from Dr. Yuen.

Amy Yuen — I think this is a good list for most pediatric indications. But I'm wondering if there should be some additional criteria included. Sometimes this might be needed for an adult with an adult onset neurodegenerative condition so they wouldn't have had developmental delays child or intellectual disability but perhaps they are showing cognitive changes in adulthood, muscle weakness, ataxia that doesn't necessarily fit with the something that you can easily test when at the Spinal Cerebellary ataxia or Huntington Disease. I've had some adults who have needed to have a genome testing. So I'm not sure that we're capturing all of that coverage. I don't know if that If the committee wants to focus on pediatric indications or all indications.

Sheila Rege — I'll have the vendor opine on our scope of what we have, because we are constricted, we have to stay within making criteria based on the evidence and our key questions could we have a.

Leila Kahwati — Yeah, so the studies that were included, included children and adults and there were studies that included ataxia, there were studies that included abnormal white matter brain disorders, there were studies of neurological conditions sort of un-further specified, I don't know that there were any studies like dedicated exclusively focused on adults with like neurodegenerative disorders, but adults were represented in the evidence space.

Sheila Rege — And for inclusion criteria in the studies, were they any discussion about the what's being referred to, I guess, is the complex neuro developmental disorder were there any specific criteria for inclusion in the studies?

Leila Kahwati — So for the studies involving children, no, they were largely just described as you know children with intellectual disability or developmental display, developmental delay. Some of them might have gone on to had more like specific criteria around age of onset, that kind of thing but nothing standardized across the evidence base.

Sheila Rege — I, if and, and I if people want to look it up I'm, I'm pulling the signal guidelines and Conor in response to yours and will have to make sure the vendor agrees that this was consistent with what the studies had. They do say symptoms of a complex neuro developmental disorder. Example, dystonia, ataxia, alternating hemiplegia, or muscular disorder. So just think about that, but let's go on to Dr. Friedly.

Leila Kahwati — Sorry, the other, so the representative who did public comments from PLUGS I think they also have a draft coverage criteria that you might want to consult. I don't remember if that's on there, but that might be another resource to consult with as you developed then.

Sheila Rege — Janna. Dr. Friedly?

Janna Friedly — I think I can, wait, I was trying to understand if could you scroll up so that we can see the top part of this. Yeah, it because this says, you know, whole genome sequencing is considered medically necessary for the evaluation of unexplained congenital or neurodevelopmental disorders. So that does seem limiting right there to more pediatric congenital issues. But I was thinking in the number 2, would the two criteria of significant abnormality affecting it minimum, a single organ system and period of unexplained developmental regression. I mean, you could consider adult onset regression to, to fit in there, but I think there's better ways of, more explicitly including that so. That's not a good suggestion.

Amy Yuen — Well, you might be able to tweak that line to say, you know, something like and explain developmental regression or cognitive, unexplained cognitive changes in adulthood. Something that Let's it be a little bit more expansive to when the person they have regressed, not just in childhood or early development maybe they are in adulthood. Had never had any developmental concerns and now as an adult they're changing cognitively.

Janna Friedly — Yeah, I think you'd still have to change above the first line to evaluation of unexplained congenital, neuro developmental, or neurodegenerative.

Sheila Rege — I think that could be an adult too though, Janna. Oh.

Amy Yuen — But if you put neuro degenerative, I think you're capturing it better.

Janna Friedly — No. Yeah. Yeah.

Sheila Rege — I think you're capturing it there. I like that. Any other comments? I think that captures the sense of what we were looking at and I'll ask the vendors that consistent with criteria in in the studies.

Leila Kahwati — Yeah, I think so.

Sheila Rege — Okay. Everybody go to number 2, then we're gonna go into number 3, point number 3. Hearing no discussion point number 4.

Conor Kleweno — A question. So in the in the section where it says at least 2 just to again, question to Dr. Yuen.

Sheila Rege — Going back to. Okay.

Conor Kleweno Is that is that going to be inclusive enough for an adult onset? Are we gonna be able to reach 2 of those? Cause it seem like a number of them are pediatric based?

Amy Yuen I think that line significant abnormality affecting at minimum is single organ system could help capture the adults. So let's say the organ system is neurologic, they have ataxia, and then they have cognitive changes, that could count as the 2.

Conor Kleweno Okay. Thank you.

Sheila Rege Going down to number point number 3. We had no discussion point number 4. Point number 5. Point number 6 and point number 7. We're gonna take that both in one. And I think that was the end of it, correct? No, 8. I don't know if we can put all of it in one page for everybody look at later, but let's look at non coverage first. Uncomplicated autism. Good with that. Can you put everything in one page or you can leave the non-covered out? Just the cover with conditions so we can look at it.

Conor Kleweno I headed that first bullet I wanted Dr. Yuen in to comment on that is that a reasonable in today's practice.

Amy Yuen There is much more.

Conor Kleweno That seems quite vague to me, but I, I don't see these clinically.

Amy Yuen Yes, I think it depends what are we calling uncomplicated autism because there is much more move to just consider autism an indication for genetic testing. Many of the patients who a genome might be ordered for have autism.

Conor Kleweno I guess I would also wonder why we wouldn't test for moderate global developmental delay. I mean, that seems like a big deal to me.

Amy Yuen Yes.

Conor Kleweno Do we need that first bullet?

Sheila Rege And the vendor for the vendor was autism and exclusion criteria, just uncomplicated autism?

Leila Kahwati No, it was not.

Amy Yuen And moderate global delay. Would often be a reason that a child would be referred for testing and we might consider a genome.

Conor Kleweno What if we remove that first bullet?

Sheila Rege What? What's the definition of global development delay? Is it very, specific? If I remember from my pediatric colleagues, they had very specific criteria.

Amy Yuen	So the delay has to affect multiple areas. So if you think of speech, fine motor and gross, a child is having delays in multiple areas that can be classified as global.
Sheila Rege	So is that pretty, pretty comprehensive there. So Conor, are you asking to remove autism? Let's see what the rest of the committee think.
Conor Kleweno	Yeah, and I think there's some hands up, so I'm sorry I cut the line there. My proposal was to delete that first line.
Sheila Rege	I would like, Dr. Schultz to plan. I don't know when you came on, but let's hold off.
Heather Schultz	I was just gonna clarify that the first bullet point I think is calling out not including mild up to moderate. So mild to moderate. It could probably be clarified to be to note that you were starting at moderate, but I don't think the intention of the whole exome decision which is this one was to exclude moderate global delay it's to that prior to getting to moderate, moderate would be the start point.
Sheila Rege	Yeah, I'm a little uncomfortable with removing that whole thing. So let's, hold off until the whole committee applies. Dr.Friedly.
Janna Friedly	I was gonna just add something separate. The second line seems redundant with one of the inclusion criteria that says the exact same thing just, just in the positive, not the negative.
Sheila Rege	Oh, that environmental exposures?
Janna Friedly	Yeah, that there's a criteria that says that it's can't be explained by other, all of those things, yeah, other circumstances do not reasonably explain the constellation symptoms. So it's just redundant to have it.
Sheila Rege	Right. I'm trying to understand. So that I'm, is everybody okay with that being redundant? That's not as much of a question. But in the uncomplicated autism, mild global development delay. Is that something that the committee would like to remove? It doesn't sound like from the vendor, it's, it was part of the studies. I'd remember that in other I was looking through some research articles and That's seems to be something excluded. I don't know why.
Leila Kahwati	So to clarify developmental delay is included in the evidence. The patients with developmental delay are in scope. They don't classify them those mild, moderate, severe.
Sheila Rege	So would have to have if autism were not excluded, autism would fall into that, with, but you'd have to have 2 criteria, correct? Anybody else want to opine on removing the non-coverage, uncomplicated autism spectrum, development delay? I'm reading it on mild global development delay. Oh, somebody's hands up, sorry, Chris.

Chris Hearne — It seems like what we probably want to discourage is just, you know, every individual with uncomplicated autism from getting this test, but from what Dr. Yuen has said, it seems like there are situations where autism would be part of the decision to obtain this testing. I think I would be comfortable with removing that verbiage from the non-covered list here on this first bullet point because it seems like those situations where it would be appropriate are pretty well covered in the inclusion criteria.

Sheila Rege — So you just remove autism spectrum disorder, but keep uncomplicated development delay, mild global development delay in there, or would you know that entire sentence?

Chris Hearne — I would at least be comfortable removing uncomplicated autism spectrum disorder and probably the others as well, I think.

Sheila Rege — Okay.

Chris Hearne — Because again, I think that the inclusion criteria pretty well carve out what would be appropriate situations for people with developmental delay to get the testing.

Sheila Rege — And we have we need 2 so that's got guardrails around it. Is, is everybody, does anybody have heartache about removing that entire sentence?

John Bramhall — No, I mean there was in the in the report at, page 15 Appendix G just, just for reference. In the vendors report, the diagnostic yield specifically for autism spectrum disorder on the slide presented is 0. It's, it's, it doesn't distinguish between the other comparator there. So in terms of just the evidence report that we've been presented with there is a comment in one of the slides about the lack of utility of WGS for specifically autism spectrum disorder. So I think it's in any case it's a bit of a confounder. In other words, the data that we've been presented with such as it is for autism suggests that WGS is not a good additional test for making that diagnosis as I understand it.

Sheila Rege — Maybe that's what I had read because I remember seeing I'm.

John Bramhall — Yeah, it's it's in Appendix G report page 15.

Leila Kahwati — Yeah, there's 1 study that was exclusively conducted among persons with autism. However, in the studies on that included people with developmental delay, some of the studies absolutely also allowed people with autism to be in those patient populations. So the evidence for people with autism is sort of spread across multiple studies, not just the single study that only looked at autism, if that makes sense?

Sheila Rege — What I'm reading is uncomplicated autism spectrum disorder is autism without another organ issue or some sort of you know, kind of the another feature there and that's kinda how I looked at it, but I didn't mean to exclude autism, like all autistic kids. They have to have autism plus something else. I, does anybody see a con of removing that entire sentence? I'm just, you know, we, are data driven and, and I'm a little concerned about removing something without discussion about unintended consequences.

I would, for the first I would say just mild global development so delete mild to moderate just say mild global developmental delay. I think everybody would be comfortable with that being deleted. So now the question is, are we okay with that knowing that autism would be included. Can you go back up to 2? So if you have somebody, you'd have significant abnormality and do we only want unexplained cognitive changes in adulthood? Because autism, uncomplicated autism would fall into one of these if you had a family history or abnormality of a single organ system. Up for discussion or we could.

Josh Morse — Yeah, and I wonder if having the exclusion criteria would make it more or potentially more challenging.

Sheila Rege — You mean keeping it there and keeping it as autism there would make it more challenging?

Josh Morse — Yeah, I think that's, that's a concern that I'm having. Because I do, I think you have, I am agreeing with those who are saying that it's the criteria and these criteria may be redundant, but they may also be problematic, I think.

Conor Kleweno — I agree with that.

Sheila Rege — Let's take a vote on who wants that remove and who doesn't. I'm sorry, we have Dr. Yuen has her hand up.

Amy Yuen — I was just gonna throw out one other consideration for that not covered list is perhaps the term high functioning autism or mild developmental delay could cover what you're trying to capture there.

Conor Kleweno — Do you, do you agree if we were to remove it that our inclusion criteria are clear and inclusive appropriate to the data and clinical practice?

Amy Yuen — I think the inclusion criteria are, are pretty good and they're going to find the right patients without having to have that second exclusion criteria line. But if you wanted to keep it that would be another.

Sheila Rege — I, I like.

Amy Yuen — Where I would throw out as rephrasing it.

Sheila Rege — I like the high functioning autism or mild development delay. It would be or mild global development delay.

Josh Morse — Oh, did I put in the wrong place?

Sheila Rege — No, no, you put, oh yeah, I guess, yeah. I'm sorry, no, no, no.

Josh Morse — Okay, there is like, gonna go, okay. Uncomomplicated, high functioning. We take the comment out here then?

Sheila Rege — You just say mild and then you'd say or mild global development delay. Just put it or there, you're good. Is that okay? Is that? Dr. Kleweno.

Conor Kleweno — I don't know, I'm still, I'm still stuck on it a bit because you know this field is as we've heard today, advancing so fast and so is today's mild developmental delay tomorrow's oh yeah that's of course that's what that is that we've now discovered that and I just you know, clearly we don't want everybody just getting this test randomly, but I feel like we have some really good inclusion criteria. And I feel like we're trying to be specific with our exclusion criteria for without a strong reason for it. But.

Sheila Rege — I'm going with the safety. I mean, if my child has a mild development issue that corrects later, I don't want to have some doctor recommending this. But.

Conor Kleweno — That would be your choice though, right? I mean.

Sheila Rege — Yeah, but sometimes some patients at the doctor recommend something, they go for it. That's what I'm trying to avoid. And every everything we saw in the studies, it was pretty significant global development delay.

Conor Kleweno — Right, which is what we have in the inclusion, but okay.

Sheila Rege — But if I just want to talk about it, if others are uncomfortable about it too. Everybody okay with this? Our vendor does, does this consistent with the data? It's not something that we've missed?

Tony Yen — Sheila, I think Chris has his hand up too.

Leila Kahwati — Yeah. Yeah, it's consistent.

Sheila Rege — Okay, I didn't see somebody saying, oh, there's a lot of hands up. Who was first. Dr. Yen, sorry.

Tony Yen — No, no Chris was before me then I'm next. Then it's Jonathan.

Chris Hearne — I was just gonna say I think. The way I'm thinking about this is that, You know, obviously I don't think the data supports using high functioning autism or a mild global developmental delay as, as a indication for the test in itself. But you can imagine somebody who did have high functioning autism who nonetheless fulfilled 2 of the criteria above and I wouldn't want there to be confusion that they would not be able to get this test covered. So they could have that mild, developmental delay and then have one of these 2 bullet points in addition and they would still none the less should be, should be eligible to get the testing. Does that make sense?

Sheila Rege Right, so you're speaking to remove that entire first sentence?

Chris Hearne Or, or say like comma without other qualifying criteria as indicated above or something like that.

Sheila Rege I hear what Josh said that we are complicating things that we add autism here and it confuses things. I'm gonna be cognizant. Let's, let's have here the others. Go ahead. Who is next?

Tony Yen I think I'm next. It's just, taking out that first bullet over there. I think the, their inclusion criteria are good enough.

Sheila Rege Okay. Anybody else speaking?

Jonathan Sham Yeah, yes, I was gonna just add on, I agree, I think by defining inclusion criteria we are by the very nature also defining exclusion criteria by that. And so I think this gets really complicated and we try and do both and as Chris just said, and turns out there could be some overlap. So I just think for the process standard, it'll be most clear to eliminate this.

Sheila Rege Okay, then Josh, I'm hearing committee members say, that we'll hear from Leila. Thank you.

Leila Kahwati Yeah, I just wanted to weigh in the evidence base does not distinguish between high functioning autism and autism or mild, moderate and profound, the, the results are not presented like that so I don't know that you can carve that out, that group out based on the evidence alone. Now you might do that based on other considerations, but I don't think you can do that based on the evidence.

Sheila Rege What I'm hearing does anybody have an objection with removing the whole first will that point? I see. Leila, do you still have your hand up? No, Dr. Yuen.

Amy Yuen I was just gonna say given the amount of discussion this bullet point has generated is probably safest to remove it because it could just lead to more confusion. And someone who's trying to figure out if their patient meets criteria.

Sheila Rege Yeah, agree. Anybody else, anything else? Otherwise we have We can project what we have come up with so far. Can we go to that first page and make the font a little smaller just to have it all on one page? Okay, maybe, can we make, make the font even smaller so we can get 6, 7, and 8 on there. Where's 8? 0h that's perfect. Any discussion? If not, our policy is to have a 5 min. Right or just a few minutes too. Look at this and make sure we don't have any other thoughts. I will take a motion for a break or a motion to continue. Seeing no motion, I'm gonna.

Chris Hearne I have a quick question.

Sheila Rege Yeah, Chris.

Chris Hearne For I don't know if this is. Really that relevant, but for bullet point number one, criteria number one. Should a, a PA who is working under a medical geneticist be allowed to order this test? As written it appears that they are not. Not sure if that was intentional or just oversight.

Sheila Rege I have not seen a PA genetic because our, you know, we've always sent it to a board certified medical geneticist. And, so family physicians even primary care physicians are not doing this test, Chris. But I'll defer to. Others? I've not seen that.

Chris Hearne Yeah, maybe it's something that's not likely to come up.

Sheila Rege Yeah, I don't I just not seen that so I would not. You know, then you open it up and Primary care physicians are gonna say, we should be able to order too. So I'm just a little concerned about opening that up.

Janna Friedly And it seems like if they are working. With a board certified geneticist that the geneticist could order the test and probably should in consultation anyway.

Sheila Rege Any other discussion before we go on break? What time is it? 12:17. Is everybody okay coming back at 12:22 or does anybody want to longer break? But please look at this when you come back. Okay, we're gonna break till 12:22.

Okay, we're back. Any more discussion on? The language we have up in front of us.

Jonathan Sham It is a quick question, Sheila. Section 5, second bullet point. I'm sorry if you guys already talked about this way to step away, but is it really intended they need to avoid multiple invasive procedures or can they just avoid a an invasive procedure? Do we need the word multiple there? Like if they can get this instead of a muscle biopsy, that would be preferred. It's the way it's run, sounds like they need to have 2 invasive procedures or need need to avoid 2 invasive procedures. To make sure that was intended, intended or not.

Sheila Rege So you just want if it would even avoid one invasive procedure you want?

Jonathan Sham Yeah, just, just then just. You can just take other word multiple and I think that's what we meant, I think, but I just wanna make sure I didn't miss something.

Sheila Rege Anybody else have an opinion on this?

Amy Yuen I would agree. Being able to avoid a muscle biopsy or sometimes it's a nerve conduction, EMG test that's painful, being able to avoid one of those is a great benefit and a muscle is actually going to cost you more then a whole genome in addition to having pain and risk of complications.

Sheila Rege Any other discussion? Not hearing any, that doesn't sound like anybody has a problem with that. Anything else? Otherwise I'll move on to the next step.

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Josh Morse	The next step is move to, to vote on this as your draft coverage determination. Val, can you, Give it.
Val Hamann	Yeah, so if you could, if you may have been kicked out of ttpolls depending upon if you have an account or not, so make sure that you are logged in and I will launch that poll. And that poll is open. Josh, if you wanted to share that coverage. That draft coverage language so they can look at it. And we're waiting on one more response. And we're still waiting on one more.
Sheila Rege	I think somebody had stepped away. I can't remember.
Val Hamann	Okay.
Laurie Mischley	I had stepped away, but I'm back. It's not me that you're waiting for it. Is it?
Val Hamann	We just got it. Perfect. Oh, sorry about that. I will. So you should be seeing. The vote.
Josh Morse	Great. Okay, so you have approved the coverage conditions is written. Val, do you have a final vote for cover, no cover or cover with the conditions as written?
Val Hamann	Are you able to see the, this is as written.
Josh Morse	I can see that. Yeah.
Sheila Rege	Josh, I don't think, I think we took a straw poll and then we went to the language. But I don't know if we've done. And help me out, the final vote on cover, unconditionally covered with conditions, or not.
Josh Morse	Yep. Yep. So, I don't know, Val, if you can put that vote together or we can use the vote that was done. It's the same as what we did before on the straw vote, but it would be the final vote on cover, no cover or cover with conditions and we would be voting on the conditions that were just approved and then the committee would vote. I think we know the answer here. But I do think we should complete that vote.
Val Hamann	Okay, so say that one more time, Josh.
Josh Morse	Yeah, the site you just showed with cover no cover. We're going to do that vote essentially again with the conditions that were just approved.
Val Hamann	Okay, and then would you be able to show those really quickly? So I can.
Josh Morse	Yeah, although they were just approved. I don't know that it's necessary. I think committee has approved this draft. We just need to know that all 9, are going to need to see in a formal vote approving coverage with conditions if that's the way the committee goes. Some committee members may have a different feeling about.

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Melanie Golob	And Josh the review of alignment with NCD and guidelines happens after the final vote, is that correct?
Josh Morse	It does. Yeah.
Val Hamann	Okay, so. I will share this and let me know if. Is this what you were thinking, Josh?
Josh Morse	Correct. Yeah.
Val Hamann	Okay, great. I will launch.
Sheila Rege	And you put that in our vote. And if we will cover with conditions since the conditions we have just worked on.
Josh Morse	Yeah, and we can look that you basically do you approve the decision? Yeah.
Sheila Rege	We're good.
Josh Morse	Fantastic. Thank you. Thanks for going through that again. So the next step is, to review if there's a national coverage determination and looking at the decision aid, I can share my screen. This is the decision aid that was provided in the meeting materials you've just completed your second vote here to cover with condition with the criteria that you wrote. There is no national coverage determination for whole genome sequencing, so it is not a question about alignment. There are some guidelines. And the same question is, do your, does your decision align or not align? And if it does not align. What is your rationale for?
Sheila Rege	I think it seems to align. Looking at it online here. We're good, Josh, I think. Go ahead.
Josh Morse	Okay, yeah, if you're, yeah, it sounds like, and it looks like you're in alignment. You've documented that. I think we have, we have reached the end of our agenda for today. So thank you very much.
Sheila Rege	And, thank you, Dr. Kleweno and Dr. Yen, were you the 2 who are keeping us on track?
Conor Kleweno	Yeah, but I think that was all you today.
Tony Yen	Yep, it was all you, Sheila.
Sheila Rege	I think it was staff. I think, the PowerPoint really helped. So I will take a motion to adjourn.
Janna Friedly	So moved.
Tony Yen	Second.
Sheila Rege	All in favor? Thank you.

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Josh Morse	Thank you all.
Sheila Rege	Thank you. Bye-bye now.
Josh Morse	Thank you, Dr. Yuen.
John Bramhall	Thank you.
Tony Yen	Bye.